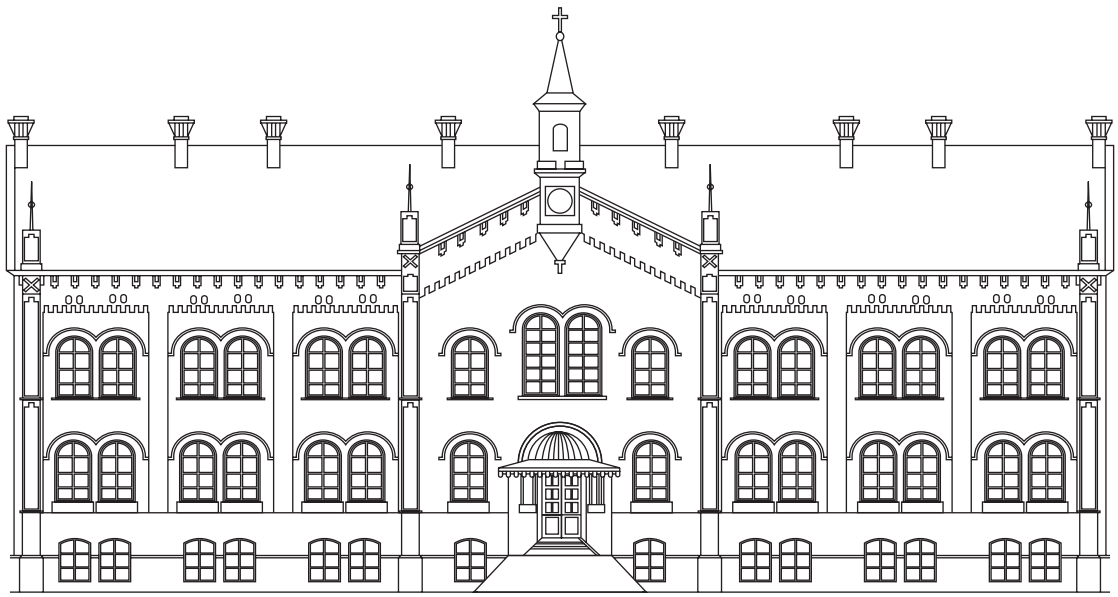
SRP ARH CELOK LEK

ISSN 0370-8179 (PRINT)
ISSN 2406-0895 (ONLINE)

COBISS.SR-ID 3378434
UDC 61(497.11)

СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО

ЧАСОПИС СРПСКОГ ЛЕКАРСКОГ ДРУШТВА

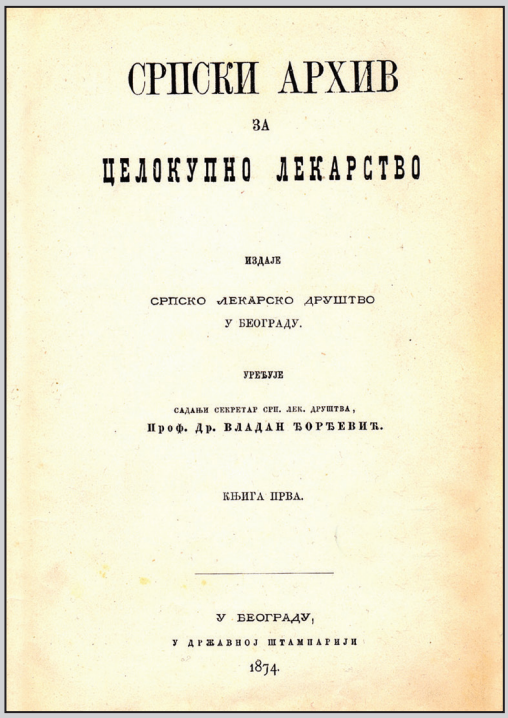


SERBIAN ARCHIVES
OF MEDICINE

JOURNAL OF THE SERBIAN MEDICAL SOCIETY

VOLUME 150 · NOVEMBER–DECEMBER · ISSUE 11–12

www.srpskiarhiv.rs



СРПСКИ АРХИВ

ЗА

ЦЕЛОКУПНО ЛЕКАРСТВО

ИЗДАЈЕ

СРПСКО ЛЕКАРСКО ДРУШТВО

У БЕОГРАДУ.

УРЕЂУЈЕ

САДАШЊИ СЕКРЕТАР СРП. ЛЕК. ДРУШТВА,

Проф. Др. ВЛАДАН ЂОРЂЕВИЋ.

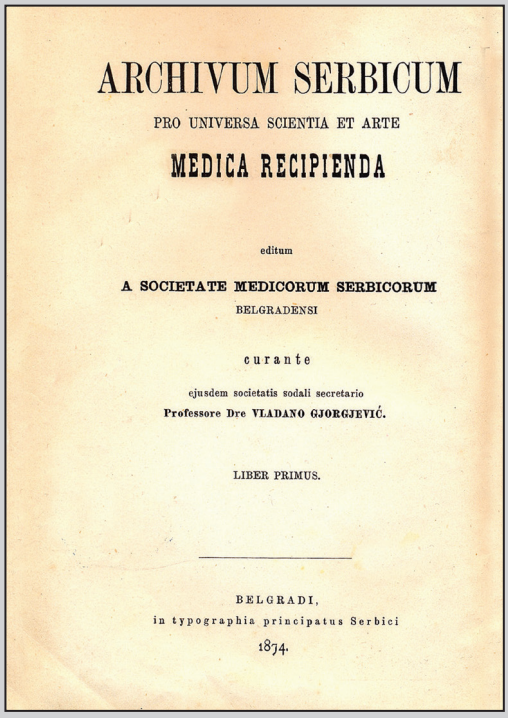
КЊИГА ПРВА.

У БЕОГРАДУ,

У ДРЖАВНОЈ ШТАМПАРИЈИ

1874.

Прва страна првог броја часописа на српском језику



ARCHIVUM SERBICUM

PRO UNIVERSA SCIENTIA ET ARTE

MEDICA RECIPIENDA

editum

A SOCIETATE MEDICORUM SERBICORUM

BELGRADENSI

curante

ejusdem societatis sodali secretario

Professore Dre VLADANO GJORGJEVIĆ.

LIBER PRIMUS.

BELGRADI,

in typographia principatus Serbici

1874.

The title page of the first journal volume in Latin

Српски архив за целокупно лекарство је часопис Српског лекарског друштва основаног 1872. године, први пут штампан 1874. године, у којем се објављују радови чланова Српског лекарског друштва, претплатника часописа и чланова других друштава медицинских и сродних струка. Објављују се: уводници, оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови, актуелне теме, радови за праксу, радови из историје медицине и језика медицине, медицинске етике и регулаторних стандарда у медицини, извештаји са конгреса и научних скупова, лични ставови, наручени коментари, писма уреднику, прикази књига, стручне вести, *In memoriam* и други прилози.

Сви рукописи који се разматрају за штампање у „Српском архиву за целокупно лекарство“ не могу да се поднесу или да буду разматрани за публиковање на другим местима. Радови не смеју да буду претходно штампани на другим местима (делимично или у потпуности).

Приспели рукопис Уређивачки одбор шаље рецензентима ради стручне процене. Уколико рецензенти предложе измене или допуне, копија рецензије се доставља аутору с молбом да унесе тражене измене у текст рада или да аргументовано образложи своје неслагање с примедбама рецензента. Коначну одлуку о прихватању рада за штампу доноси главни и одговорни уредник.

За објављене радове се не исплаћује хонорар, а ауторска права се преносе на издавача. Рукописи и прилози се не враћају. За репродукцију или поновно објављивање неког сегмента рада публикованог у „Српском архиву“ неопходна је сагласност издавача.

Радови се штампају на енглеском језику са кратким садржајем на енглеском и српском језику (ћирилица), односно на српском језику, са кратким садржајем на српском и енглеском језику.

Аутори прихватају потпуну одговорност за тачност целокупног садржаја рукописа. Материјал публикације представља мишљење аутора и није нужно одраз мишљења Српског лекарског друштва. С обзиром на брз напредак медицинске научне области, корисници треба да независно процењују информацију пре него што је користе или се на њу ослањају. Српско лекарско друштво, уредник или Уређивачки одбор „Српског архива за целокупно лекарство“ не прихватају било какву одговорност за наводе у радовима. Рекламни материјал треба да буде у складу с етичким (медицинским) и правним стандардима. Рекламни материјал укључен у овај часопис не гарантује квалитет или вредност оглашеног производа, односно тврдње произвођача.

Поднесени рукопис подразумева да је његово публиковање одобрио одговорни ауторитет установе у којој је истраживање обављено. Издавач се неће сматрати правно одговорним у случају подношења било каквог захтева за компензацију. Треба да се наведу сви извори финансирања рада.

Srpski Arhiv Za Celokupno Lekarstvo (Serbian Archives of Medicine) is the Journal of the Serbian Medical Society founded in 1872, and with first issue published in 1874. Serbian Archives of Medicine publishes articles of the Serbian Medical Society members, subscribers, as well as members of other associations of medical and related fields. The journal publishes the following article types: editorials, original papers, preliminary and short communications, case reports, video-articles, images in clinical medicine, review articles, current topics, articles for practitioners, history of medicine articles, language of medicine articles, medical ethics (clinical ethics, publication ethics) and regulatory standards in medicine, congress and scientific meeting reports, personal view articles, invited commentaries, letters to the editor, book reviews, professional news, In memoriam and other articles.

All manuscripts under consideration in the Serbian Archives of Medicine may not be offered or be under consideration for publication elsewhere. Articles must not have been published elsewhere (in part or in full).

The submitted manuscripts are forwarded by the Editorial Board to reviewers for editing and evaluation. If the reviewers find that the manuscript needs to be modified or amended, the copy of the report is sent to the author(s), requiring of them to make necessary modifications or amendments of the text or to provide argumentative explanation of their disagreement with the suggested reviewer's remarks. The final decision on acceptance of the article for publication is made by the Editor-in-Chief.

The authors shall not be remunerated for the published articles, and they are required to assign copyright of their papers to the publisher. Manuscripts and enclosures shall not be returned to the authors. Reproduction or repeated publication of any section of the manuscript already published in the "Serbian Archives" requires the publisher's approval.

The articles are printed in the English language with an abstract both in English and Serbian, or in the Serbian language, Cyrillic alphabet, with an abstract in Serbian and English.

Authors accept full responsibility for the accuracy of all content within the manuscript. Material in the publication represents the opinions of the authors and does not necessarily reflect opinions of the Serbian Medical Society. Because of rapid advances in the medical sciences, users should independently evaluate information before using or relying on it. Serbian Medical Society, the Editor or Editorial Board of the Serbian Archives of Medicine do not accept any responsibility for the statements in the articles. Advertising material is expected to conform to ethical (medical) and legal standards. Inclusion of advertising material in this publication does not guarantee the quality or value of such product or claims made by its manufacturer.

Submission of the manuscript implies that its publication has been approved by the responsible authorities at the institution where the work has been carried out. The publisher will not be held legally responsible should be any claims for compensation. Details of all funding sources for the work should be given.

Srp Arh Celok Lek
ISSN 0370-8179
UDC 61(497.11)
COBISS.SR-ID 3378434
Српски архив за целокупно лекарство
Званичан часопис Српског лекарског друштва
Излази шест пута годишње

ГОДИШТЕ 150. НОВЕМБАР–ДЕЦЕМБАР 2022. СВЕСКА 11–12

Часопис „Српски архив за целокупно лекарство" је индексиран у базама: Science Citation Index Expanded, Journal Citation Reports/Science Edition, Web of Science, Scopus, EBSCO, Directory of Open Access Journals, DOI Serbia.

ОСНИВАЧ, ВЛАСНИК И ИЗДАВАЧ
Српско лекарско друштво
Џорџа Вашингтона 19, 11000 Београд, Србија
Председник
Академик Радоје Чоловић
Интернет страна: http://www.sld.org.rs

ИЗДАВАЧКИ САВЕТ
Проф. др Павле Миленковић, председник
Академик Владимир Бумбаширевић
Проф. др Љубица Ђукановић
Академик Небојша Лалић
Проф. др Милица Чоловић

АДРЕСА УРЕДНИШТВА
Српски архив
Краљице Наталије 1, 11000 Београд, Србија
Телефон: +381 (0)11 409 27 76
+381 (0)11 409 44 79
Е-пошта: office@srpskiarhiv.rs
Интернет страна: www.srpskiarhiv.rs

ПРЕТПЛАТА И ЕКСПЕДИЦИЈА
Српско лекарско друштво
Џорџа Вашингтона 19, 11000 Београд, Србија
Телефон: +381(0)11 3245-149
Текући рачуни: 205-8041-21 и
355-1009094-22

Чланци у целости доступни су на интернет страници: www.srpskiarhiv.rs

Цена претплате за календарску годину је 3.000,00 динара за појединце, 6.000,00 динара за установе и 100 евра за читаоце ван Србије. Цена појединачног примерка из текуће године је 600,00 динара, а свеске из претходних година 300,00 динара.

Штампање „Српског архива за целокупно лекарство" током 2022. године помогло је Министарство просвете, науке и технолошког развоја Републике Србије

ISSN 0370-8179; ISSN Suppl 0354-2793

eISSN 2406-0895
Отворен приступ

Штампано у Србији

РЕДАКЦИЈА
Технички уредник: Јасмина Живковић
Лектор за српски језик: Дивна Продановић
Лектори за енглески језик: Мирко Рајић, Ана Миловановић
Корице: *MaxNova Creative*

Штампа: ЈП „Службени гласник", Београд

Тираж: 850 примерака

Srp Arh Celok Lek
ISSN 0370-8179
UDC 61(497.11)
COBISS.SR-ID 3378434
Serbian Archives of Medicine
Official Journal of the Serbian Medical Society
Published six times per year

VOLUME 150 NOVEMBER–DECEMBER 2022 ISSUE 11–12

The journal "Srpski arhiv za celokupno lekarstvo" (Serbian Archives of Medicine) is indexed in: Science Citation Index Expanded, Journal Citation Reports/Science Edition, Web of Science, Scopus, EBSCO, Directory of Open Access Journals, DOI Serbia.

EDITORIAL OFFICE
Technical editor: Jasmina Živković
Serbian language editor: Divna Prodanović
English language editors: Mirko Rajić, Ana Milovanović
Cover & Logo: MaxNova Creative

Printed by: JP "Službeni glasnik", Belgrade

Circulation: 850 copies

FOUNDER, OWNER & PUBLISHER
Serbian Medical Society
President
Academician Radoje Čolović

PUBLISHER'S ADVISORY BOARD
Prof. Pavle Milenković, MD, PhD, president
Academician Vladimir Bumbaširević
Prof. Ljubica Đukanović, MD, PhD
Academician Nebojša Lalić
Prof. Milica Čolović, MD, PhD

EDITORIAL OFFICE
Serbian Archives of Medicine
Kraljice Natalije 1, 11000 Belgrade, Serbia
Phone: +381 (0)11 409 27 76
+381 (0)11 409 44 79
E-mail: office@srpskiarhiv.rs
Website: www.srpskiarhiv.rs

SUBSCRIPTION AND DISTRIBUTION
Serbian Medical Society
Džordža Vašingtona 19, 11000 Belgrade
Serbia
Phone: +381(0)11 3245-149
Bank accounts: 205-8041-21 and
355-1009094-22

Full-text articles are available at website: www.srpskiarhiv.rs

Calendar year subscription prices are as follows: 3,000 dinars for individuals, 6,000 dinars for institutions, and 100 euros for readers outside Serbia. The price of a current year issue is 600 dinars, and of issues from previous years 300 dinars.

The publishing of the Serbian Archives of Medicine during 2022 is supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia.

ISSN 0370-8179; ISSN Suppl 0354-2793

eISSN 2406-0895
Open Access
(CC BY-NC)

Printed in Serbia

САДРЖАЈ • CONTENTS

EDITORIAL • УВОДНИК

ORIGINAL ARTICLES • ОРИГИНАЛНИ РАДОВИ

CASE REPORTS • ПРИКАЗИ БОЛЕСНИКА

REVIEW ARTICLES / ПРЕГЛЕДИ ЛИТЕРАТУРЕ

CURRENT TOPIC / АКТУЕЛНА ТЕМА

IN MEMORIAM

DOI: https://doi.org/10.2298/SARH221221117T

EDITORIAL / УВОДНИК

150th anniversary of the Serbian Medical Society – the year in review

As we look back at the year just wrapping up, we inevitably ponder on whether it met our expectations, and if it did answer our hopes, to what extent? In the wake of its 150th birthday, the Serbian Archives of Medicine welcomed the year 2022 filled with ancestral pride and joy the future is yet to bring. The Serbian Archives of Medicine is the official journal of the Serbian Medical Society (SMS), the oldest society of its kind in modern medical Serbian history, founded in Belgrade (Serbia), on April 22, 1872 (according to the Julian calendar), i.e. May 4, 1872 (according to the Gregorian calendar) [1, 2]. About this historic action of a group of medical doctors who were practicing in Belgrade and who were led by Dr. Vladan Đorđević, one could read in the Invited Editorial by the President of the SMS – Professor Radoje Čolović, Member of the Serbian Academy of Sciences and Arts [3].

This year will be proudly remembered, first of all, as the one when Academician Čolović, as our President, was the recipient of the national Sretenje Order of the 1st Class that the Serbian President, Mr. Aleksandar Vučić, awarded the SMS, upon the recommendation of the President of the Serbian Academy of Sciences and Arts, on February 15, 2022 – the anniversary of Candlemas (Sretenje) Constitution of 1835 that Serbia celebrates as a national holiday (Figure 1) [4].

The 150th birthday of the SMS was marked by numerous events throughout 2022 with the first one held at the Ceremonial Hall of the Serbian Academy of Sciences and Arts on May 4, 2022 – the day the Society was founded [1, 2, 3, 5]. In attendance were Mr. Ivica Dačić, President of the Serbian National Assembly, Prof. Marina Soković, Deputy-Minister of Education, Sciences and Technological Development of the Republic of Serbia, Professor Zoran Radojičić, Mayor of the City of Belgrade and renowned paediatric surgeon at the Belgrade University Faculty of Medicine, Professor George Rakovich, renowned cardiothoracic surgeon from the University of Montreal (Canada), of Serbian descent and the official representative of North American MD group preserving traditional values of Serbian medicine and humanity, as well as other distinguished guests, academicians and members of the Society (Figure 2). Later on this year, the 20th Congress of Serbian Doctors, twice postponed since 2020 due to COVID-19 pandemic, finally took place in Belgrade, November 25–26, 2022 [6].

The era we live in embraced electronic media in a comprehensive fashion nationally and internationally. Although the world is turning more and more aggressive in all walks of life, and is aiming to replace the paper editions of anything and everything, the SMS endeavours to maintain a healthy balance, unconcerned with global discussions even in the medical circles to completely cease publication as we know it. In that way, the SMS enables the May 4, 2022 anniversary at the Serbian Academy of

Figure 1. The national Sretenje Order of the 1st Class that the Serbian President, Mr. Aleksandar Vučić, awarded the Serbian Medical Society on February 15, 2022 – the anniversary of Candlemas (Sretenje) Constitution of 1835 that Serbia celebrates as a national holiday

Figure 2. Ceremonial Hall of the Serbian Academy of Sciences and Arts (SASA) on May 4, 2022 – the day the Serbian Medical Society was founded in 1872. *Right to left:* Prof. Aleksa Marković, Dean of School of Dental Medicine, University of Belgrade, Academician Ljubomir Maksimović, SASA Vice-President, Prof. Zoran Radojičić, Mayor of the City of Belgrade, Academician Prof. Vladimir S. Kostić, SASA President, Mr. Ivica Dačić, President of the Serbian National Assembly, Academician Zoran Knežević, SASA Secretary-General, Prof. Marina Soković, Deputy-Minister of Education, Sciences and Technological Development RS, Academician Prof. Radoje Čolović, President of the Serbian Medicial Society and Prof. George Rakovich from University of Montreal, Canada

Figure 3. The 150th anniversary stamp for the Serbian Medical Society designed by the Post of Serbia

Science and Arts to be followed live via its website, but the Anniversary Book dedicated to 150 years of the SMS [5] and the paper edition of the Abstract Book of the 20th Meeting [6] have been published, as well. The perseverance in maintaining its paper editions might have been misinterpreted as the SMS leadership's "old school" sentimental approach; still, in the energy-deficient times that the world faces due to geopolitical struggles in far Eastern Europe, the Society's position from earlier this year had turned to be more far-sighted than expected, for the Serbian Archives of Medicine are still readily available for our global readership and not depending on electricity cuts Serbia has been spared, so far, in contrast to the rest of the world.

One of the last in a long line of SMS 150th Anniversary celebrations will be the promotion of the Serbian edition of Emmerich Lindermeier's book *Serbien, dessen Entwicklung und Fortschritt im Sanitætswesen, mit Andeutungen über die gesammten Sanitäts-Verhältnisse im Oriente* [7]. The book was first published in 1876 in Timişoara (Romania). Chief of Staff of the First Serbian Military Medical Service for seven years, and joint Military and Civil Medical Services Chief of Staff the next 13 years, Dr. Emmerich Lindermeier's work is of great importance for the history of the development of Medical Services in Serbia in the 19th century. With promotion scheduled for December 23, 2022, in the Serbian Academy of Sciences and Arts, the book will be introduced by academicians and professors: Vladimir Kostić and Radoje Čolović, and Dr. Zoran Vacić, President of the SMS History of Medicine Division as keynote speakers.

Nation-wide support to the SMS as one of national oldest institutions was felt and well-noted all along 2022 and we would like to take this opportunity to thank the oldest national daily "Politika" and the Post of Serbia: the former for publishing daily excerpts of the 150th Anniversary publication over 30 days and the latter designed a 150th Anniversary stamp for the SMS (Figure 3).

As I write these lines on what would have been the 147th birthday of Mileva Marić-Einstein – a researcher in her own right who never got the credit she deserved – and as the world as we know it changes by the minute while we embrace the new 2023 with challenges of its own, last but not the least, as I wish you all a healthy and prosperous new year, I would like to remind you never to give up in publishing your own work irrelevant of your sex, gender, colour or creed for science should be free of bias towards all who bring progress no matter how small it seems.

Conflict of interest: None declared.

Editor-in-Chief
Prof. Gordana Teofilovski-Parapid, M.D., Ph.D.
Honorary President, Serbian Anatomical Society
Honorary President, International Committee of Symposia on Morphological Sciences,
IPP, European Federation for Experimental Morphology
University of Belgrade, Faculty of Medicine, Belgrade, Serbia
gordana.teofilovski.parapid@srpskiarhiv.rs

REFERENCES

1. Postanak Srpskog lekarskog društva. Prvi prethodni sastanak 22. aprila 1872. Srp Arh Celok Lek. Odeljak I, knjiga I (1874), str. 1–2. (In Serbian)
2. Teofilovski Parapid G. The Serbian Archives of Medicine – the 150 Years' Long Tradition. Srp Arh Celok Lek. 2022;150(1–2):6–9. [DOI: 10.2298/SARH2202006T]
3. Čolović R. 150 years of the Serbian Medical Society. Srp Arh Celok Lek. 2022;150(3–4):132–7. [DOI: 10.2298/SARH220404039C] (In Serbian)
4. Predsednik Republike Srbije, Ukazi o odlikovanjima, Ukazi o odlikovanjima koje je potpisao predsednik Republike Srbije Aleksandar Vučić (https://www.predsednik.rs/predsednik/ukazi-o-odlikovanjima)
5. Čolović R. (urednik knjige i autor najvećeg broja poglavlja i priloga u poglavljima u toj knjizi). 150 godina Srpskog lekarskog društva. Beograd: Srpsko lekarsko društvo; 2022.
6. Čolović R. U susret XX kongresu lekara Srbije. 20. kongres lekara Srbije 24–25. (In Serbian)novembar 2022. Zbornik radova i sažetaka. Beograd: Srpsko lekarsko društvo; 2022. str. 9–34. (In Serbian)
7. Čolović R. Predgovor za prevod knjige:„Srbija, njen razvoj i napredak u sanitetu sa napomenama o celokupnom sanitetskom stanju na Orijentu" od dr Emeriha P. Lindenmajera. Beograd: Srpsko lekarsko društvo; 2022. str. IX–XII. (In Serbian)

DOI: https://doi.org/10.2298/SARH220722105D
UDC: 615.8-056.34/.36(536.2); 616.98:578.834(536.2)

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Pediatric rehabilitation services during COVID-19 pandemic in the United Arab Emirates

Dragana Đurić[1], Sunitha Bhagavathi Mysore[1], Adam Zeghan[2], Areen Oudeh[3], Belal Al Qerem[4], Abdula Al Humaidan[4], Muhammed Al Jarrah[1]

[1]Fatima College of Health Sciences, Abu Dhabi, UAE;
[2]Cerebral Palsy Foundation, Amman, Jordan;
[3]Star Key Health, Abu Dhabi, UAE;
[4]Zayed Higher Organization for People of Determination, Abu Dhabi, UAE

SUMMARY

Introduction/Objective COVID-19 pandemic has changed the rehabilitation practice across the globe. A sudden transition from in-person therapy at the center to remote therapy challenged the managers and multi-disciplinary team members providing pediatric rehabilitation. The main objective of this research was to assess the provision of services for children with disabilities during COVID-19 in the United Arab Emirates.

Methods Two surveys were developed by the research team, one for the managers and the others for multidisciplinary team members. Both surveys were validated through experts followed by a pilot study. The final versions of the survey were sent to all the pediatric rehabilitation centers within the United Arab Emirates in September 2020. A total of 44 managers and 434 multidisciplinary team members completed the survey.

Results The accessibility of the pediatric rehabilitation services was reported to be very high with 77%. Regarding the cost for running the services, almost half (46%) of managers reported them to be costlier than normal. Telerehabilitation was the most common approach utilized with synchronized live video calls (86%), YouTube video clips (88%), and created own videos (65%).

Conclusion Telerehabilitation appeared to be the most efficient model used for pediatric rehabilitation during the pandemic. The future investments for the continued use of telerehabilitation require planning, budgeting, investing, and creating supportive environments for parents, children, and multidisciplinary team members. There is a need for sharing platforms for educational and therapeutic resources created during the pandemic, with ongoing research on telerehabilitation.

Keywords: COVID-19; pediatric rehabilitation; telerehabilitation; pandemic

INTRODUCTION

COVID-19 pandemic has seen changes in professional practice across the globe. Most healthcare services that provided non-emergency, long-term care were closed in early 2020 in several countries [1]. But within a span of fortnight to a month, the healthcare sectors considered alternate ways of providing services in several countries including the United Arab Emirates (UAE).

British Broadcasting Corporation (BBC) in one of their articles published on May 1, 2020 titled *Coronavirus: Disabled people 'forgotten' by governmental strategy* highlighted the importance of continued care for those with long-term disability. They emphasized providing better funding and resources during the pandemic. They also raised concerns about the vulnerability of the disabled and that confining them at home without proper therapy could seriously impact physical and mental health [2, 3, 4]. The other main concern during the lockdown was deterioration in a child's physical and mental health as there was alarmingly high percentage of children who lost access to one or more multidisciplinary team (MDT) members [5].

An MDT-approach for pediatric rehabilitation is crucial [6]. During COVID-19, it became imperative to provide services from all MDT members mirroring the one that would run physically in the center. With little or no prior experience, many MDT members were challenged to use remote services for their patients. It was crucial to adopt a biopsychosocial model in rehabilitation, thus strengthening the role of families during COVID-19 [7].

One of the popular options during the pandemic for receiving special education, behavioral therapies, and therapeutic intervention was through telerehabilitation (TR) [8–11]. Camden et al. [6] in their systematic review prior to COVID-19 found that TR was used for children but more as a blended approach mainly by psychologists for coaching the families and addressing behavioral issues. Some studies reported on TR for musculoskeletal disorders [12, 13], but very seldom for neurological conditions particularly for children with disabilities [14].

This sudden need for transition from in-person pediatric rehabilitation services to

Received • Примљено: July 22, 2022
Revised • Ревизија: October 14, 2022
Accepted • Прихваћено: October 16, 2022
Online first: November 1, 2022

Correspondence to:
Dragana ĐURIĆ
Fatima College of Health Sciences
Abu Dhabi, UAE
dragana.djuric11@gmail.com
dragana.djuric@fchs.ac.ae

remote therapy became very challenging for organizations and MDT members. There were growing concerns about preparedness of centers and MDT members working in pediatric rehabilitation centers. Given the lack of studies in this area, this research was undertaken with an intention of exploring the provision of rehabilitation services for children with disabilities during COVID-19 in the UAE. The goals of the study were to determine the following: 1) what approaches were taken by managers and MDT members to continue pediatric rehabilitation services within the UAE during COVID-19; 2) what support has been received by the organizations in terms of funding, resources, and training since pandemic in the UAE; are these resources sustainable if the pandemic continues; 3) what barriers were faced by the MDT in continuing services during the pandemic; 4) what the plans for utilization of these approaches post-pandemic are.

To accomplish these goals, a survey method was employed with subsequent descriptive analysis that included quantitative and qualitative analysis of the data.

METHODS

The study was conducted as collaborative research between an academic institution and rehabilitation center in the early stages of pandemic during the lockdown period in the UAE. During the lockdown period, only essential services were open, and the rest of the services were offered online and remotely to all residents. The survey was developed by the research team in May–June 2020 based on the concepts of remote therapy and considering the lockdown situation during the COVID-19 pandemic. Ethical approval for the study was obtained from the Fatima College of Health Sciences (INTSTF013PHY20) by September 2020. This study employed survey methods using an online survey tool, which was sent to pediatric rehabilitation centers in the UAE that provided short- and long-term care. The survey was open for a total of six weeks from September to November 2020 to acquire the maximum response.

The survey questions were in English and were validated using a two-step process – face validity and pilot study. The survey questions were sent to eight professionals who had experience in pediatric rehabilitation and research. Once the expert feedback was received, the survey questions were revised, and a pilot study was conducted with two managers and 10 MDT members. The final version of the survey was then updated. The survey had questions that were both open and with choices. Those hospitals providing emergency pediatrics care were excluded from the study. Two different surveys were sent through the Abu Dhabi Statistical Center in September 2020, one for the managers and another one for the therapists were opened for three weeks to get maximum responses. All those professionals (special educators and allied health professionals) working in rehabilitation centers for children with disabilities were included in the study.

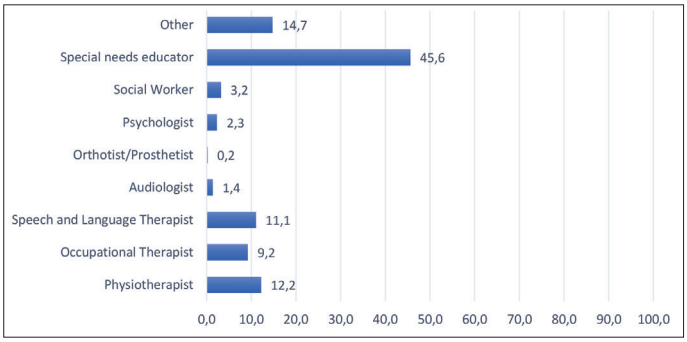


Figure 1. Disciplinary background of a multidisciplinary team, in %

The survey for managers contained questions related to demographic data, if their organization was operational fully or partially, if the support provided for service users, employees will continue services during the pandemic, and if there was a post-pandemic plan for utilizing these modes. The questionnaire for MDT members included demographic data, type of approaches utilized during the pandemic to provide therapy or education, the challenges and barriers they faced in using the new means.

The survey was analyzed using descriptive statistics. Numbers and percentages were used to present the data. Since the participants were allowed to choose more than one option, the percentages in most questions went beyond 100.

RESULTS

The responses were received by all seven emirates of the UAE from 44 therapy managers and 434 MDT members. Of the 44 managers (12 males and 32 females) responded to our survey, eight were managing over 50 members of staff, 20 were managing 20–50 members of staff, and 16 were managing up to 20 members of staff.

A total of 434 MDT members (122 male and 312 female) responded to our survey, of which 382 were working full time. The healthcare professionals completing the survey were special educators (197), nurses and doctors (64), physiotherapists (54), speech and language therapists (48), occupational therapists (40), social workers (14), psychologists (10), audiologist (6), orthotists (1) (Figure 1). Responses were received from a variety of centers, including governmental (58.5%), semi-governmental (15.5%), private (15%), non-profitable and charitable institutions (11%) providing one or more of the following services for disabled children – school-based rehabilitation centers; long-term outpatient departments; acute rehabilitation centers; home care services; long-term in-patient services.

The responses from the managers showed that about 50% of the centers were fully open during the pandemic, about 30% were opened partially, and 20% were closed. The accessibility of services for children with disabilities during the pandemic was reported to be very high (77%). During the pandemic, the managers reported major organizational adaptations, such as reorganization of their team, crisis management, organizing staff training,

reallocation and planning of the new budget. Regarding the cost for running the services, almost half of the managers (46%) reported them to be costlier than normal, 32% reported less than normal, and 22% reported a similar cost.

TR for pediatrics during COVID-19 as reported by MDT members

Most of the institutions used multimodal approach during the COVID-19 pandemic. TR (86.2%), followed by phone consultations (41.5%), institution-based therapy (6%), no therapy provided (4.8%), mobile clinic (3%), home visits (3%), were mainly utilized for providing therapy for children during the pandemic (Figure 2). Only 22% of the participants (95) reported to have used TR before the pandemic for pediatric services. During the pandemic, MDT members reported to have utilized TR in mild (90%), moderate cases (63%), and severe disabilities (13%). It was also reported to have been used in patients with multiple disabilities (11%).

Two main methods of TR were pre-recorded video clips (88%), and live video-calls synchronized with the sessions (86%), found to be utilized either on their own or in combination (Table 1). About 77% of the participants reported using videos from YouTube for therapy sessions; 65% of them reported to have additionally created their own videos. The videos created during the pandemic were filmed by participants themselves and/or by their peers (72%). Only 12% of them managed to obtain professional videographer services. The quality check before releasing the videos were reported by only 28% but it was not clear how this was done. Other platforms such as Physio Tool or Rehab My Patient were reported to have been utilized by a small percentage of participants (13%).

Several barriers in providing continued care through TR for the clients during the pandemic were mentioned in the survey. The participants felt that the parents appeared to be busy at work or engaged in other tasks (75.1%), had network issues or technical difficulties of using online programs (61.5%), reported parents' unresponsiveness and poor commitment (59.4%) and parents' anxiety about providing therapy (43%). The participants were asked to provide the positive and the negative effects of working remotely during the pandemic using TR. The positives were flexible hours (67.3%) and better family and personal time (32.7%). Some of the negative aspects were as follows: therapy sessions consumed longer hours than usual (67.5%), anxiety (44.9%), lack of teamwork (44.2%), increased tiredness (38.2%), lack of personal time (34.1), lack of sleep (22.8), and lack of working efficiency (18%).

The participants expressed the importance of continued TR at home during the pandemic (88%). They were concerned about the consequences of discontinuing therapy and its impact on impairments, function, and the quality of life (58%). Hotline numbers to reach different members of MDT were arranged by the centers (37%). The therapists scheduled online sessions well in advance with the parents (78%), centers provided electronic devices for home use (43%), educated parents on how to use video-calling application (59%), provided therapeutic equipment for home use (42%), encouraged parents to maintain therapy logs (35%), and ensured the supervision of parents during TR sessions (74%).

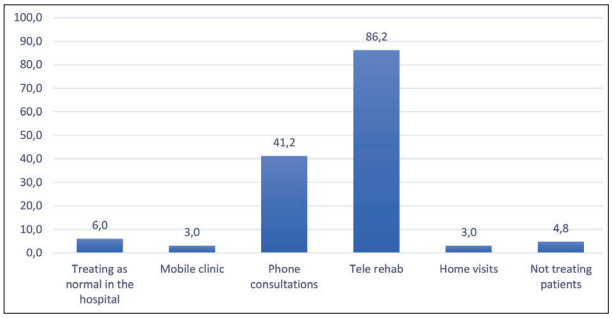


Figure 2. Type of approach provided by a multidisciplinary team, in %

Table 1. Telerehabilitation methods during the COVID-19 pandemic

Methods	% of therapists utilizing the method
Pre-recorded video clips	88
Live video call synchronized with the sessions	86
Created own videos	65

Utilization of TR post pandemic

Both managers (75%) and MDT members (69%) felt that the utilization of TR post-pandemic would be minimal and would only be used in exceptional circumstances once the services return to normal post pandemic. It was also acknowledged by both sets of participants (68.7%) that TR would be an additional method of providing therapy only in exceptional circumstances.

Both managers and MDT members (70%) reported that the response of children to TR was good to excellent.

With the ongoing pandemic situation, the managers reported to have been budgeting for both short- and medium-term plans for continuing services and investing in TR (81.1%), opening new ways through artificial intelligence (54.5%), plans for home visits (34.1) and mobile clinics (25%).

The managers felt that during the pandemic it was crucial to provide backing to the therapists and clients in terms of psychological support, managing infection control, reassurance and financial support. They further felt that there should be far more financial support from the government for research and subsidies for healthcare. The insurance companies did not recognize and pay for the TR services for those clients that depended on the insurance for the payments, and this could be one of the reasons for the decline in patient numbers.

Similarly, the therapists identified the areas in which investments must be caried out if TR was to continue during the pandemic and the main requirements were investing in servers (72.8%) and developing mobile applications (67.1%), building websites (62.7%) with an opportunity share common resources between the centers (70.5), printing educational leaflets (44.5%) and producing marketing

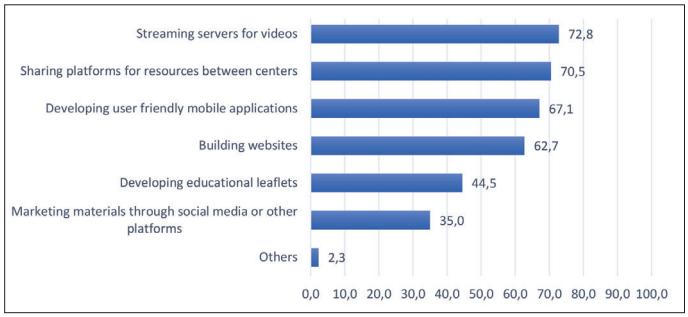


Figure 3. Investment for future telerehabilitation by a multidisciplinary team

material through social media and other platforms (35%) (Figure 3).

DISCUSSION

The primary aim of this research was to assess the provision of rehabilitation services with associated opportunities and challenges for children with disabilities in the UAE. Abu Dhabi and Dubai have multiple centers that provide pediatric rehabilitation, which is in contrast to the other emirates; hence, the response rate was higher in the former. Most rehabilitation centers in the UAE are large and public, providing school-based rehabilitation services that employ many special educators; hence, the responses from special educators were higher when compared to healthcare professionals.

It was important to attain the perspectives of the special educators as they were posed with unique challenges during the COVID-19 pandemic. The preparedness of these educators was of great importance for the continuation of education for autistic, visually, and hearing-impaired students [15]. It was required of them to be as innovative and creative as possible to rapidly respond to the needs of the family and child [16].

Our findings showed that most centers were functioning during the COVID-19 pandemic and the accessibility of rehabilitation services was very high. The centers were aware of the negative impact of discontinuing the services and the best alternative method had to be considered. Our study showed that TR was utilized during the lockdown of the COVID-19 pandemic.

Telemedicine or telehealth is not a new concept, but the popularity grew during the pandemic for most aspects of healthcare delivery. Its use in pediatric rehabilitation had been very limited prior to the pandemic. Our results show that only 22% of participants had used TR prior to the COVID-19 pandemic, but it is not clear for what type of services it was used. Previous research showed that psychologists utilized the approach for coaching, in order to improve parents' approach and children's behavior [6]. This could not be confirmed from our study due to the number of responses received from psychologists.

With regard to the modes of TR, our study showed both synchronized video-sessions and pre-recorded videos were equally utilized. It was found that the participants spent long hours in searching for suitable videos on social platforms but due to the limited resources they reported to have created videos. Invested time and resources in creating these videos demand a suitable platform for sharing these resources for wider use. This calls for creating more sharing space and the need for policies to protect intellectual property.

The sudden shift from in-person service to TR posed challenges for MDT members, parents, and organizations. The lack of prior experience in using TR by physiotherapist and occupational therapists working on motor skills is also reported by Kaur et al. [11]. The limited use of TR in pediatrics to improve motor skills was found by Camden et al. [6], who reported that it had effect on only a few outcomes. TR in our study was mainly used for mild to moderate cases of disability. This could be because it was employed only by those requiring simple hands-on therapies that could be safely applied by parents, as opposed to those with moderate and severe cases of disability [9].

Although TR sessions were scheduled well in advance with the parents, they found it difficult to manage their daily schedule during the lockdown. This could be because most families in the UAE live in extended families, usually with three or more children, and during the lockdown, they had to give attention to other members of the family working or studying at home. Parents who would normally accompany the child to the rehabilitation center got much busier during the lockdown as most of them also had to support online learning of their other children. Parental distraction and non-engagement were also reported in other studies and with the ongoing situation regarding the COVID-19 pandemic, it is suggested to consider individual family circumstances prior to arranging TR sessions, which could lead to better collaboration between the MDT and parents [1]. Pellicano and Stears [17] highlighted similar issues faced by families of disabled children and increased vulnerability during the COVID-19 pandemic.

The effectiveness of TR depended on the availability of equipment and technical support to run the sessions. Although our study indicated that some centers provided the needed devices to the families, other technical issues were reported, such as an unstable internet connection and difficulties in using online programs and equipment. Considering that the UAE is a high-income country with a developed infrastructure, it was easier to overcome the barriers by improving internet connections, developing user-friendly apps, and employing other telehealth solutions [18]. The importance of digital literacy is emphasized in Scott Kruse et al. [19]. Similar barriers to an effective implementation were identified in other studies done within the Gulf region [9, 20]. This could be easier for people living in urban areas and for high-income families, but might always be a challenge for families with low income and in rural areas [4, 21].

Although our study indicates that the post-pandemic use of TR for pediatric patients is minimal, we believe that there can be a continued employment of TR, used only in exceptional circumstances – due to the fact that there are several advantages of using it in situations such as when

the child is unable to physically be present at the center, for short consultations, for clarification of any doubts, and infection control. Concurring with Albahrouh and Buabbas [9] and Kaur et al. [11], we too suggest investing, drawing policies and practice guidelines to facilitate the effective use of TR for its ongoing use.

Maintaining child interest during the TR sessions is challenging. Engagement during TR is much lower compared to face-to-face sessions due to attention deficit, screen fatigue, inadequate supervision from parents and the presence of other siblings [11, 14]. The authors suggest using interactive play-based therapy, creating virtual community and support groups for parents.

Fear and anxiety of parents therapeutically handling the child was reported by the therapists in our study. Parents who were not previously involved in handling some of the motor impairments had to engage, and this could pose issues related to parents' confidence and low satisfaction in therapeutically handling the child [22]. With the uncertainty based around COVID-19, it was difficult to determine the timeline to return to therapy centers. Parental burnout during the COVID-19 pandemic is discussed by Griffith [21], who highlighted child abuse or neglect. High caregiver engagement is emphasized by Hall et al. [23].

The COVID-19 pandemic has accelerated the implementation of TR in clinical care, and it is becoming a new norm in clinical practice both during and beyond the pandemic [24]. Concurring with previous research, we too believe that TR as an important alternate method that provides novel opportunities due to its cost-effectiveness, remote accessibility, time saving, flexible scheduling for families, and the ability to overcome geographical barriers [14, 25, 26]. We further believe that it is a means of empowering parents and a way of being actively involved in decision making [27, 28]. We acknowledge the need for technological support, standardization of teleassessment, TR delivery guidelines, and effective strategies to increase motivation and enhance cooperation of child and parents [11, 23]. The post-pandemic use of TR is, according to our study, still questionable – whether it would be used in situations in which the child is unable to attend therapy in person at the center. There is a need for planning, budgeting, investing, and creating supportive environments for parents, children, and MDT members to effectively apply TR services for pediatric rehabilitation.

One of the bigger strengths of our study is that it included managers and diverse MDT members covering all the major pediatric rehabilitation centers from the seven emirates of the UAE. The collective perspectives as presented in our study could serve to draw guidelines for the provision of remote pediatric rehabilitation within and beyond the UAE.

There are several limitations of this study. The data for the study were collected during the early phases of the COVID-19 pandemic, at the time when alternative services, such as TR, were just being considered, with no clear policies and procedures. As it has been over two years since the beginning of the pandemic, there is a need for a follow-up study to examine how well TR has been engaged with throughout the lockdown period and if policies or practices for its ongoing use have been developed. Another limitation of our survey was the opportunity to choose more than one option – we had some mixed or missed responses and this could be due to misinterpretation of the questions or to not paying attention to all the options. This could have been overcome by an in-depth interview and future research should consider the option. Our study had disproportional representation of MDT members and we might have missed the opportunities to obtain the balanced view from all professionals involved in providing services.

CONCLUSION

The main goal of our study was to explore the methods utilized for providing services by pediatric rehabilitation centers during the COVID-19 pandemic. TR was the most common method that enabled the continuation of the services followed by phone consultations. However, commitment and engagement of parents, technical issues, and fear/anxiety of parents were some of the challenges of using TR. Future research can focus on understanding the journey of TR throughout the COVID-19 pandemic, which could assist in developing best practice guidelines for pediatric rehabilitation.

ACKNOWLEDGMENTS

The authors would like to extend their gratitude to the Abu Dhabi Statistics Center for assisting in data collection and to Mr. Hisham Elmahi for his contribution in developing the survey.

Conflict of interest: None declared.

REFERENCES

1. Cacioppo M, Bouvier S, Bailly R, Houx L, Lempereur M, Mensah-Gourmel J, et al; ECHO Group. Emerging health challenges for children with physical disabilities and their parents during the COVID-19 pandemic: The ECHO French survey. Ann Phys Rehabil Med. 2021;64(3):101429. [DOI: 10.1016/j.rehab.2020.08.001] [PMID: 32818674]
2. Haynes C. Coronavirus: Disabled people 'forgotten' by government strategy, BBC. Accessed on July 2020. Retreived from https://
3. Mesa Vieira C, Franco OH, Gómez Restrepo C, Abel T. COVID-19: The forgotten priorities of the pandemic. Maturitas. 2020;136:38–41. [DOI: 10.1016/j.maturitas.2020.04.004] [PMID: 32386664]
4. Kuper H, Banks LM, Bright T, Davey C, Shakespeare T. Disability-inclusive COVID-19 response: What it is, why it is important and what we can learn from the United Kingdom's response. Wellcome Open Res. 2020;5:79. [DOI: 10.12688/wellcomeopenres.15833.1] [PMID: 32500099]

5. Jeste S, Hyde C, Distefano C, Halladay A, Ray S, Porath M, et al. Changes in access to educational and healthcare services for individuals with intellectual and developmental disabilities during COVID-19 restrictions. J Intellect Disabil Res. 2020 Sep 17. Online ahead of print. [DOI: 10.1111/jir.12776] [PMID: 32939917]
6. Camden C, Pratte G, Fallon F, Couture M, Berbari J, Tousignant M. Diversity of practices in telerehabilitation for children with disabilities and effective intervention characteristics: results from a systematic review. Disabil Rehabil. 2020;42(24):3424–36. [DOI: 10.1080/09638288.2019.1595750] [PMID: 30978110]
7. Longo E, de Campos AC, Schiariti V. COVID-19 Pandemic: Is This a Good Time for Implementation of Home Programs for Children's Rehabilitation in Low- and Middle-Income Countries? Phys Occup Ther Pediatr. 2020;40(4):361–4. [DOI: 10.1080/01942638.2020.1759947] [PMID: 32408834]
8. Kumar R, Osborne C, Rinaldi R, Smith JAD, Juengst SB, Barshikar S. Rehabilitation Providers' Experiences with Rapid Telerehabilitation Implementation During the COVID-19 Pandemic in the United States. J Phys Med Rehabil. 2021;3(2):51–60.
9. Albahrouh SI, Buabbas AJ. Physiotherapists' perceptions of and willingness to use telerehabilitation in Kuwait during the COVID-19 pandemic. BMC Med Inform Decis Mak. 2021;21(1):122. [DOI: 10.1186/s12911-021-01478-x] [PMID: 33832473]
10. Prvu Bettger J, Resnik LJ. Telerehabilitation in the Age of COVID-19: An Opportunity for Learning Health System Research. Phys Ther. 2020;100(11):1913–6. [DOI: 10.1093/ptj/pzaa151] [PMID: 32814976]
11. Kaur M, Eddy EZ, Tiwari D. Exploring Practice Patterns of Pediatric Telerehabilitation During COVID-19: A Survey Study. Telemed J E Health. 2022;28(10):1505–16. [DOI: 10.1089/tmj.2021.0506] [PMID: 35263191]
12. Cottrell MA, Galea OA, O'Leary SP, Hill AJ, Russell TG. Real-time telerehabilitation for the treatment of musculoskeletal conditions is effective and comparable to standard practice: a systematic review and meta-analysis. Clin Rehabil. 2017;31(5):625–38. [DOI: 10.1177/0269215516645148] [PMID: 27141087]
13. Grona SL, Bath B, Busch A, Rotter T, Trask C, Harrison E. Use of videoconferencing for physical therapy in people with musculoskeletal conditions: A systematic review. J Telemed Telecare. 2018;24(5):341–55. [DOI: 10.1177/1357633X17700781] [PMID: 28403669]
14. Krasovsky T, Silberg T, Barak S, Eisenstein E, Erez N, Feldman I, et al. Transition to Multidisciplinary Pediatric Telerehabilitation during the COVID-19 Pandemic: Strategy Development and Implementation. Int J Environ Res Public Health. 2021;18(4):1484. [DOI: 10.3390/ijerph18041484] [PMID: 33557395]
15. Yakut AD. Educators' experiences in special education institutions during the COVID-19 outbreak. J Res Spec Educ Needs. 2021;21(4):345–54. [DOI: 10.1111/1471-3802.12533] [PMID: 34539246]
16. Crane L, Adu F, Arocas F, Carli R, Eccles S, Harris S, et al. Vulnerable and Forgotten: The Impact of the COVID-19 Pandemic on Autism Special Schools in England. Front Educ. 2021;6:629203. [DOI: 10.3389/feduc.2021.629203]
17. Pellicano E, Stears M. The hidden inequalities of COVID-19. Autism. 2020;24(6):1309–10. [DOI: 10.1177/1362361320927590] [PMID: 32423232]
18. Blandford A, Wesson J, Amalberti R, AlHazme R, Allwihan R. Opportunities and challenges for telehealth within, and beyond, a pandemic. Lancet Glob Health. 2020;8(11):e1364–e1365. [DOI: 10.1016/S2214-109X(20)30362-4] [PMID: 32791119]
19. Scott Kruse C, Karem P, Shifflett K, Vegi L, Ravi K, Brooks M. Evaluating barriers to adopting telemedicine worldwide: A systematic review. J Telemed Telecare. 2018;24(1):4–12. [DOI: 10.1177/1357633X16674087] [PMID: 29320966]
20. Aloyuni S, Alharbi R, Kashoo F, Alqahtani M, Alanazi A, Alzhrani M, et al. Knowledge, Attitude, and Barriers to Telerehabilitation-Based Physical Therapy Practice in Saudi Arabia. Healthcare (Basel). 2020;8(4):460. [DOI: 10.3390/healthcare8040460] [PMID: 33158298]
21. Griffith AK. Parental Burnout and Child Maltreatment During the COVID-19 Pandemic. J Fam Violence. 2022;37(5):725–31. [DOI: 10.1007/s10896-020-00172-2] [PMID: 32836736]
22. Sutter EN, Francis LS, Francis SM, Lench DH, Nemanich ST, Krach LE, et al. Disrupted Access to Therapies and Impact on Well-Being During the COVID-19 Pandemic for Children With Motor Impairment and Their Caregivers. Am J Phys Med Rehabil. 2021;100(9):821–30. [DOI: 10.1097/PHM.0000000000001818] [PMID: 34091465]
23. Hall JB, Woods ML, Luechtefeld JT. Pediatric Physical Therapy Telehealth and COVID-19: Factors, Facilitators, and Barriers Influencing Effectiveness-a Survey Study. Pediatr Phys Ther. 2021;33(3):112–8. [DOI: 10.1097/PEP.0000000000000800] [PMID: 34086621]
24. Boronat S. Neurologic Care of COVID-19 in Children. Front Neurol. 2021;11:613832. [DOI: 10.3389/fneur.2020.613832] [PMID: 33679571]
25. Olson CA, McSwain SD, Curfman AL, Chuo J. The Current Pediatric Telehealth Landscape. Pediatrics. 2018;141(3):e20172334. [DOI: 10.1542/peds.2017-2334] [PMID: 29487164]
26. Irgens I, Rekand T, Arora M, Liu N, Marshall R, Biering-Sørensen F, et al. Telehealth for people with spinal cord injury: a narrative review. Spinal Cord. 2018;56(7):643–55. [DOI: 10.1038/s41393-017-0033-3] [PMID: 29515211]
27. Akhbari Ziegler S, Hadders-Algra M. Coaching approaches in early intervention and paediatric rehabilitation. Dev Med Child Neurol. 2020;62(5):569–74. [DOI: 10.1111/dmcn.14493] [PMID: 32065385]
28. Pinkerton LM, Murphy A, Bruckner E, Risser H. Therapy service delivery for children with disabilities during COVID-19: Parent perceptions and implementation recommendations. J Community Psychol. 2022:10.1002/jcop.22899. Epub ahead of print. [DOI: 10.1002/jcop.22899] [PMID: 35695353]

Педијатријска рехабилитација током ковида 19 у Уједињеним Арапским Емиратима

Драгана Ђурић[1], Сунита Багавати Мајсор[1], Адам Зеган[2], Арин Оде[3], Белал ел Кирим[4], Абдула ел Хумејдан[4], Мухамед ел Џара[1]

[1]Колеџ здравствених наука „Фатима", Абу Даби, УАЕ;
[2]Рехабилитациони центар „Фондација церебралне парализе", Аман, Јордан;
[3]Рехабилитациони центар „Звездани кључ здравља", Абу Даби, УАЕ;
[4]Рехабилитациони центар организације за особе са посебним потребама „Зајед", Абу Даби, УАЕ

САЖЕТАК

Увод/Циљ Пандемија вируса корона променила је организацију рехабилитације болесника у целом свету. Стандардни третман у рехабилитационим установама је замењен рехабилитацијом на даљину и представљао је изазов како за менаџере тако и за чланове мултидисциплинарног тима у педијатријској рехабилитацији.

Главни циљ овог рада је био да истражи како су организовани рехабилитациони сервиси деце са посебним потребама током пандемије ковида 19 у Уједињеним Арапским Емиратима.

Методе Истраживачки тим је креирао два упитника, један за менаџере и други за чланове мултидисциплинарног рехабилитационог тима. Оба упитника су валидирана и урађена је пилот студија. Финална верзија упитника је послата у септембру 2020. рехабилитационим установама. Четрдесет четири менаџера и 434 стручњака су попунили упитник.

Резултат Доступност дечје рехабилитације током ковида 19 је висока и представљена је са 77%. Скоро половина менаџера (46%) сматра да је организација рехабилитације финансијски захтевнија у односу на период пре пандемије. Телерехабилитација је најчешће коришћен приступ терапије; синхронизоване видео позиве је примењивало 86% испитаника, *YouTube* видео-снимке 88% испитаника и креирање сопствених видеа 65% испитаника.

Закључак Телерехабилитација је била најчешће коришћени метод рехабилитације током пандемије. Уколико би се убудуће користила телерехабилитација, потребно је планирање буџета, инвестирање у виртуално окружење које би било пријатно за децу, родитеље и чланове рехабилитационог тима. Испитаници сматрају да је повезивање дечјих установа и упознавање са едукативним материјалом, виртуалним платформама које би се користиле, као и упознавање са резултатима спроведених истраживања у области телерехабилитације педијатријске популације неопходан корак улагања уколико би се телерехабилитација наставила.

Кључне речи: ковид 19; педијатријска рехабилитација; телерехабилитација; пандемија

DOI: https://doi.org/10.2298/SARH220314104M
UDC: 616.31-053.2(497.16)

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The accuracy of Belgrade Age Formula method for dental age estimation in Montenegrin children aged 10–12 years

Jovan Marković[1], Nemanja Marinković[1], Ivan Arsić[1], Ksenija Zelić[2], Zorana Stamenković[1], Bojan Glamočanin[3], Nenad Nedeljković[1]

[1]University of Belgrade, School of Dental Medicine, Clinic for Orthodontics, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Institute of Anatomy, Laboratory for Anthropology, Belgrade, Serbia;
[3]University of Novi Sad, Faculty of Medicine, Department of Dental Medicine, Novi Sad, Serbia

SUMMARY

Introduction/Objective The aim of the study was to test the accuracy of Belgrade Age Formula (BAF) for dental age estimation on the sample of Montenegrin children.

Methods The radiographs of 134 Montenegrin children (67 females and 67 males) saved as "jpeg" files were analyzed with Image J software. Sex, the number of teeth with complete development, apex width and tooth length of the mandibular canine and second molar were used in order to calculate dental age with the BAF formula.

Results The discrepancy between estimated dental age and chronological age was -0.088 ± 0.64 years; the absolute difference was 0.52 ± 0.39 years. The percentage of participants whose estimated dental age differed six months from their chronological age was 61.2 and 53.7 for females and males, respectively, while the percentage of participants whose estimated dental age differed 12 months from their chronological age was 94 and 83.6 for females and males, respectively.

Conclusion The BAF may be an accurate approach for estimating dental age in Montenegrin children aged 10–12 years with uncompleted tooth development. However, BAF has to be evaluated on a larger sample of Montenegrin infants in future studies.

Keywords: dental age; age estimation; BAF; Montenegro

INTRODUCTION

Numerous external and internal factors affect individual growth and development [1]. These effects can be manifested differently on the maturation of children and their development. Assessing biological age is important for determining the degree of maturity of a child, which has already become a standard diagnostic procedure in many areas of medicine and dentistry [2]. In orthodontics, assessing the maturity of the patients can help clinicians to define the type of orthodontic treatment, appropriate time to begin and the prognosis of proposed orthodontic treatment [3]. Initiating orthodontic treatment at the right time leads to shortening the duration of treatment and makes it more efficient [3]. Moreover, this assessment could help clinicians to recognize the beginning of the pubertal growth spurt, a period of intense changes in growth that can be additionally helpful for the treatment of orofacial skeletal discrepancies [3]. Approximately, the start of the pubertal growth spurt is expected around 10 years for females and 12 years for males [4].

Estimating biological age can be a considerable process, in which valuable information is, in addition to medical sciences, provided by researchers of other scientific fields such as anthropology (examination of skeletal remains), criminology (identification of undocumented persons, for example in major accidents when it is difficult to identify the persons), forensic medicine, archeology, and others [5].

Over time, different ways of estimating biological age of children and adolescents have been developed. The biological age of a patient is most often based on the analysis of skeletal and dental changes observed on different types of X-rays. The European formula, developed by Cameriere et al. [6] in 2006, is currently one of the most used quantitative methods for dental age estimation. The European formula analyzes different linear parameters of permanent teeth with incomplete development on panoramic radiography of the patient [5, 6]. The accuracy of the European formula, compared with other methods for assessing dental age, in different population, has been confirmed in many studies [7].

Recently, a group of authors developed a new regression formula for assessing dental maturity. Belgrade Age Formula (BAF) is also a quantitative method that uses panoramic radiography for dental age analysis [8]. The parameters included in the BAF are the sex of the patient, the number of permanents teeth on the left side of the lower jaw with complete root development, the tooth length, and the apex width of the canine and the

Received • Примљено: March 14, 2022
Revised • Ревизија: October 11, 2022
Accepted • Прихваћено: October 12, 2022
Online first: October 19, 2022

Correspondence to:
Nemanja MARINKOVIĆ
Gastona Gravijea 2
11000 Belgrade, Serbia
nemanja.marinkovic@stomf.bg.ac.rs

second molar with incomplete apex closure [8]. By reducing the number of teeth whose length and apical width are measured, the process of determining dental age is accelerated and the procedure is facilitated, whereby equally accurate results could be obtained [8]. However, the accuracy of the BAF was tested only for Serbian and Italian populations [8].

The aim of the study was to examine the applicability of BAF on Montenegrin children in late mixed and early permanent dentition with incomplete teeth development.

METHODS

A sample of 160 panoramic radiographs of healthy Montenegrin children (80 females and 80 males) aged 10–12.99 years were collected to perform a cross-sectional retrospective study. Ethical principles for medical research involving human subjects defined by the Declaration of Helsinki were the main guide according to which we designed the study. Ethics Board of the University of Montenegro, Faculty of Medicine, approved this study (KCCG No. 03/01-13013/1).

The analyzed panoramic radiographs that were randomly taken from the medical histories of patients from the Clinical Center of Montenegro were recorded between 2018 and 2020 as part of a standard clinical or diagnostic procedure. Parents or guardians have signed an agreement informing them that any dental documentation, including panoramic radiography, may only be used for scientific or educational purposes without any possibility of revealing the child's identity. Since the population of Montenegro is composed of Croats, Bosniaks, Albanians, Serbs, and Montenegrins, selected panoramic radiographs were retrieved from medical histories of patients with Montenegrin heritage established by their name and surname.

Sex, date of birth, panoramic radiography record date, medical history, and a patient's identification number were documented by a researcher who did not assess the dental age. The inclusion criteria were as follows: healthy children without systemic or development disorders that could potentially have an impact on the growth and development of the craniofacial complex, with no previous orthodontic treatment and absence of any alveolar bone pathology. The exclusion criteria were poor quality of panoramic radiography, dental agenesis, hyperdontia and the presence of impacted or rotated mandibular teeth. Due to systemic disorders, dental agenesis, and a previous orthodontic treatment, 26 panoramic radiographs were excluded. Therefore, panoramic radiographs of 134 age-matched Montenegrin children (67 females and 67 males) were included in the final study group. All panoramic radiographs were recorded in a computer as "jpeg" files and Image J software (Public domain open-source software, National Institute of Mental Health Bethesda, Maryland, USA) was used for all required measurements. Date of record and date of birth were gathered in an Excel spreadsheet, chronological age was calculated and expressed in decimals with the "yearfrac" function.

The BAF regression formula was applied for dental age estimation [8]. Mandibular left permanent teeth, except the third molar, were evaluated on panoramic radiographs. Sex, the number of teeth with completed development, apex width (the area between the mesial and the distal inner side of the open apex), and tooth length of the canine and the second molar are parameters needed to calculate the BAF formula. The difference between dental age and chronological age was assessed; an overestimation or an underestimation depending on whether the result was positive or negative. After a four-week interval, 20 panoramic radiographs were reevaluated by the researchers to determine the intra- and inter-examiner reproducibility.

Statistics

The results are presented as count (%), means ± standard deviation or median (25th–75th percentile) depending on the data type and distribution. Intra- and inter-observer reliability of age estimation was verified one month after the first measurement on 20 randomly selected panoramic radiographs. All p values less than 0.05 were considered significant. All data were analyzed using the IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The study included 134 patients, both sexes. The chronologically youngest patient was 10.07 years old, and the oldest one was 12.99 years old. The mean difference between estimated dental age with the BAF method and chronological age was -0.088 ± 0.64 years; while absolute deference was 0.52 ± 0.39 years. Table 1 shows that the average values are very similar, respectively the relative and absolute differences are approximate, which indicates the accuracy of the BAF method.

Intra- ($r = 0.98$, $p < 0.001$) and inter-observer ($r = 0.84$, $p < 0.001$) reliability of age estimation shows that the person and the time of measurement had no influence on the measurement values.

Linear, logical regression indicated that chronological age was found as an independent predictor for the BAF

Table 1. The mean chronological age (CA), estimated age (based on Belgrade Age Formula – BAF) and residuals (mean differences between them, i.e., BAF - CA) in the Montenegro population

CA/Sex	n	CA mean ± SD	BAF mean ± SD	BAF - CA mean ± SD	Absolute value BAF - CA mean ± SD
female					
10–10.99	21	10.45 ± 0.26	10.29 ± 0.51	0.16 ± 0.54	0.43 ± 0.35
11–11.99	26	11.53 ± 0.29	11.43 ± 0.63	0.10 ± 0.51	0.43 ± 0.29
12–12.99	20	12.53 ± 0.29	12.28 ± 0.64	0.05 ± 0.65	0.54 ± 0.34
male					
10–10.99	21	10.43 ± 0.25	10.51 ± 0.6	-0.08 ± 0.66	0.54 ± 0.37
11–11.99	26	11.55 ± 0.28	11.46 ± 0.54	0.08 ± 0.36	0.30 ± 0.22
12–12.99	20	12.53 ± 0.29	12.31 ± 1.13	0.22 ± 1.06	0.97 ± 0.44

Table 2. Regression equation

Sample		B	95% CI B	95% CI B	Slope	95% CI for SLB	95% CI for SLB	Adjusted R2	R2	p
Total sample		0.53	-0.94	2	0.95	0.82	1.07	0.79	0.62	< 0.001
Sex	Male	1.34	-0.95	3.74	0.87	0.67	1.08	0.52	0.53	< 0.001
	Female	-0.34	-2.18	1.50	1.02	0.86	1.18	0.71	0.71	< 0.001

B – unstandardized coefficients B, intercept; CI – confidence interval; SLB – slope lower bound

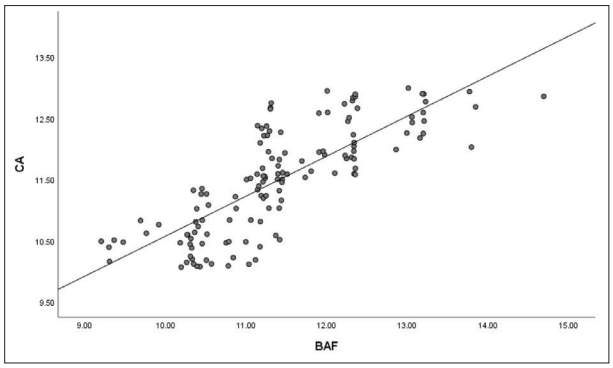


Figure 1. Plot of correlation between chronological and estimated age in total sample;
CA – chronological age; BAF – Belgrade Age Formula

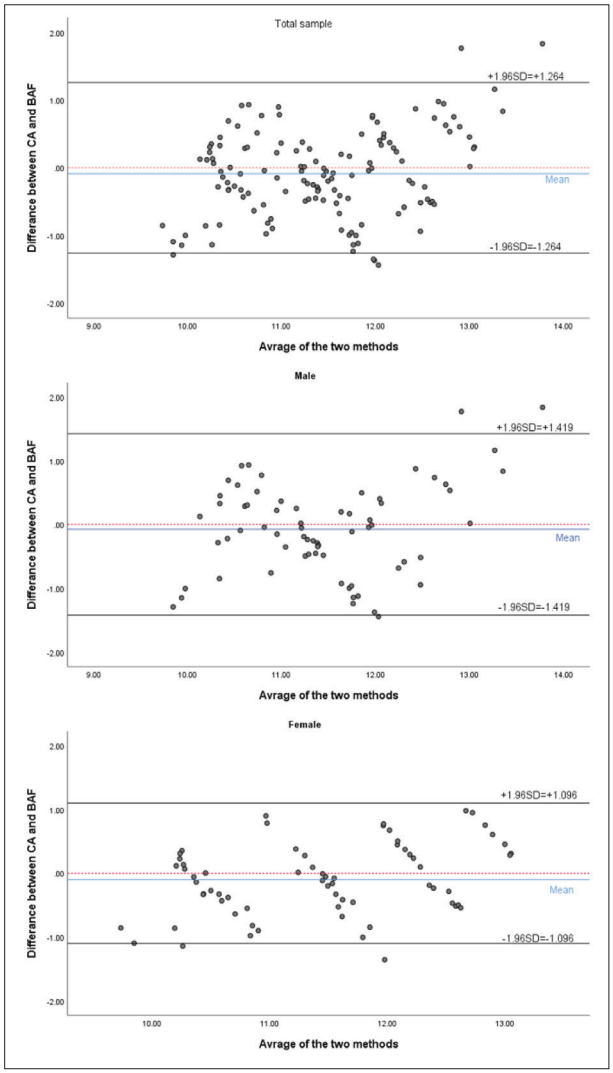


Figure 2. Bland–Altman plot;
CA – chronological age; BAF – Belgrade Age Formula

in a high percentage of the total sample (Table 2). It is noticeable that in the female sample the value of the intercept is slightly lower and that the value of the slope is slightly higher compared to the male population.

The percentage of participants whose estimated dental age differed ± 6 months compared to chronological age was 61.2 and 53.7 for females and males, respectively, while within ± 12 months it was 94 and 83.6 for females and males, respectively.

The correlation between the BAF and chronological age is positive, strong, and statistically significant ($r = 0.822$, $p < 0.001$) (Figure 1). There is better correlation in the male population ($r = 0.831$, $p < 0.001$) then in the female one ($r = 0.826$, $p < 0.001$). Figure 1 shows central groupings as they are diluted to higher values. The Bland–Altman method shows no systematic error, although there are some influential outliers (Figure 2).

DISCUSSION

Dental age estimation is a method that assesses an individual's age based on dental maturity [9]. It is an important aspect of the age estimation process, which also includes a physical examination, obtaining personal information, and skeletal maturity assessment [10]. The most used approaches for determining dental age are based on the sequence in which permanent teeth emerge and radiographic evaluation of the degree of the crown and roots' mineralization of permanent teeth [11, 12]. The variability of tooth development and emergence is influenced by gene mutations, generalized and/or localized insults [13, 14]. Understanding the fundamental patterns of growth and development in children, as well as identifying various environmental factors that might directly or indirectly interfere with the maturation process, can be aided by studying the dental maturity [9].

Researchers generally compare the dental maturity of a specific population to previously set standards based on the findings of studies of a certain population, such as French-Canadian children [15]. The use of standards that are not specific to the population of interest has a number of challenges, and their application can lead to incorrect conclusions concerning dental maturity [15].

Cameriere et al. [5] published in 2007 a research with a study sample that included participants from several countries, and the European formula was used for determining dental age. The authors analyzed over 2000 orthopantomographic radiographs of children aged 4–16 years from different European countries, including Croatia, Germany, Slovenia, Spain, Italy, Kosovo*, and the United Kingdom [5]. One of the findings of the study was that nationality had no impact on the age estimation process [5]. In

* Editorial note: this designation is without prejudice to positions on status, and is in line with UNSC 1244 and the ICJ Opinion on the Kosovo declaration of independence.

the years thereafter, a significant number of studies have validated the accuracy and reliability of this method for determining dental maturity [16–19]. A great number of researches have also modified the European formula and created their own population-specific formulas [8, 20–23].

In a study from 2018, the authors tested the European formula on 423 orthopantomographic radiographs of Serbian children (231 females and 191 males) aged 5–15 years and found that the formula is applicable to determine dental age in the Serbian population [19]. Zelic et al. [8] developed a simplified formula (BAF) for estimating dental age, which was tested on the Serbian and Italian populations. The BAF was found to be more accurate for dental age estimation in the Serbian population (particularly in females), although the accuracy of both the BAF and the European formula was nearly identical in the Italian group [8]. Therefore, we decided to test the BAF formula in Montenegrin children who are in the mixed dentition stage since it has been shown that BAF could be a reliable method for assessing the dental age in other populations as well as the Serbian population [8].

The findings of this study revealed that dental age calculated with the BAF formula underestimated the chronological age of Montenegrin children. This finding is consistent with an earlier research, in which the European formula or the BAF was employed to estimate dental age [8]. In almost every age category, the discrepancy between the predicted dental age and chronological age was less than six months, showing that the BAF could be a reliable tool for estimating age and dental maturity of Montenegrin children. Within six months, the difference between the estimated dental age and chronological age was assessed in 61.2% of female and in 53.7% of male Montenegrin children who participated in the study. Furthermore, in 94% and 83.6% of female and male Montenegrin children, respectively, estimated dental age differed from chronological age within 12 months. The BAF demonstrated greater accuracy in the Montenegrin population compared to the results of a previously conducted study in which dental and chronological age differed within six months in 46.3% and 44.7% of female and male Serbian children, respectively, and within 12 months in 76.3% and 74.7% of female and male Serbian children, respectively, aged 5–14 years [8]. These results can possibly be explained by the fact that the Montenegrin study sample was smaller and included fewer age categories than the Serbian study sample.

The difference between the estimated dental age and chronological age assessed in male participants aged 12–12.99 years was nearly one year (Table 1). When the BAF formula was tested on the Serbian population sample, similar findings were reported, according to which the highest disparities between the estimated dental age and chronological age were observed in male participants aged 12–12.99 years and 13–13.99 years [8]. In this age category the development of all permanent teeth, or at least the development of the second molar and the canine, the key predictors of dental maturity according to the BAF, could be completed, which might affect the final result significantly. Therefore, this finding could suggest that both the BAF method and the European formula should be applied in children with incomplete tooth development. Future research should compare the accuracy of other qualitative and quantitative methods for assessing dental maturity of a larger population of Montenegrin children, and determine which method provides the most accurate results and help develop a population-specific formula for dental age estimation process.

CONCLUSION

The BAF could be an accurate method for dental age estimation of Montenegrin children with incomplete tooth development; however, the additional research with large sample is needed to confirm this assumption.

Conflict of interest: None declared.

REFERENCES

1. Almotairy N, Pegelow M. Dental age comparison in patients born with unilateral cleft lip and palate to a control sample using Demirjian and Willems methods. Eur J Orthod. 2018;40(1):74–81. [DOI: 10.1093/ejo/cjx031] [PMID: 28472275]
2. Pan J, Shen C, Yang Z, Fan L, Wang M, Shen S, et al. A modified dental age assessment method for 5- to 16-year-old eastern Chinese children. Clin Oral Investig. 2021;25(6):3463–74. [DOI: 10.1007/s00784-020-03668-9] [PMID: 33420828]
3. Kirschneck C, Proff P. Age assessment in orthodontics and general dentistry. Quintessence Int. 2018;49(4):313–23. [DOI: 10.3290/j.qi.a39960] [PMID: 29532818]
4. Soliman A, De Sanctis V, Elalaily R, Bedair S. Advances in pubertal growth and factors influencing it: Can we increase pubertal growth? Indian J Endocrinol Metab. 2014;18(Suppl 1):S53–62. [DOI: 10.4103/2230-8210.145075] [PMID: 25538878]
5. Cameriere R., De Angelis D, Ferrante L, Scarpino F, Cingolani M. Age estimation in children by measurement of open apices in teeth: A European formula. Int J Leg Med. 2007;121(6):449–53. [DOI: 10.1007/s00414-007-0179-1] [PMID: 17549508]
6. Cameriere R, Ferrante L, Cingolani M. Age estimation in children by measurement of open apices in teeth. Int J Leg Med. 2006;120(1):49–52. [DOI: 10.1007/s00414-005-0047-9] [PMID: 16283352]
7. Hostiuc S, Diaconescu I, Rusu MC, Negoi I. Age Estimation Using the Cameriere Methods of Open Apices: A Meta-Analysis. Healthcare (Basel). 2021;9(2):237. [DOI: 10.3390/healthcare9020237] [PMID: 33672206]
8. Zelic K, Marinkovic N, Milovanovic P, Cameriere R, Djuric M, Nedeljkovic N. Age estimation in children based on open apices measurement in the Serbian population: Belgrade Age Formula (BAF). Ann Hum Biol. 2020;47(3):229–36. [DOI: 10.1080/03014460.2020.1764621] [PMID: 32460570]
9. Liversidge HM. The assessment and interpretation of Demirjian, Goldstein and Tanner's dental maturity. Ann Hum Biol. 2012;39(5):412–31. [DOI: 10.3109/03014460.2012.716080] [PMID: 23035647]
10. Smith DEM, Humphrey LT, Cardoso HFV. Age estimation of immature human skeletal remains from mandibular and cranial bone dimensions in the postnatal period. Forensic Sci Int. 2021;327:110943. [DOI: 10.1016/j.forsciint.2021.110943] [PMID: 34455396]

11. Koç A, Özlek E, Öner Talmaç AG. Accuracy of the London atlas, Willems, and Nolla methods for dental age estimation: a cross-sectional study on Eastern Turkish children. Clin Oral Investig. 2021;25(8):4833–40. [DOI: 10.1007/s00784-021-03788-w] [PMID: 33459890]
12. Gelbrich B, Carl C, Gelbrich G. Comparison of three methods to estimate dental age in children. Clin Oral Investig. 2020;24(7):2469–75. [DOI: 10.1007/s00784-019-03109-2] [PMID: 31728732]
13. Marković E, Vuković A, Perić T, Kuzmanović-Pfićer J, Petrović B. Prevalence of developmental dental anomalies in Serbian orthodontic patients. Srp Arh Celok Lek. 2020;148(1–2):17–23. [DOI: 10.2298/SARH190701096]
14. Galovic J, Vukojevic T, Nikolic Ivosevic J, Perin M, Vicko K, Demko Rihter I, et al. Tooth Loss and Survival Analysis after Traumatic Injuries in Primary Dentition. Balk J Dent Med. 2017;21(3):146–51. [DOI: 10.1515/bjdm-2017-0025]
15. Esan TA, Yengopal V, Schepartz LA. The Demirjian versus the Willems method for dental age estimation in different populations: A meta-analysis of published studies. PLoS One. 2017;12(11):e0186682. [DOI: 10.1371/journal.pone.0186682] [PMID: 29117240]
16. Mazzilli LEN, Melani RFH, Lascala CA, Palacio LAV, Cameriere R. Age estimation: Cameriere's open apices methodology accuracy on a southeast Brazilian sample. J Forensic Leg Med. 2018;58:164–8. [DOI: 10.1016/j.jflm.2018.06.006] [PMID: 30005336]
17. Rivera M, De Luca S, Aguilar L, Velandia Palacio LA, Galić I, Cameriere R. Measurement of open apices in tooth roots in Colombian children as a tool for human identification in asylum and criminal proceedings. J Forensic Leg Med. 2017;48:9–14. [DOI: 10.1016/j.jflm.2017.03.005] [PMID: 28399461]
18. De Luca S, De Giorgio S, Butti AC, Biagi R, Cingolani M, Cameriere R. Age estimation in children by measurement of open apices in tooth roots: Study of a Mexican sample. Forensic Sci Int. 2012;221(1–3):155.e1–7. [DOI: 10.1016/j.forsciint.2012.04.026] [PMID: 22595338]
19. Marinkovic N, Milovanovic P, Djuric M, Nedeljkovic N, Zelic K. Dental maturity assessment in Serbian population: A comparison of Cameriere's European formula and Willems' method. Forensic Sci Int. 2018;288:331.e1-331.e5. [DOI: 10.1016/j.forsciint.2018.04.019] [PMID: 29776802]
20. Angelakopoulos N, De Luca S, Palacio LAV, Coccia E, Ferrante L, Pinchi V, et al. Age estimation by measuring open apices in teeth: a new formula for two samples of South African black and white children. Int J Legal Med. 2019;133(5):1529–36. [DOI: 10.1007/s00414-019-02096-z] [PMID: 31197452]
21. Halilah T, Khdairi N, Jost-Brinkmann PG, Bartzela T. Age estimation in 5-16-year-old children by measurement of open apices: North German formula. Forensic Sci Int. 2018;293:103.e1-103.e8. [DOI: 10.1016/j.forsciint.2018.09.022] [PMID: 30414708]
22. Rai B, Kaur J, Cingolani M, Ferrante L, Cameriere R. Age estimation in children by measurement of open apices in teeth: an Indian formula. Int J Legal Med. 2010;124(3):237–41. [DOI: 10.1007/s00414-010-0427-7] [PMID: 20198380]
23. Manjrekar S, Deshpande S, Katge F, Jain R, Ghorpade T. Age Estimation in Children by the Measurement of Open Apices in Teeth: A Study in the Western Indian Population. Int J Dent. 2022;2022:9513501. [DOI: 10.1155/2022/9513501] [PMID: 35140790]

Тачност методе Београдске формуле старости за процену денталне старости црногорске деце узраста 10–12 година

Јован Марковић[1], Немања Маринковић[1], Иван Арсић[1], Ксенија Зелић[2], Зорана Стаменковић[1], Бојан Гламочанин[3], Ненад Недељковић[1]

[1]Универзитет у Београду, Стоматолошки факултет, Клиника за ортопедију вилица, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Институт за анатомију, Лабараторија за антропологију, Београд, Србија;
[3]Универзитет у Новом Саду, Медицински факултет, Клиника за стоматологију, Нови Сад, Србија

САЖЕТАК

Увод/Циљ Циљ истраживања био је да се испита тачност методе Београдске формуле старости (БФС) за процену денталне старости узорка деце из Црне Горе.

Методе Радиографски снимци 134 црногорске деце (67 девојчица и 67 дечака) сачувани су као *jpeg* фајлови и анализирани су софтвером *Image J*. За израчунавање денталне старости помоћу БФС коришћен је пол, број зуба са завршеним развојем, ширина врха корена и дужина мандибуларног очњака и другог молара.

Резултати Неслагање између процењене денталне и хронолошке старости је -0,088 ± 0,64 године; апсолутна разлика је била 0,52 ± 0,39 година. Проценат учесника чија се процењена дентална старост разликује шест месеци од њихове хронолошке старости био је 61,2 и 53,7 за девојчице и дечаке, док је проценат учесника чија се процењена дентална старост разликовала 12 месеци од њихове хронолошке старости био 94 и 83,6 за жене и мушкарце.

Закључак БФС може бити тачан метод за процену денталне старости код црногорске деце узраста 10–12 година са незавршеним развојем зуба. Међутим, БФС мора бити испитана на већем узорку деце из Црне Горе у будућим студијама.

Кључне речи: дентална старост; процена старости; БФС; Црна Гора

DOI: https://doi.org/10.2298/SARH220727098J
UDC: 572.54.087; 611.92

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Balance and thickness of soft tissue of the lower third of the face in different vertical patterns of growth

Predrag Janošević
University of Niš, Faculty of Medicine, Niš Clinic of Dental Medicine, Dental Department, Niš, Serbia

SUMMARY
Introduction/Objective Variations in thickness of soft tissues can influence the position of facial structures as well as facial aesthetics.
The objective of the study was to determine whether the frequency of soft tissues imbalance depends on the vertical growth pattern of the face.
Methods The present study consisted of 90 pretreatment lateral cephalograms of adult Serbian Caucasian orthodontic patients (30 male and 60 female), between 18–27 years of age, average 23.6 years. Only the patients with the skeletal class I, based on the values of A-Nasion-point B angle and Wits appraisal, were chosen for the study. All patients were divided into three groups of 30 patients, those with hyperdivergent, hypodivergent and normal vertical growth patterns based on the values of Frankfort mandibular plane angle. Soft tissue of each patient was evaluated following the method given by Merrifield.
Results The obtained results showed that soft tissues of the chin and upper lip were thickest in hypodivergent and thinnest in patients with hyperdivergent growth type. The largest number of patients with soft tissue imbalance was observed in the normal and hyperdivergent vertical growth pattern groups, eight out of 30 patients. The number of patients with imbalance greater than 3 mm was largest in the group with hyperdivergent growth pattern.
Conclusion The pathological skeletal pattern of growth combined with the common occurrence of soft tissue imbalance makes orthodontic treatment in hyperdivergent group of patients more difficult in comparison to patients with normal or hypodivergent growth pattern.
Keywords: soft tissue; face; imbalance

INTRODUCTION

Orthodontic therapy can affect the facial profile of a patient in both positive and negative ways. It is therefore important to devote special attention to the facial appearance of a patient within a diagnostic procedure and planning of orthodontic treatment. It is necessary to define what affects the profile. The pattern of facial skeletal growth, the position of the incisors but also soft tissues significantly contribute to the appearance of a patient profile. Variations in thickness of soft tissues can influence the position of facial structures as well as facial aesthetics [1].

Facial disharmonies that are not the results of skeletal or dental distortions are generally the result of poor soft tissue distribution [2].

Before starting to move teeth, an orthodontist needs to understand the consequences of these movements on profile aesthetics [3].

Charles Tweed was one of the first people to show interest in the facial proportion and harmony of a patient within the orthodontic treatment [3]. There are a lot of methods of profile aesthetics assessment in orthodontics, and some of them are based on Ricketts' E lines, Merrifield's Z lines or Steiner's S lines [4, 5, 6].

It seems that modern orthodontic literature does not pay enough attention to the importance of soft tissue analysis when it comes to establishing the diagnosis and making the therapy plan. The largest number of studies are concerned with tracking the changes in thickness of soft tissues which occur during the treatment [7, 8]. There are also studies which deal with the analysis of soft tissues in horizontal type of malocclusion [9, 10]. Krooks et al. [11] claim that sagittal dimensions of the face influence facial esthetics more than the vertical dimensions.

Just a small number of studies investigate the thickness of facial soft tissues in relation to the vertical facial growth pattern [12].

The knowledge of soft tissue characteristics of the lower part of the face in correlation to the vertical facial growth pattern would certainly contribute to a better understanding of the vertical types of malocclusions and help us to make easier decisions and treatment plans in these patients.

The aims of the conducted research were to establish the difference in thickness of the soft tissues of the lower third of the face in patients with the first skeletal class and different vertical growth patterns and to determine whether the frequency of soft tissues imbalance (STI) depends on the vertical growth pattern.

Received • Примљено: July 27, 2022
Revised • Ревизија: October 3, 2022
Accepted • Прихваћено: October 5, 2022
Online first: October 14, 2022

Correspondence to:
Predrag JANOŠEVIĆ
Bulevar Zorana Đinđića 81
18108 Niš
predragjanosevic82@gmail.com

METHODS

This cross-sectional retrospective clinical research was conducted on 90 lateral cephalograms of adult Caucasian orthodontic patients of the Clinic of Dentistry in Niš, Serbia (30 male and 60 female), between 18–27 years of age, average 23.6 years, obtained as part of a diagnostic procedure before the beginning of the orthodontic treatment.

All lateral cephalograms were taken by orthophos SL 3D (Densply, Sirona, Charlotte, NC, USA) under standardized conditions with the mandible in centric occlusion and without contraction of the facial soft tissues. All cephalograms were traced manually by the same investigator on acetate paper. The linear measurements were made with the help of a millimeter ruler. Corrected values of linear measurements were recorded to eliminate magnification error of 10%.

Signed information documents and the consent of patients to participate in the study were obtained. The study was approved by the Ethics Committee of the Clinic of Dentistry in Niš, No 14/8-2019-2 EO.

The criteria for the participation in the study were the following: patients should not have a history of orthodontic or prosthetic treatment; they should not be undergoing an orthodontic treatment; they should not have dentofacial deformity or a forced bite.

Only the patients with the skeletal class I, based on the values of Steiner A-Nasion-point B (ANB) angle ($1° \leq ANB \leq 3°$) and Wits appraisal (±1) were chosen for the study [13].

The radiographs without matching between ANB angle and Wits appraisal values were excluded from the study.

The patients who participated in the study were divided into three groups of 30 patients, 10 male and 20 female: those with hyperdivergent, hypodivergent and normal growth patterns based on the values of Frankfort mandibular plane angle (FMA) from Tweed-Merrifield analysis [6]. This angle is formed by the Frankfort plane (orbitale-porion) and the mandibular plane, constructed by the points of menton and gonion.

Patients with FMA angle 21° or less were considered to have hypodivergent growth patterns [3].

The ones with FMA angle values between 22–28° were considered to have normal growth patterns, while the patients with the angle wider than 28° were considered to have hyperdivergent growth patterns [3].

The analysis of sex differences was not conducted due to the uneven distribution between the sexes.

Each patient was evaluated following the method given by Merrifield [6] (Figure 1). The thickness of the upper lip was measured as the distance from the greatest curvature of the labial surface of the maxillary central incisors to the vermilion border of the upper lip. The chin thickness was measured as the distance between the skin pogonion and perpendicular projection of this point on the NB (Nasion-pt B) line.

All the measurements of the profile image were performed by the same examiner (orthodontist). The analysis of 20 profile images was repeated after two weeks in order to insure reliability. Intra-class correlation coefficients were performed to assess the reliability for the measurements. The values of coefficients of reliability were found to be greater than 0.90 for all the variables.

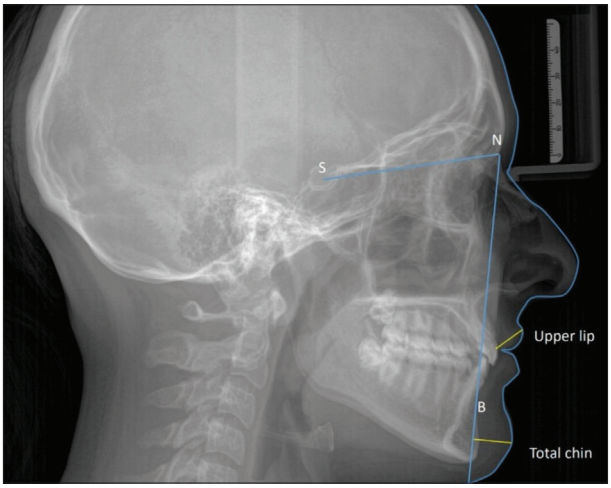


Figure 1. Facial soft tissue analysis given by Merrifield

It was considered that the patients with the same thickness of the chin and upper lip or patients whose chin thickness exceeded the thickness of the lips had a balanced soft tissue ratio.

On the other hand, the patients with the thickness of the upper lip greater than the chin thickness had soft tissue imbalance.

All patients with diagnosed STI were divided into those whose upper lip thickness exceeded chin soft tissue thickness by 3 mm or less and those whose imbalance was bigger than 3 mm. We considered that a soft tissue imbalance greater than 3 mm can lead to noticeable profile disorders even in those patients with a good skeletal growth pattern and a position of the frontal teeth.

Statistical data analysis was performed by the SPSS program (IBM Corp., Armonk, NY, USA). Continuous variables are given as means, SD (standard deviations) and (medians). Categorical variables are given as absolute numbers (N) and in percentages (%). Normality of the distribution of continuous variables was established by the Shapiro–Wilk test. The comparison of the examined parameters between the groups was performed by the Student's t-test of independent samples. Intra-class correlation coefficients were used to assess the reliability of the measurements.

RESULTS

Soft tissues of the chin and upper lip are thickest in hypodivergent growth pattern patients, thinner in normal vertical growth pattern, and certainly thinnest in patients with hyperdivergent growth type (Table 1).

Thickness of the chin soft tissue is statistically significantly higher in hypodivergent growth pattern group compared to the normal and hyperdivergent growth pattern group ($p < 0.001$).

Table 1. Values of total chin and upper lip thickness in regard to vertical pattern of facial growth

Parameters	Hypodivergent GP	Normal GP	Hyperdivergent GP
Chin	13.6 ± 2.0[ab]*** (13.5)	11.6 ± 2.0 (11.5)	10.7 ± 1.6 (11)
Upper lip	13.4 ± 2.4[a*b]*** (13)	12.0 ± 2.5 (12.2)	11.1 ± 1.7 (11)

Continues variables are given as means ± SD (medians); SD – standard deviation;
GP – growth pattern;
*p < 0.05;
*** p < 0.001 (Independent samples t-test);
[a] *vs*. normal;
[b] *vs*. high;

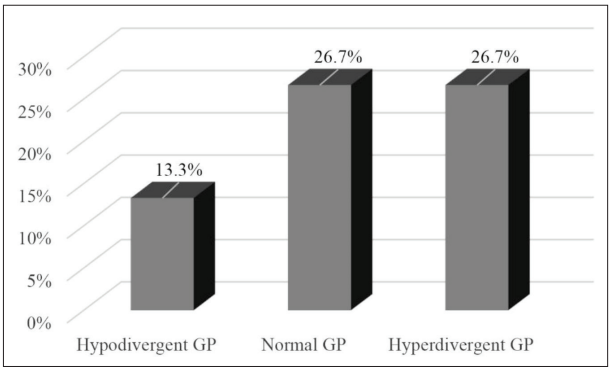


Figure 2. Percentage of patients with soft tissue imbalance in different vertical growth pattern groups

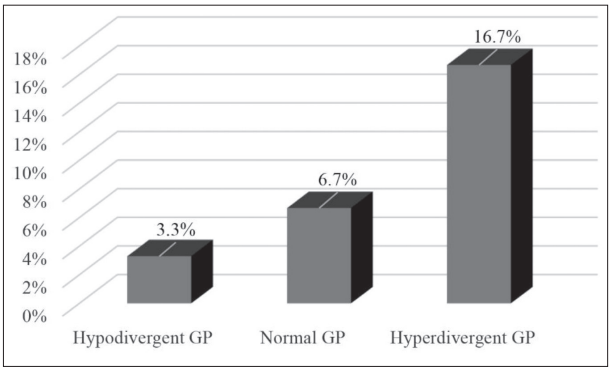


Figure 3. Percentage of patients with soft tissue imbalance bigger than 3 mm in different ver-tical growth pattern groups

The values of the upper lip thickness in hypodivergent group are statistically significantly higher compared to the normal growth pattern group ($p < 0.05$) and hyperdivergent growth pattern group ($p < 0.001$) (Table 1).

The largest number of patients with STI was observed in the normal and hyperdivergent vertical growth pattern groups, eight out of 30 patients, (26.7%), while the smallest number was observed in the hypodivergent growth pattern group, four out of 30, (13.3%) (Figure 2).

In the normal vertical growth pattern group, only two patients (6.7%) had soft tissue imbalance greater than 3 mm; in the hyperdivergent growth pattern group there were five patients (16.7%), while in hypodivergent growth pattern group there was only one patient (3.3%) (Figure 3).

Intra-class correlation coefficients were performed to assess the reliability for the measurements in the study. The values of coefficients of reliability were found to be greater than 0.90 for all the variables.

DISCUSSION

The analysis of soft tissues plays a significant role in orthodontic diagnosis and in achievement of good facial aesthetics [14]. Even though soft tissue is often overlooked in modern orthodontic practice, Holdaway [15] claims that the results of an orthodontic therapy are significantly better if soft tissue is taken into consideration during the process of establishing a diagnosis.

Considering that there are differences in the thickness of the facial soft tissues in patients with different sagittal malocclusions [10], the conducted research included just patients in skeletal class I based on the values of ANB angle. Wits analysis was used in order to overcome the limitations of ANB angle like recording a wrong value with altered antero-posterior or vertical position of nasion or in case of increased or decreased vertical height of the face [16].

Our research has shown that soft tissues of the chin are thickest in hypodivergent patients, slightly thinner in patients with the normal vertical growth pattern, and definitely thinnest in patients with hyperdivergent growth type. Such a result is expected having in mind that soft tissues are stretched due to the rotation of the mandible in clockwise direction in patients with hyperdivergent growth type.

Changes in the facial soft tissue thickness also occur with aging. The thickness of the soft tissues of the chin, increases for example [17]. Ferrario et al. [17] noted that the signs of facial aging appear even after the age of 30. It should be emphasized that the patients in our examined group were significantly younger than the mentioned age.

Our results coincide with the results of Ashraf et al. [14], Perović et al [18], Somaiah et al. [1], Al-Mashhadany at al. [19] as well as Celikoglu et al. [20]. In fact, Celikoglu et al. [20] claim that statistically significant difference in chin soft tissue thickness of patients with different vertical growth patterns exists only in females, not males. Female patients prevail in our study, which explains the coincidence of our and their results.

Our results do not coincide with those of Nanda and Ghosh [21] who came to the conclusion, while investigating southern Europeans, that the greatest thickness of soft tissues of the chin in the area of pogonion is present in people with hyperdivergent growth patterns. Vertical pattern implies that the chin is distally positioned. They further explain the results by the tendency of soft tissues to preserve normal profile by their thickness [21].

The conducted research has shown that the upper lip thickness correlates with the vertical growth pattern, too. Here, as a rule, its thickness is greatest in hypo, then normal and lowest in patients with the hyperdivergent growth pattern. These results also coincide with those of Ashraf et al. [14].

A balanced relationship of the upper lips and soft tissues of the chin has a direct impact on the beauty and harmony of the face [21]. Upper lip thickness should be equal or somewhat lower than the soft tissue thickness of the chin.

If there is the opposite situation, there is an imbalance of soft tissues which means that the upper incisors have to be moved distally in order to improve the profile aesthetics [22].

Our research has shown that the number of people with STI was largest in the groups with the normal and hyperdivergent vertical growth pattern. Still, the number of patients with STI greater than 3 mm was largest in the group with hyperdivergent growth pattern.

Pathological skeletal pattern of growth combined with severe soft tissue imbalance makes orthodontic treatment in hyperdivergent group of patients more difficult in comparison to the other vertical types of growth. Retraction of the upper incisors in these group of patients is often needed in order to obtain a more balanced facial profile because lip retraction follows tooth retraction.

There is no similar data with which we could compare ours in the reference literature. New research on this topic should be conducted on a larger sample in order to get more relevant data and compare it to the obtained results.

CONCLUSION

Soft tissues of the chin and the upper lip are thickest in patients with hypodivergent, and thinnest in patients with hyperdivergent growth pattern. The largest number of people with severe soft tissue imbalance is present in the hyperdivergent growth pattern group, which implies that special attention is required in treatment of these patients. Pathological skeletal pattern of growth combined with soft tissue imbalance means that it takes more efforts in order to achieve good facial aesthetics at the end of treatment.

Conflict of interest: None declared.

REFERENCES

1. Somaiah S, Khan MU, Muddaiah S, Shetty B, Reddy G, Siddegowda R. Comparison of soft tissue chin thickness in adult patients with various mandibular divergence patterns in Kodava population. Int J Orthod Rehabil. 2017;8(2):51–6. [DOI: 10.4103/ijor.ijor_38_16]
2. Burstone CJ. Lip posture and its significance in treatment planning. Am J Orthod. 1967;53(4):262–84. [DOI: 10.1016/0002-9416(67)90022-x] [PMID: 5227460]
3. Graber TM, Vanarsdall RL. Vig K. Orthodontics Current Princples and Techniques. 4th ed. St. Louis: Mosby Inc; 2007.
4. Pandey S, Kapoor S, Agarwal S, Shukla I. Evaluation of Lip Position in Esthetically Pleasing Profiles Using Different Reference Lines: A Photographic Study. J Indian Orthod Soc. 2021;55(3):261–9. [DOI: 10.1177/0301574220960307]
5. Otuyemi O, Afolabi D, Oyewole T. Ricketts' E-line profile preferences among Nigerian orthodontists, orthodontic trainees, and a young undergraduate students' population. Niger J Clin Pract. 2022;25(4):541–7. [DOI: 10.4103/njcp.njcp_1873_21]
6. Merrifield LL. The profile line as an aid in critically evaluating facial esthetics. Am J Orthod. 1966;52(11):804–22. [DOI: 10.1016/0002-9416(66)90250-8] [PMID: 5223046]
7. Milutinović J, Stamenković Z, Zelić K, Marinković N, Nedeljković N. Soft tissue profile changes during treatment of patients with class II malocclusion. Srp. Arch Celok Lek. 2022;150(5–6):261–6. [DOI: 10.2298/SARH210913048M]
8. Pavoni C, Gazzani F, Franchi L, Loberto S, Lione R, Cozza P. Soft tissue facial profile in Class III malocclusion: long-term post-pubertal effects produced by the Face Mask Protocol. Eur J Orthod. 2019;41(5):531–6. [DOI: 10.1093/ejo/cjz003] [PMID: 30865768]
9. Ajwa N, Alkhars FA, AlMubarak FH, Aldajani H, AlAli NM, Alhanabbi AH, et al. Correlation Between Sex and Facial Soft Tissue Characteristics Among Young Saudi Patients with Various Orthodontic Skeletal Malocclusions. Med Sci Monit. 2020;26:e919771. [DOI: 10.12659/MSM.919771] [PMID: 32101535]
10. Perović T, Blažej Z. Male and Female Characteristics of Facial Soft Tissue Thickness in Different Orthodontic Malocclusions Evaluated by Cephalometric Radiography. Med Sci Monit. 2018;24:3415–24. [DOI: 10.12659/MSM.907485] [PMID: 29791323]
11. Krooks L, Pirttiniemi P, Tolvanen M, Kanavakis G, Lähdesmäki R, Silvola AS. Association of facial sagittal and vertical characteristics with facial aesthetics in the Northern Finland Birth Cohort 1966. Eur J Orthod. 2019;41(3):279–85. [DOI: 10.1093/ejo/cjy062] [PMID: 30215708]
12. Patil HS, Golwalkar S, Chougule K, Kulkarni NR. Comparative Evaluation of Soft Tissue Chin Thickness in Adult Patients with Skeletal Class II Malocclusion with Various Vertical Growth Patterns: a Cephalometric Study. Folia Med (Plovdiv). 2021;63(1):74–80. [DOI: 10.3897/folmed.63.e52165] [PMID: 33650399]
13. McNamara JA Jr, Ellis E 3rd. Cephalometric analysis of untreated adults with ideal facial and occlusal relationships. Int J Adult Orthodon Orthognath Surg. 1988;3(4):221–31. [PMID: 3254378]
14. Ashraf K, Kulshrestha R, Azam A, Shabir S, Kaur H. Soft tissue analysis of chin, upper lip length and thickness in patients with different mandibular divergent patterns - A cephalometric study. IP Indian J Orthod Dentofacial Res. 2018;4(2):88–93. [DOI: 10.18231/2455-6785.2018.0018]
15. Holdaway RA. A soft-tissue cephalometric analysis and its use in orthodontic treatment planning. Part I. Am J Orthod. 1983;84(1):1–28. [DOI: 10.1016/0002-9416(83)90144-6] [PMID: 6575614]
16. Ghani S, Jabbar A. Correlation of ANB angle and wits appraisal in different malocclusion groups. J Pak Dent Assoc. 2013;22:130–3.
17. Ferrario VF, Sforza C, Serrao G, Ciusa V, Dellavia C. Growth and aging of facial soft tissues: A computerized three-dimensional mesh diagram analysis. Clin Anat 2003;16(5):420–33. [DOI: 10.1002/ca.10154]
18. Perović TM, Blažej M, Jovanović I. The influence of mandibular divergence on facial soft tissue thickness in class I patients: a cephalometric study. Folia Morphol (Warsz). 2022;81(2):472–80. [DOI: 10.5603/FM.a2021.0029] [PMID: 33778942]
19. Al-Mashhadany SM, Al-Chalabi HMH, Nahidh M. Evaluation of facial soft tissue thickness in normal adults with different vertical discrepancies. Int J Sci Res. 2017;6(2):938–42. [DOI: 10.21275/ART2017603]
20. Celikoglu M, Buyuk SK, Ekizer A, Sekerci AE, Sisman Y. Assessment of the soft tissue thickness at the lower anterior face in adult patients with different skeletal vertical patterns using cone-beam computed tomography. Angle Orthod. 2015;85(2):211–7. [DOI: 10.2319/040114-237.1] [PMID: 24998911]
21. Nanda RS, Ghosh J. Facial soft tissue harmony and growth in orthodontic treatment. Semin Orthod. 1995;1(2):67–81. [DOI: 10.1016/s1073-8746(95)80094-8] [PMID: 8935046]
22. Johnston L. Nothing personal, Newsletter of the Great Lakes. Association of Orthodontists. 1997;33:3.

Баланс и дебљина меких ткива доње трећине лице код различитих вертикалних образаца раста

Предраг Јаношевић

Универзитет у Нишу, Медицински факултет, Клиника за денталну медицину Ниш, Стоматолошки одсек, Ниш, Србија

САЖЕТАК

Увод/Циљ Варијације у дебљини меких ткива утичу на положај структура лица, као и на естетику лица.

Циљ спроведеног истраживања је био да се утврди разлика у учесталости појаве дисбаланса меких ткива лица у зависности од вертикалног обрасца раста лица.

Методе Спроведеним истраживањем је обухваћено 90 профилних снимака главе одрађених пре почетка ортодонтске терапије код одраслих пацијената беле расе, српске националности (30 мушког и 60 женског пола), узраста 18–27 година старости, просечно 23,6. Основни критеријум за укључивање у студију је било постојање I скелетне класе на основу вредности угла АНБ и на основу процене. Сви пацијенти су подељени у три групе од по 30 пацијената, оне са хипердивергентним, хиподивергентним и нормалним вертикалним обрасцем раста на основу вредности угла који заклапају франкфуртска хоризонтала и мандибуларна раван. Анализа меких ткива је спроведена на основу Мерифилдове анализе.

Резултати Добијени резултати су показали да су мека ткива браде и горње усне најдебља код пацијената са хиподивергентним, а најтања код пацијената са хипердивергентним обрасцем раста лица. Највећи број пацијената са дисбалансом меких ткива присутан је у групи са нормалним и хипердивергентним обрасцем раста, осам од 30. Број пацијената са дисбалансом меких ткива већим од 3 *mm* је највећи у групи са хипердивергентним обрасцем раста лица.

Закључак Патолошки образац раста комбинован са честом појавом дисбаланса меких ткива лица чини ортодонтску терапију пацијената са хипердивергентним обрасцем раста захтевнијом у односу на пацијенте са нормалним и хиподивергентним обрасцем раста.

Кључне речи: мека ткива; лице; дисбаланс

DOI: https://doi.org/10.2298/SARH220511102S
UDC: 616.314-007.26-77

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Changes during treatment of Class III malocclusion by Y appliance and appliance with screw according to Bertoni

Zorana Stamenković[1], Vanja Stojić[1], Nemanja Marinković[1], Ivan Arsić[1], Jovan Marković[1], Bojan Glamočanin[2]

[1]University of Belgrade, School of Dental Medicine, Department of Orthodontics, Belgrade, Serbia;
[2]University of Novi Sad, Faculty of Medicine, Department of Dentistry, Novi Sad, Serbia

SUMMARY

Introduction/Objective Class III malocclusion is caused by changes in skeletal and/or dentoalveolar structures with a typical mesial relationship of posterior teeth. The "Y" appliance and the appliance with screw according to Bertoni can be used in treating Class III malocclusion caused by maxillary retrognathism in the period of mixed dentition. The aim of the study was to determine and compare changes on skeletal and dentoalveolar structures in patients with Class III malocclusion treated with the Y appliance and the appliance with screw according to Bertoni.

Methods Forty patients with Class III malocclusion were included in this study. The sample was divided into two groups, with 20 patients in each group. The including criteria were maxillary retrognathism, the period of mixed dentition, and pubertal growth. The excluding criteria were mandibular prognathism, patients with genetical predisposition for skeletal Class III malocclusion, patients with cleft lip and palate or craniofacial syndrome, and the period of permanent dentition. The appliances which caused most changes on the maxilla were used in this study because all patients had a deficiency of maxillary growth. Anamnesis, clinical and functional testing, study casts analysis, analysis of orthopantomograms, lateral cephalograms, extraoral and intraoral photos were done for each patient. Therapeutic effects were analyzed on study casts and lateral cephalograms after this phase of orthodontic treatment.

Results The main dentoalveolar effect was protrusion of the upper incisors. Skeletal effects were not significant.

Conclusion The Y appliance and the appliance with screw according to Bertoni caused greater changes on dentoalveolar structures compared to skeletal changes.

Keywords: Class III malocclusion; Y appliance; Bertoni screw

INTRODUCTION

Class III malocclusion is an orthodontic problem in the sagittal direction with a mesial relationship of the posterior teeth. The cause of this malocclusion could be the changes in skeletal and/or dentialveolar structures [1]. The skeletal form of Class III malocclusion can be caused by maxillary retrognathism and underdeveloped maxilla, mandibular prognathism and overdeveloped mandible, and a combination of these two changes. Patients with skeletal Class III malocclusion caused by maxillary retrognathism have a typical concave profile and backward position of the maxilla and the upper lip [1]. The maxilla is underdeveloped in the sagittal and the transversal direction. Patients with cleft lip and palate and some syndromes (Apert, Crouzon) often have a mesial bite due to insufficient growth of the maxilla. The frequency of this malocclusion increases over time [2, 3]. The prevalence of skeletal mesial bite in deciduous dentition is 23%, in mixed dentition 30%, and in permanent dentition 34% [1].

The "Y" appliance is an active removable orthodontic appliance. This appliance has an acrylic plate cut in the shape of the letter "Y", with two screws in the area of the canines. the main effect of the appliance is protrusion of the upper incisors if a patient turns both screws at the same time. This appliance is useful in the treatment of patients with Class III malocclusion caused by maxillary retrognathism during mixed dentition [4].

The appliance with screw according to Bertoni is an active, mobile orthodontic appliance. This appliance has a special screw which acts in two directions – the sagittal and the transversal one. The appliance is useful in the treatment of patients with insufficient growth of the maxilla. The screw can consist of two or three guides. One screw causes a protrusion of the upper incisors, while the other one or two screws (depending on the design) cause transversal expansion of the upper dental arch. A patient turns the screws one after the other and not simultaneously [4].

The aim of this investigation was to determine and compare skeletal and dentoalveolar changes in patients with Class III malocclusion treated with the Y appliance and the appliance with screw according to Bertoni.

Received • Примљено: May 11, 2022
Revised • Ревизија: October 1, 2022
Accepted • Прихваћено: October 4, 2022
Online first: October 18, 2022

Correspondence to:
Zorana STAMENKOVIĆ
Nevesinjska 12/I/5
11000 Belgrade, Serbia
zorana.stamenkovic@stomf.bg.ac.rs

METHODS

In this retrospective study, 40 patients of the Department of Orthodontics, School of Dental Medicine, University of Belgrade, were included. The study was approved by the Ethics Committee, School of Dental Medicine, University of Belgrade, Serbia (No. 10/1). None of the patients had previous orthodontic treatment. This sample included patients with a decreased value of the ANB angle (less than 2°) caused by maxillary retrognathism (the SNA angle less than 82°).

The patients were divided into two following groups: group I – patients treated with the Y appliance (20 patients) (Figure 1), and group II – patients treated with the appliance with a screw according to Bertoni (20 patients) (Figure 2). The Y appliance and the appliance with a screw according to Bertoni were worn 16–18 hours during the day. In the Y appliance the screws were turned at the same time, while in the appliance with a screw according to Bertoni the screws were turned at different times. The appliance with a screw according to Bertoni was used in patients with a narrow upper arch and retrusion of the upper incisors, while the Y appliance was used in patients with retrusion of the upper incisors without deficient growth of the maxilla in the transversal direction. The active phase of treatment lasted 18 months.

These appliances can be used during the treatment of skeletal Class III malocclusion caused by maxillary retrognathism.

All the patients were in the period of mixed dentition, during the pubertal growth spurt period. The average chronological age in group I was nine years and two months, and in group II it was nine years and nine months. The dental age was determined according to Demirjian's method. The average dental age in group I was nine years and seven months, and in group II it was nine years and 11 months. The skeletal age was estimated by Baccetti method of cervical vertebral maturation [5]. In group I, three patients (15%) were in stage 1, 11 patients (55%) were in stage 2, and six patients (30%) in stage 3. In group II, four patients (20%) were in stage 1, 12 patients (60%) were in stage 2, and four patients (20%) in stage 3. The average duration of orthodontic treatment was 17 months in group I and 20 months in group II. Chronological, dental, and skeletal age, the duration of treatment, and sex distribution are shown in Table 1.

The inclusion criteria were maxillary retrognathism, the period of mixed dentition, positive overjet, mesial byte, and age in correlation with the best period for treatment for each appliance. The exclusion criteria were patients with cleft lip and palate or some craniofacial syndrome, mandibular prognathism, permanent dentition, late age for this kind of treatment or premature contact during the movement of the mandible from physiological rest to the central occlusion. No patients withdrew from the therapeutic procedure. Only patients with a complete treatment protocol were included in this study. Patients with a genetic predisposition to this malocclusion were not included.

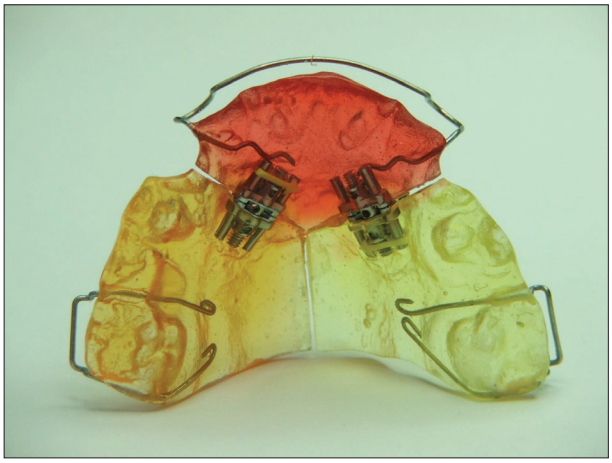


Figure 1. The "Y" appliance

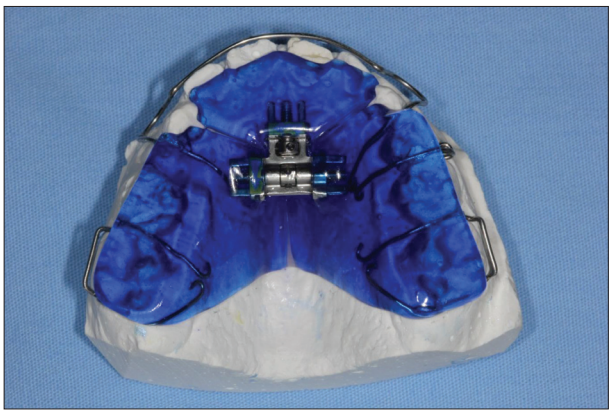


Figure 2. The appliance with a screw according to Bertoni

The diagnostic procedure had been done for each patient before the orthodontic treatment. The procedure included anamnesis, clinical and functional testing, study casts analysis, analysis of orthopantomograms, lateral cephalograms, and extraoral and intraoral photos. Lateral cephalograms and study casts were done after this phase of orthodontic treatment to assess therapeutic effects of each appliance used.

Cephalometric parameters

The following parameters were included and analyzed:
- angle SNA – sagittal position of the maxilla;
- angle SNB – sagittal position of the mandible;
- angle ANB – relationship between the maxilla and the mandible in the sagittal direction;

Table 1. Chronological, dental, and skeletal age, treatment time, and distribution by sex

Appliance	Chronological age	Dental age	Skeletal age	Treatment time	Sex	
					Male	Female
Y n = 20	9 years 2 months	9 years 7 months	Stage 1 (n = 3) Stage 2 (n = 11) Stage 3 (n = 6)	17 months	11	9
Bertoni n = 20	9 years 9 months	9 years 11 months	Stage 1 (n = 4) Stage 2 (n = 12) Stage 3 (n = 4)	20 months	13	7

Table 2. Parameters in the sagittal direction – changes during treatment with different appliances

Parameter	T1 x ± SD	T2 x ± SD	Δ (T2-T1) x ± SD	Significance[a] at T1	Significance[a] at T2	Significance[b/c]	Significance[d]	Significance[e]
SNA (°)								
Y app n = 20	76.6 ± 1.96	77.9 ± 1.86	1.3 ± 0.66			p = 0.000*	p < 0.001*	
Bertoni app n = 20	76.8 ± 1.83	77.85 ± 1.92	1.05 ± 1.84	0.660	0.939	p = 0.000*	p < 0.001*	
SNB (°)								
Y app n = 20	79 ± 1.92	79.45 ± 1.7	0.45 ± 1.85			p = 0.089	p = 0.004*	
Bertoni app n = 20	79.2 ± 2.12	79.5 ± 1.93	0.3 ± 2.06	0.159	0.204	p = 0.078	p = 0.307	
ANB (°)								
Y app n = 20	-2.4 ± 1.09	-1.55 ± 1.19	0.85 ± 0.99			p = 0.065	p = 0.000*	p = 0.007*
Bertoni app n = 20	-1.8 ± 1.95	-1.35 ± 1.64	0.45 1.92	0.450	0.033*	p = 0.123	p = 0.102	p = 0.012*

*statistically significant difference;
[a]monofactorial variance analysis;
[b]two-factor analysis of the variance, factor time;
[b/c]two-factor analysis of the variance, factor time-group;
[d]t-test;
[e]Wilcoxon matched-pairs test

– angle SpP/MP – vertical position of the maxilla;
– angle SN/SpP – vertical position of the mandible;
– angle SN/MP – relationship between the maxilla and the mandible in the vertical direction;
– sum of angles of Bjork's polygon – type of facial growth;
– relationship between the anterior and the posterior facial height – type of facial growth;
– distance Sna–A' – length of the maxillary corpus;
– distance Pg'–Go' – length of the mandibular corpus;
– distance Cd'–Go' – height of the mandibular ramus;
– angle I/SpP – inclination of the upper incisors;
– angle i/MP – inclination of the lower incisors.

Manual drawing and analysis of the lateral cephalogram was performed. Computer analysis was not done. The measurements were made by one impartial researcher. The researcher had no insight into which group of patients he was analyzing.

Statistical analysis

Statistical analysis included mean values, maximum and minimum values, and standard deviation, as a part of standard descriptive statistical analysis. Two-factor analysis of the variance with repeated measuring was used in relation to the factor time and factor time and group allocation. ANOVA, Wilcoxon matched pairs test and Student's t-test were used for determining the statistical significance of acquired differences. PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA) was used.

RESULTS

Parameters in sagittal direction

Both appliances caused increased values of the SNA angle. We used a two factor analysis of the variance with repeating measuring to determine effects of the two removable appliances on the sagittal position of the maxilla before and after orthodontic treatment. Statistically significant differences between these two periods were evaluated in both groups. The values of the SNB angle increased in both groups of patients. Statistically significant difference was determined only in the group of patients treated with the Y appliance. Increased value of the SNB angle is a direct consequence of the mandibular growth, which is very intense at this age. The ANB angle increased significantly in both groups. Student's t-test and Wilcoxon matched pairs test indicated significant differences in both groups (Table 2).

Parameters in vertical direction

Value of the SN/SpP angle increased in both groups of patients. When we compared the two groups of patients, only the Y appliance caused statistically significant changes of the SN/SpP angle during treatment. The SN/MP angle increased insignificantly in both the group treated with the Y appliance and the Bertoni's screw. When we compared groups after treatment, we evaluated significant changes. Both appliances caused an increase of the SpP/MP angle. Statistically significant differences existed in both groups when we compared values before and after treatment (Table 3).

Parameters of maxillary and mandibular development

With both appliances, the length of the maxilla increased significantly during treatment. Two-factor analysis of the variance with repeated measurements determined statistically significant differences in the pretreatment and post-treatment values of the length of the maxilla. The length of the mandible increased in both groups. Height of the mandibular ramus increased in both treated groups of

Table 3. Parameters in the vertical direction – changes during treatment with different appliances

Parameter	T1 x ± SD	T2 x ± SD	Δ (T2-T1) x ± SD	Significance[a] at T1	Significance[a] at T2	Significance[b/c]	Significance[d]
SN/SpP (°)							
Y app n = 20	11.75 ± 1.55	12.75 ± 1.48	1 ± 1.21			p = 0.228	p = 0.002*
Bertoni app n = 20	11.20 ± 2.14	11.6 ± 2.23	0.4 ± 2.02	0.005*	0.001*	p = 0.334	p = 0.136
SN/MP (°)							
Y app n = 20	36.85 ± 5.02	38.9 ± 4.34	2.05 ± 2.39			p = 0.245	p = 0.001*
Bertoni app n = 20	36.25 ± 4.83	37.85 ± 4.12	1.6 ± 2.23	0.587	0.769	p = 0.173	p = 0.003*
SpP/MP (°)							
Y app n = 20	25.05 ± 4.86	26.15 ± 4.26	1.1 ± 1.86			p = 0.999	p = 0.016*
Bertoni app n = 20	24.75 ± 4.18	25.55 ± 3.92	0.8 ± 3.23	0.891	0.549	p = 0.712	p = 0.012*

*statistically significant difference;
[a]monofactorial variance analysis;
[b]two-factor analysis of the variance, factor time;
[b/c]two-factor analysis of the variance, factor time-group;
[d]t-test

Table 4. Maxillary and mandibular development – changes during treatment with different appliances

Parameter	T1 x ± SD	T2 x ± SD	Δ (T2-T1) x ± SD	Significance[a] at T1	Significance[a] at T2	Significance[b/c]	Significance[d]
Cmax (mm)							
Y app n = 20	46.87 ± 2.04	48.35 ± 2.11	1.48 ± 0.75			p = 0.000*	p < 0.001*
Bertoni app n = 20	45.1 ± 2.17	46.2 ± 2.05	1 ± 1.93	0.471	0.690	p = 0.014*	p < 0.001*
Cmand (mm)							
Y app n = 20	73.55 ± 3.72	74.75 ± 3.48	1.2 ± 0.94			p = 0.941	p < 0.001*
Bertoni app n = 20	71.1 ± 3.43	72.2 ± 3.18	1.1 ± 2.67	0.742	0.970	p = 0.726	p = 0.114
Rmand (mm)							
Y app n = 20	54.15 ± 2.37	54.95 ± 2.23	0.8 ± 0.95			p = 0.771	p = 0.001*
Bertoni app n = 20	53.1 ± 2.25	53.85 ± 2.02	0.75 ± 2.11	0.092	0.075	p = 0.675	p = 0.043*

*statistically significant difference;
[a]monofactorial variance analysis;
[b]two-factor analysis of the variance, factor time;
[b/c]two-factor analysis of the variance, factor time-group;
[d]t-test

patients. Statistically significant differences determined by a comparison of both groups of patients were also evaluated (Table 4).

Parameters of facial growth

Sum of angles of Bjork's polygon increased in both groups of patients. There were no significant differences between groups during treatment. The relationship between the anterior and posterior facial height decreased in the group treated with the appliance with Bertoni's screw, while it increased in the group treated with the Y appliance. There were no statistically significant changes between the groups and during treatment (Table 5).

Dentoalveolar parameters

The I/SpP angle was decreased in both groups of patients. Two-factor analysis of variance with repeated measurements determined a statistically significant difference in the group treated with the Y appliance and the appliance with Bertoni's screw. When comparing effects of treatment, significant differences existed in both treated groups. The i/MP angle increased in the group treated with the appliance with Bertoni's screw, while the Y appliance caused insignificant decrease of this angle. Statistically significant changes in both groups were evaluated with two-factor analysis of the variance with repeated measurements (Table 6).

Table 5. Parameters of facial growth – changes during treatment with different appliances

Parameter	T1 x ± SD	T2 x ± SD	Δ (T2-T1) x ± SD	Significance[a] at T1	Significance[a] at T2	Significance[b/c]	Significance[d]
Σ Bjork (°)							
Y app n = 20	394.05 ± 4.5	395.05 ± 4.26	1 ± 2.34	0.359	0.669	p = 0.599	p = 0.071
Bertoni app n = 20	394.7 ± 4.14	395.5 ± 3.83	0.8 ± 3.26			p = 0.634	p = 0.142
SGo/NMe × 100 (%)							
Y app n = 20	63.73 ± 1.7	64.3 ± 2.84	0.57 ± 1.74	0.237	0.132	p = 0.328	p = 0.555
Bertoni app n = 20	63.5 ± 2.2	63.1 ± 2.36	0.4 ± 2.45			p = 0.423	p = 0.478

*statistically significant difference;
[a]monofactorial variance analysis;
[b]two-factor analysis of the variance, factor time;
[b/c]two-factor analysis of the variance, factor time-group;
[d]t-test

Table 6. Dentoalveolar parameters – changes during treatment with different appliances

Parameter	T1 x ± SD	T2 x ± SD	Δ (T2-T1) x ± SD	Significance[a] at T1	Significance[a] at T2	Significance[b/c]	Significance[d]
I/SpP (°)							
Y app n = 20	71.3 ± 2.81	68.7 ± 3.06	2.6 ± 1.05	0.420	0.015*	p = 0.000*	p < 0.001*
Bertoni app n = 20	72.2 ± 2.53	70.1 ± 2.37	2.1 ± 1.87			p = 0.007*	p < 0.001*
i/MP (°)							
Y app n = 20	90.15 ± 2.83	90.05 ± 2.46	0.1 ± 1.07	0.406	0.705	p = 0.000*	p = 0.681
Bertoni app n = 20	89.7 ± 2.18	90.1 ± 2.45	0.4 ± 1.67			p = 0.012*	p = 0.437

*statistically significant difference;
[a]monofactorial variance analysis;
[b]two-factor analysis of the variance, factor time;
[b/c]two-factor analysis of the variance, factor time-group;
[d]t-test

DISCUSSION

Early treatment of skeletal Class III malocclusion caused by maxillary retrognathism can provide correct occlusion, functional stability, and acceptable facial aesthetics. At the same time, we can avoid the need for a later complex and expensive orthodontic treatment or combined orthodontic and surgical treatment [6]. For this reason, most important are effects on the skeletal structures of the maxilla. It was very important to determine the scope of changes on skeletal and dentoalveolar structures depending on the used appliances and the mechanism of their application. All patients in this study were in the period of pubertal acceleration of growth, without earlier orthodontic treatment. Patients included in this study were treated at the Department of Orthodontic, School of Dental Medicine, University of Belgrade. The standard diagnostic procedure included anamnesis, clinical and functional examinations, analysis of study casts, orthopantomograms and lateral cephalograms, and extraoral and intraoral photos. All the patients were divided into two groups according to type of used appliance: group I treated by the Y appliance and group II treated by a removable appliance with a screw according to Bertoni. In some cases, fixed appliance 4 × 2 can be used, for example in patients with an allergic reaction to materials used for mobile appliances, in patients with epilepsy or in patients with cancer who need frequent and repeated MRI. Also, for significant anterior growth of the maxilla and skeletal effects, Fränkel functional regulator type III can be used in early treatment [7–10].

Position and development of the maxilla were analyzed using the values of SNA and SN/SpP angles and the Cmax linear distance, which determined the length of the maxilla. An increase of the maxillary corpus length was a result of simultaneously intensive pubertal growth and effects of an orthodontic appliance. Stimulation of the sagittal growth of the maxilla caused forward-moving of point A. This moving caused an increased SNA angle. Also, both appliances caused an expansion of the upper dental arch, which was in correlation with posterior rotation of the mandible and the distal movement of point B [8, 9, 11]. Vertical position of the maxilla was changed according to an increased value of the SN/SpP angle [12, 13].

There was far less effect on the mandible than on the maxilla. The Y appliance and the appliance with a screw according to Bertoni did not have any influence on the position of the mandible, because these appliances were located only on the maxilla. These devices were used precisely because the essence of the problem was the underdevelopment of the maxilla.

The relationship between the maxilla and the mandible was evaluated by values of angles ANB and SpP/MP. Both appliances caused significant increase in value of the ANB angle, so it changed skeletal Class III malocclusion to

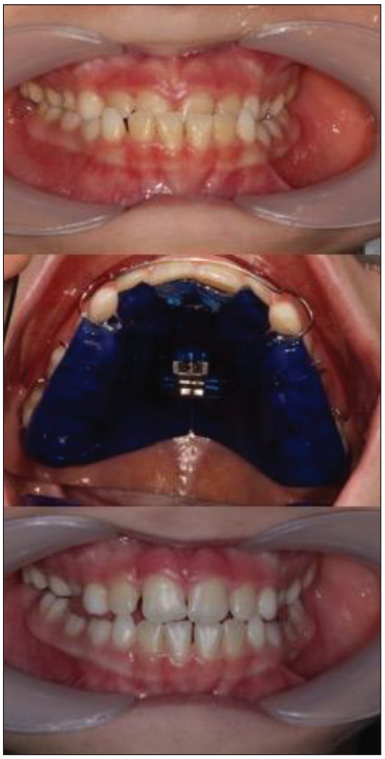


Figure 3. Intraoral photos before and after treatment with appliance with a screw according to Bertoni

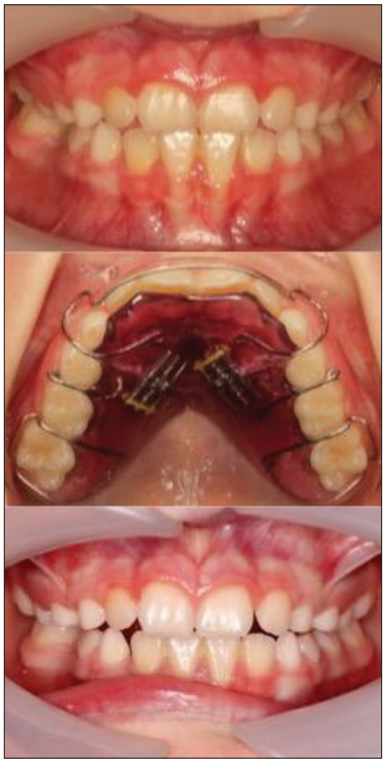


Figure 4. Intraoral photos before and after treatment with the Y appliance

skeletal Class I thanks to the anterior movement of point A [14, 15]. The increased value of the ANB angle was a consequence of the increased SNA angle [9, 16, 17]. The Y appliance and the appliance with a screw according to Bertoni mostly affected dentoalveolar structures, while skeletal changes were minimal [4, 18, 19].

Facial growth was analyzed by the Björk and Jarabak method. Generally, treatment with both appliances caused a slight backward facial rotation and a tendency towards the vertical facial growth [8, 20, 21, 22].

Position of the upper incisors was evaluated by the I/SpP angle. Mostly, patients with Class III malocclusion (except patients with real mandibular prognathism) had normoinclination of the upper incisors [8, 12]. Used appliances changed inclination of the upper incisors, with protrusion of these teeth [21, 22]. It was a consequence of design of these appliances, which were located only on the upper dental arch. Dentoalveolar effects that corrected the overjet were a protrusion of the upper incisors and a retrusion of the lower incisors [14, 23, 24]. Retrusion of the lower incisors was not a consequence of orthodontic treatment. It was some kind of dentoalveolar compensation. Active mobile appliances caused more intense changes on dentoalveolar structures, with severe proclination of the upper incisors [9, 13, 16] (Figures 3 and 4).

Changes in dentoalveolar and skeletal structures are accompanied by an improvement in overall facial aesthetics, which has been confirmed by numerous studies [14, 18, 25, 26].

CONCLUSION

This study indicates that the Y appliance and the appliance with a screw according to Bertoni caused more dental changes during treatment of Class III malocclusion caused by maxillary retrognathism. Treatment with the Y appliance and the appliance with a Bertoni's screw mostly caused changes in dentoalveolar structures. These two appliances contributed to the correction of negative overjet due to the protrusion of the upper incisors. The use of these removable appliances can be useful in the early correction of skeletal Class III malocclusion. Active mobile appliances, Y appliance and the appliance with a screw according to Bertoni, did not cause significant changes on skeletal structures of the craniofacial complex.

Conflict of interest: None declared.

REFERENCES

1. Bishara SE. Textbook of orthodontics. St Louis: Elsevier; 2001. p. 608.
2. Proffit WR, Fields HW, Larson BE, Sarver DM. Contemporary orthodontics. 6th ed. St Louis: Mosby Elsevier; 2018. p. 744.
3. McNamara JA. The Frankel appliance: biological basis and appliance design. J Clin Orthod. 1982;16(5):320–37. [PMID: 6957418]
4. Isaacson KG, Muir JD, Reed RT. Removable Orthodontic Appliances. Oxford: Wright; 2002. p. 124.
5. Baccetti T, Franchi L, McNamara JA. The Cervical Vertebral Maturation (CVM) Method for the Assessment of Optimal Treatment Timing in Dentofacial Orthopedics. Semin Orthod. 2005;11(3):119–29. [DOI: 10.1053/j.sodo.2005.04.005]
6. Zere E, Chaudhari PK, Sharan J, Dhingra K, Tiwari N. Developing Class III malocclusions: challenges and solutions. Clin Cosmet Investig Dent. 2018;10:99–116. [DOI: 10.2147/CCIDE.S134303] [PMID: 29950903]
7. Stamenković Z. Klinički efekti primene Fränkelovih regulatora funkcije u terapiji distalnog i mezijalnog zagrižaja, dissertation. Belgrade: University of Belgrade; 2011. Serbian.
8. Stamenković Z. Upotreba Frenklovog regulatora funkcije u tretmanu skeletne klase III. Belgrade: Zadužbina Andrejević; 2014. Serbian.
9. Stamenković Z, Raičković V. Fränkel Functional Regulator in Early Treatment of Skeletal Distal and Mesial Bite. In: Virdi M, editors. Emerging Trends in Oral Health Sciences and Dentistry. Intech; 2015. p. 363–86. [DOI: 10.5772/59228]
10. Ji LL, Sun DX, Shi LB, Kyung HM, Bing L, Wu XP. Morphological Changes of Frankel Functional Regulator III in Mixed Dentition with Class III Malocclusion. Int J Morphol. 2020;38(4):1053–9. [DOI: 10.4067/S0717-95022020000401053]
11. Lim LI, Choi JY, Ahn HW, Kim SH, Chung KR, Nelson G. Treatment outcomes of various force applications in growing patients with skeletal Class III malocclusion. A comparative lateral

cephalometric study. Angle Orthod. 2021;91(4):449–58. [DOI: 10.2319/090320-768.1] [PMID: 33587106]
12. Liu Y, Yang K. Three-dimensional changes in the upper airway and craniomaxillofacial morphology of patients with Angle Class III malocclusion treated with a Frankel III appliance. BMC Oral Health. 2021;21(1):634. [DOI: 10.1186/s12903-021-02013-0] [PMID: 34886826]
13. Indugu V, Sleeva Raju N, Ravivarma M, Cheepaurupalli S, Neelima K, Likhita C. Early Orthopedic Correction of Skeletal Class III Malocclusion in Growing Child: A Case Report. Int J Med Res Prof. 2021;7(1):33–7. [DOI: 10.21276/ijmrp]
14. Ghorbanyjavadpour F, Rakhshan V. Factors associated with the beauty of soft-tissue profile. Am J Orthod Dentofacial Orthop. 2019;155(6):832–43. [DOI: 10.1016/j.ajodo.2018.07.020] [PMID: 31153504]
15. Wu TY, Chang TF, Wu CH. True vertical changes in patients with skeletal class III malocclusion after nonsurgical orthodontic treatment-a retrospective study comparing different vertical facial patterns. J Dent Sci. 2022;17(3):1096–101. [DOI: 10.1016/j.jds.2022.02.008] [PMID: 35784149]
16. Sarangal H, Namdev R, Garg S, Saini N, Singhal P. Treatment modalities for early management of Class III skeletal malocclusion: a case series. Contemp Clin Dent. 2020;11(1):91–6. [DOI: 10.4103/ccd.ccd_393_19] [PMID: 33110317]
17. Nedeljković N, editor. Funkcionalni ortodontski aparati – teorija i terapija. Belgrade: Stomatološki fakultet u Beogradu; 2021. Serbian
18. Woon SC, Thiruvenkatachari B. Early orthodontic treatment for Class III malocclusion: A systematic review and meta-analysis. Am J Orthod Dentofacial Orthop. 2017;151(1):28–52. [DOI: 10.1016/j.ajodo.2016.07.017] [PMID: 28024779]
19. D'Apuzzo F, Grassia V, Quinzi V, Vitale M, Marzo G, Perillo L. Paediatric Orthodontics. Part 4: SEC III protocol in Class III malocclusion. Eur J Paediatr Dent. 2019;20(4):330–4. [DOI: 10.23804/ejpd.2019.20.04.14] [PMID: 31850779]
20. Pereira da Silva HCF, De Paiva JB, Rino Neto J. Anterior crossbite treatment in the primary dentition: Three case reports. Int Orthod. 2018;16(3):514–29. [DOI: 10.1016/j.ortho.2018.06.027] [PMID: 30097417]
21. Xu FY, Kwon TG, Rong H, Kyung HM, Bing L, Wu XP. Morphological Changes of Skeletal Class III Malocclusion in Mixed Dentition with Protraction Combined Activities. Int J Morphol. 2018;36(2):430–4. [DOI: 10.4067/S0717-95022018000200430]
22. Martina R, D'Anto V, De Simone V, Galeotti A, Rongo R, Franchi L. Cephalometric outcomes of a new orthopaedic appliance for Class III malocclusion treatment. Eur J Orthod. 2020;42(2):187–92. [DOI: 10.1093/ejo/cjz037] [PMID: 31314883]
23. Martina S, Martina R, Franchi L, D'Antò V, Valletta R. A new appliance for Class III treatment in growing patients: Pushing Splints 3. Case Rep Dent. 2019;2019:1–10.
24. Fleming P, Lee R, editors. Orthodontic Functional Appliances – theory and practice. Wiley Blackwell; 2020. p. 176.
25. Paoloni V, De Razza FC, Franchi L, Cozza P. Stability prediction of early orthopedic treatment in Class III malocclusion: morphologic discriminant analysis. Prog Orthod. 2021;22(1):34. [DOI: 10.1186/s40510-021-00379-z] [PMID: 34541628]
26. Tekucheva SV, Postnikov MA, Persin LS. Primenenie ortodonticheskogo apparata sobstvennoĭ konstruktsii dlia lecheniia patsientov s mezial'noĭ okkliuzieĭ v sochetanii s anomaliiami zubnykh riadov na rannem étape smeny zubov. Klinicheskiĭ sluchaĭ [Early orthodontic treatment of the patients with Class III malocclusion combined with the arches discrepancies using the own design appliance. Clinical case]. Stomatologiia (Mosk). 2018;97(4):58–65. Russian. [DOI: 10.17116/stomat20189704158] [PMID: 30199071]

Промене током третмана малоклузија класе III применом апарата *Y* и апарата са шрафом по Бертонију

Зорана Стаменковић[1], Вања Стојић[1], Немања Маринковић[1], Иван Арсић[1], Јован Марковић[1], Бојан Гламочанин[2]

[1]Универзитет у Београду, Стоматолошки факултет, Клиника за ортопедију вилица, Београд, Србија;
[2]Универзитет у Новом Саду, Медицински факултет, Одсек за стоматологију, Нови Сад, Србија

САЖЕТАК

Увод/Циљ Малоклузије III класе могу бити узроковане променама на скелетним и/или дентоалвеоларним структурама са мезијалним односом у регији бочних зуба. У раном третману класе III изазване максиларним ретрогнатизмом може се користити апарат *Y* и апарат са шрафом по Бертонију.

Циљ овог истраживања је био да се утврде и упореде скелетне и дентоалвеоларне промене код пацијената са класом III који су лечени применом апарата *Y* и апарата са шрафом по Бертонију.

Методе У истраживање је укључено 40 пацијената. Цео узорак подељен је у две групе, са по 20 пацијената у свакој групи. У студију су укључени пацијенти код којих је узрок мезијалног загрижаја био максиларни ретрогнатизам, у мешовитој дентицији и пубертетском убрзању раста. Нису укључени пацијенти са правим мандибуларним прогнатизмом, особе са генетском предиспозицијом за настанак мезијалног загрижаја, пацијенти са расцепом усне и непца или неким краниофацијалним синдромом, као ни пацијенти са сталном дентицијом. Изабрани су апарати чија се примена базира на изазивању промена на структурама горње вилице. За пацијенте је урађена анамнеза, клиничко и функционално испитивање, анализа студијских модела, анализа ортопантомографског снимка и профилног цефалограма, као и екстраоралних и интраоралних фотографија. Терапијски ефекти анализирани су на студијским моделима и профилним цефалограмима урађеним после ове фазе ортодонтског третмана.

Резултати Главни дентоалвеоларни ефекат била је протрузија горњих секутића. Скелетни ефекти нису били значајни.

Закључак Апарат *Y* и апарат са шрафом по Бертонију изазивају значајне промене на дентоалвеоларним структурама у поређењу са скелетним структурама, где су промене биле мање уочљиве.

Кључне речи: малоклузије III класе; апарат *Y*; апарат са шрафом по Бертонију

DOI: https://doi.org/10.2298/SARH220509096D
UDC: 616.12:616.61-78-056.24

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Chronic heart failure phenotypes in prevalent patients treated with hemodialysis – a single-center experience

Marija Dobričić[1], Vesna Pakić[1], Aleksandra Arsenović[1], Vesna Pejović[1], Aleksandra Kuzmanović[1], Miodrag Milić[1], Višnja Ležaić[2]

[1]Special Hospital for Internal Diseases, Lazarevac, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY

Introduction/Objective Heart failure (HF) is the main cause of morbidity and mortality of hemodialysis (HD) patients. The aim of this cross-sectional single-center study was to examine the following: 1. frequency and characteristics of HF phenotypes in prevalent HD patients, 2. association of HF with traditional and non-traditional risk factors for cardiovascular diseases.

Methods We included all 96 maintenance HD patients from Special Hospital for Internal Diseases, Lazarevac, Serbia, and determined the prevalence of HF with preserved ejection fraction (HFpEF) (per the 2016 criteria of the European Society of Cardiology) and HF with reduced and moderately reduced EF – HFrEF + HFmrEF – together in a group HFrEF (EF < 50%) using standardized post-HD transthoracic echocardiography. Clinical, routine laboratory and volume status parameters (by bioimpedance spectroscopy) was assessed.

Results Sixty-three out of 96 examined patients (65.6%) had HF, among them 42 had HFpEF (66.7%), and 21 had HFrEF (33.3%). HFrEF was more common in older males, with diabetic nephropathy as underlying kidney disease, with a longer dialysis vintage and in those with a previous history of ischemic heart disease. HFpEF was more common in males, with lower HD quality (kT/V) and higher pre-dialytic systolic blood pressure. In multivariable regression analysis, HFrEF was associated with diabetic nephropathy, hypervolemia (positively) and triglycerides (negatively), while HFpEF was associated negatively with hemoglobin, iron, and triglycerides.

Conclusion In order to control patients on maintenance HD with HF, in addition to appropriate drug therapy, it is advice to control of volemia and maintaining triglyceride, hemoglobin, and iron concentration approximately within normal limits.

Keywords: heart failure; hemodialysis; associated factors

INTRODUCTION

Patients on hemodialysis (HD) are at a higher risk of developing cardiovascular disease (CVD), which is a leading cause of death and accounts for approximately 30–35% of all-cause mortality among patients on HD [1]. Besides coronary artery disease (CAD), heart failure (HF) is the most common CVD in HD patients [2]. It is known that one-third of patients have HF at the initiation of HD, and 25% of patients develop HF *de novo* during dialysis treatment [2].

Patients treated with HD have an increased risk of HF. In addition to the traditional (age, hypertension, diabetes, and dyslipidemia), many non-traditional factors mostly related to chronic kidney disease and dialysis itself are involved in the development of CVD and HF (volume load, hypertrophy and impaired left ventricular function (systolic and diastolic), valvular defects, arteriovenous fistula, anemia, mineral metabolism disorders, oxidative stress, inflammation) [2].

Three types of HF in general population are recognized: HF with preserved ejection fraction (EF), known as diastolic HF, HF with reduced EF, known as systolic HF, and HF with moderately reduced EF [3]. Their clinical presentation and risk factors are similar, but the approach to treatment and response to treatment is different. Having in mind that HF is a poor predictor of HD patient outcome [1, 4], timely identification of HF risk factors, and clinical presentation would be helpful in prevention and management of those patients [5].

In order to contribute to the timely diagnosis of HF in HD patients, we conducted this study aiming to define the following: 1. frequency and characteristics of left ventricular function in prevalent patients treated with chronic HD, 2. association of HF with traditional and non-traditional risk factors for CVD.

METHODS

Patients

The study population consisted of 96 maintenance HD patients treated at the Special Hospital for Internal Diseases, Lazarevac, Serbia. Only patients older than 18 years who

Received • Примљено: May 9, 2022
Revised • Ревизија: August 31, 2022
Accepted • Прихваћено: September 14, 2022
Online first: September 20, 2022

Correspondence to:
Marija DOBRIČIĆ
Special Hospital for Internal Diseases
Dr Đorđa Kovačevića 27
11550 Lazarevac, Serbia
marija.dobricic@yahoo.com

spent more than six months on HD were included. They were all asymptomatic for chest pain and had no history of acute coronary syndrome in the past three months. Exclusion criteria was the inability of the patients to provide informed consent. According to the criteria of the American and European Society of Cardiology and based on signs and/or symptoms of heart failure, and left ventricular function indicators obtained by transthoracic echocardiography, patients were divided into the following groups: 1. with HF and reduced EF-rEF (EF < 40%), plus moderately reduced HFmrEF (EF = 40–50%) – 21 patients; 2. with HF and preserved EF-HFpEF (EF ≥ 50%) – 42 patients; and 3. without overt HF – 33 patients [5].

The participants were monitored from January 2020 to the end of September 2020. The approval of the local ethics committee was obtained (number 110/21.1.2020) and written informed consent was obtained from all the participants.

The study variables were as follows:

1. Demografic data: age, sex, renal disease, comorbidities (coronary artery disease, hypertension, diabetes mellitus, dyslipidemia, and peripheral obstructive arterial disease), residual diuresis, and body mass index (BMI) including history of coronary artery disease defined as prior revascularization (through angioplasty or coronary artery bypass). Also, each patient was physically examined and questioned for signs and/or symptoms of HF including edema of the lower extremities, (exertional) dyspnea graded by the New York Heart Association criteria (NYHA I–IV) and paroxysmal nocturnal dyspnea/orthopnea [6].

2. Dialytic data: duration of dialysis session (four hours three times a week), dialysis vintage, dialysis membrane (low- and high-flow polysulfone membrane), single-pool Kt/V [7], interdialytic weight gain, dialysis access, and systolic and diastolic blood pressure before HD session, volume status checked by bioimpedance spectroscopy, using Body Composition Monitor – BCM (Fresenius Medical Care AG & Co. KGaA, Bad Homburg, Germany).

3. Laboratory data: urea, creatinine, markers of anemia, lipid fraction, lipoprotein subfraction, biomarkers of mineral bone disorder were determined by routine laboratory analyses at the respective dialysis session.

4. Transthoracic echocardiography characteristics: left ventricular function, right ventricular function, pulmonary hypertension, diastolic dysfunction, pericardial effusion, and valvular heart disease. All echocardiographic measurements were performed by two experienced echocardiographers (cardiologists) who were blinded to the clinical status of the patients. Intra-observer variability was 4%.

To avoid the effect of volume load, all echocardiographic data were collected on dialysis days when the HD was done [8]. Atrial volume and ejection fraction (EF) were assessed using the modified Simpson biplane method [9]. Left ventricular (LV) mass was calculated using the Devereux formula and normalized by body surface area [LV mass index (LVMI)]. Relative wall thickness was calculated as 2 times posterior wall divided by the LV diastolic diameter. Early and late diastolic peak filling velocities E and A waves were measured at the mitral leaflet tips. The early (e') and late (a') diastolic velocities at septal and lateral corner of mitral annulus were assessed with pulse-wave tissue Doppler from a standard apical four-chamber view [9].

Statistical analyses

IBM SPSS Statistics, Version 25.0 (IBM Corp., Armonk, NY, USA) and R software Version 3.6.1 (R Core Team 2019) were used in the statistical analyses. Continuous variates with normal distribution were presented as mean ± standard deviation and compared using the Student's t-test. Variables without normal distribution data were presented as median with interquartile ranges and compared using the Mann–Whitney U test. Categorical data were presented as the number of cases and percentages and compared using the χ^2 test. Multivariable logistic regression model including all significantly different characteristics in the univariate logistic regression models (at a significance level of 0.05) as well as those predictors that are known to affect the dependent variable, was used to determine the independent association with HF. Two-sided p-values < 0.05 were considered significant.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

RESULTS

Baseline characteristics

The baseline data on studied patients are presented in Table 1. Out of 96 examined patients, 63 (65.6%) had HF, among them 42 patients had HFpEF (66.7%), and 21 patients had HFrEF (33.3%). These groups compared with the control group consisted of 33 patients with no HF. The average patients' age in all three groups was higher than 60 years, but patients with HF were significantly older than patients without HF. Also, there were predominantly males in the groups with HF. In the previous history, a significantly smaller number of patients with HFpEF had myocardial infarction (MI) and coronary artery bypass grafting (CABG) compared to the other two groups of patients. Angiotensin-converting enzyme inhibitors, calcium channel antagonists, and beta blockers were most often used antihypertensive drugs in combination, or less often alone. Only beta-blockers were used in the smallest number of patients in group 3, compared to the other two groups of patients (data on treatment is not presented). Insignificantly but a slightly larger number of patients in group 1 were treated with statins. No difference was found among groups regarding underlying kidney disease, comorbidities, BMI, and smoking habit.

Data on HD characteristics, predialysis blood pressure, and NYHA are showed in Table 2. Patients with HF had

Table 1. Baseline characteristics of examined patients

Characteristics	Group 1 HFrEF + HFmrEF	Group 2 HFpEF	Group 3 No HF	p
Number of patients	21	42	33	
Sex, m/f*	16 (76.2) / 5 (23.8)	32 (76.2) / 10 (23.8)	15 (45.5) / 18 (54.5)	f - (1 + 2):3 = 0.003 1:3 = 0.04 2:3 = 0.008
Age, years[1]	69 ± 1.88	68.62 ± 2.07	63.60 ± 1.67	1:3 = 0.042
Kidney diseases*: DN Nscl Others	 8 (38.1) 6 (28.6) 7 (33.3)	 10 (23.8) 19 (45.3) 13 (30.9)	 4 (12.1) 14 (42.4) 15 (45.5)	NS
BMI	25.6 (19.2)	24.7 (5.9)	24.5 (6.5)	NS
Smoking*	6 (28.6)	9 (21.4)	7 (21.2)	NS
Comorbidities*: Hypertension CVI PVD Diabetes Malignancies COBD	 13 (61.9%) 1 2 1 1 2	 19 (45%) 2 - 3 2 5	 16 (48.5%) 2 1 3 1 2	
Coronary heart disease*: MI	 7	 1	 4	 1:2 = 0.0013
PCI	1	0	1	
CABG	5	1	3	1:2 = 0.013

Nscl – nephroangiosclerosis; DN – diabetic nephropathy; BMI – body mass index; CVI – cardiovascular insult; PVD – peripheral vascular disease; COBD – chronic obstructive pulmonary disease; MI – myocardial infarction; PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting;
[1]mean ± SD or median (IQR);
*frequency (%)

Table 2. Data on hemodialysis duration, kT/V, volemia, and pre-dialysis blood pressure

Parameter	Group 1 HFrEF + HFmrEF	Group 2 HFpEF	Group 3 No HF	p
HD duration, months[1]	57 (227)	31.50 (143)	36 (58.5)	1:2 = 0.027
kT/V	1.08 ± 0.06	1.07 ± 0.04	1.22 ± 0.05	(1+2):3 = 0.036 2:3 = 0.042
Interdialytic weight gain, kg*	3.41 ± 0.33	3.02 ± 0.17	2.83 ± 0.18	NS
Pre-dialysis BP*: Systolic, mmHg	149.04 ± 5.30	151.38 ± 3.49	141.09 ± 3.26	(1 + 2):3 = 0.044 1:3 = 0.029 2:3 = 0.039
Diastolic, mmHg	71.38 ± 2.92	74.88 ± 1.9	75.15 ± 2.03	
NYHA class, No. I II III	 4 (19%) 11 (52.4%) 6 (28.6%)	 8 (19.05%) 26 (61.9%) 8 (19.05%)	 9 (27.3%) 20 (60.6%) 4 (12.1%)	NS
OH	3.2 (5.93)	2.9 (3.8)	2.1 (1.8)	1:3 = 0.005 2:3 = 0.035
ECW %	19.8 (21.83)	16.7 (16.8)	11.8 (10.9)	NS
OH/ECW	18.63 ± 2.59	16.55 ± 2.11	12.69 ± 1.43	1:2 = 0.035
OH/ECW > 15%	12/20 (60%)	13/39 (33.33%)	9/30 (30%)	1:2 = 0.05 1:3 = 0.045
Water load	37.74 ± 7.01	36.7 (12.3)	33.1 (6.43)	2:3 = 0.04
Volume of urea distribution	35.5 (7.33)	34.4 (11.6)	30.45 (5.67)	1:3 = 0.036 2:3 = 0.031
ECW/ICW	1.15 ± 0.04	1.09 ± 0.03	1.03 ± 0.03	1:3 = 0.013

NYHA – New York Heart Association classification of heart failure; OH – overhydration; ECW – extracellular water; ICW – intracellular water;
*mean ± SD median (IQR)

lower kT/V, higher predialysis systolic pressure and OH than patients without HF. Dialysis lasted the longest in patients of group 1. The most common access for HD was arteriovenous fistula in all three studied groups (data not presented). The mean value of OH (overhydration) / ECW (extracellular water) measured by bioimpedance and indicating hyperhydration was the highest in patients of group 1, in which 60% had OH/ECW > 15%, which is higher than in the other two groups. No difference was found in NYHA classes groups between the examined patients with and without HF.

Laboratory analyses and echocardiographic parameters

The lowest serum concentration of hemoglobin, iron, and TG was observed in groups with HF and HFpEF who additionally had the lowest iPTH concentration (Table 3). Also, almost half of the patients from groups 1 and 2 had TG below lower laboratory limit. Patients from group 1 had the lowest total cholesterol and LDL-C. The HDL/LDL ratio as an indicator of atherosclerosis risk in all three groups was within the normal limit and similar in almost all three groups. Other laboratory analyses were similar. Unhealthy lean body mass was found in all studied patients (data not shown).

Echocardiographic findings are presented in Table 4. Several echocardiographic parameters distinguished both the HF groups from that without HF, as these patients had larger left ventricular, left atrial diameters and mass index, as well as E/e' (Table 4).

Predictors of heart failure

The likelihood of HF (all HF, HFrEF, HFpEF) in comparison to no HF in prevalent hemodialysis patients is presented in Figure 1.

In multivariable regression analysis, HF was associated with patients' age, urea volume distribution, and use of beta blockers, but HFrEF was associated with diabetic nephropathy and hypervolemia (positively) and triglycerides (negatively), while HFpEF was associated negatively with hemoglobin, iron, and triglyceride.

Table 3. Laboratory analyses

Analysis	Group 1 HFrEF + HFmrEF	Group 2 HFpEF	Group 3 No HF	p
Hemoglobin, g/l	103.78 ± 4.73	97.94 ± 2.87	113.1 ± 3.7	(1+2):3 = 0.002; 2:3 = 0.001
Sodium, mmol/l	137.9 ± 0.44	139 ± 4.0	139.4 ± 0.43	1:3 = 0.014
Potassium, mmol/l	5.48 ± 0.18	5.3 (0.6)	5.3 ± 0.16	NS
Calcium, mmol/l	2.14 ± 0.05	2.15 (0.28)	2.18 ± 0.04	NS
Phosphate, mmol/l	1.36 ± 0.09	1.45 ± 0.09	1.53 ± 0.08	NS
Ferritin, ng/ml	438.78 ± 16.09	405 (119)	395 (135)	NS
Iron, µmol/l	15.03 ± 1.1	13.01 ± 2.5	15.48 ± 0.72	(1 + 2):3 = 0.03; 1:3 = 0.004 2:3 = 0.002
iPTH, pg/ml	463.3 (662.3)	189.5 (239.5)	340.5 (795.47)	2:3 = 0.05
Total cholesterol, mmol/l	3.88 (1.87)	4.16 (1.38)	4.72 (0.18)	1:3 = 0.017
TG, mmol/l	1.2 (1.06)	1.31(0.8)	2.07 (1.57)	(1 + 2):3 = 0.001; 1:3 = 0.013 2:3 = 0.002
< 1.35, No. (%)	10 (47.6)	19 (45.2)	7 (22.5)	
> 1.7, No. (%)	8 (38.1)	12 (28.6)		
HDL-C, mmol/l	1.47 (0.68)	1.18 (0.93)	1.14 (0.64)	NS
LDL-C, mmol/l	1.7 (1.25)	2.41(0.84)	2.42 (0.96)	1:2 = 0.05
HDL/LDL	1.87 ± 0.26	2.05 ± 0.13	2.19 ± 0.15	NS

PTH – parathyroid hormone; TG – triglyceride; HDL-C – high-density lipoprotein cholesterol particles; LDL-C – low-density lipoprotein cholesterol particles

Table 4. Echocardiographic parameters

Parameters	Group 1 HFrEF + HFmrEF	Group 2 HFpEF	Group 3 No HF	p
EF, %	43 (7)	57.7 ± 0.9	59.7 ± 6.2	1:2. 1:3 = 0.0001
EDD, cm	5.85 ± 0.11	5.55 ± 0.1	4.75 ± 0.08	1:3 = 0.0001
				2:3 = 0.0001
ESD, cm	4.39 ± 0.13	3.73 ± 0.1	3.1 (0.35)	1:2. 2:3. 1:3 = 0.0001
IVs	1.1 (0.25)	1.1 (0.2)	1.0 (0.1)	1:2:3. p = 0.000
Posterior wall, cm	1.1 (0.20)	1.1 (0.2)	0.9 (0.2)	1:2:3. p = 0.019
LVM index	145.86 ± 6.6	133.1 ± 4.7	90 (23)	1:3. 2:3 p = 0.0001
LA	4.3 ± 0.1	4.24 ± 0.1	3.63 ± 0.6	1:2. 2:3. p = 0.0001
LAVi	59.2 ± 3.9	53 (21.3)	29 (11.6)	1:3. 2:3. p = 0.0001
E/ A index	0.6 (0.73)	0.64 (0.28)	0.8 (0.26)	1:3. 2:3. p = 0.001–0.021
e', cm/s	6 (2.25)	6 (1)	11.54 ± 0.3	1:3. 2:3. p = 0.000
≥ 8*	14 (66.6%)	0	31 (93.9%)	
E/e'	10.36 ± 1.1	10.87 ± 0.7	5.46 ± 0.3	1:3. 2:3. p = 0.000
≥ 8*	14 (66.6%)	34 (80.9%)	4 (12%)	

EF – ejection fraction; EDD – left ventricular end diastolic diameter; ESD – left ventricular end systolic diameter; LAVi – left atrial volume index; LVMi – left ventricular mass index; LA – left atrial; E – early mitral valve flow velocity; A – late mitral valve flow velocity; E/A – ratio of early to late mitral valve flow velocity; e' – early diastolic wave; E/e' – ratio of early mitral valve flow velocity to early tissue Doppler lengthening velocity;
*number of patients; mean ± SEM; M(IQR)

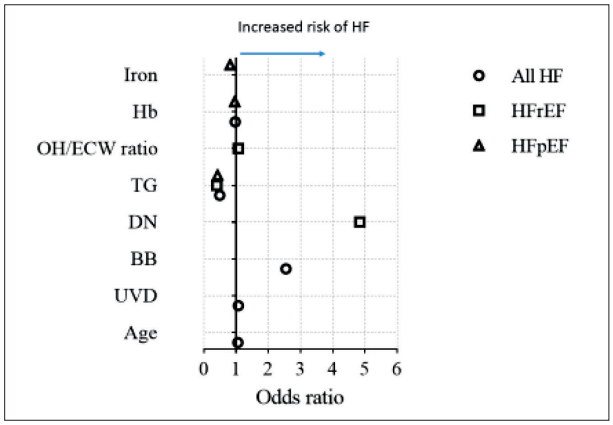


Figure 1. Multivariate prediction model of each contributing factor for heart failure (HF), HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF) *vs*. no HF;
Hb – hemoglobin; TG – triglyceride; DN – diabetic nephropathy; BB – beta blocker; UVD – urea volume distribution

DISCUSSION

Presence and risk factors of HF in patients on maintenance HD were analyzed in this single-center study. The key findings are the following: 1. 65.6% of all studied HD patients fulfilled the diagnostic criteria for HF, among them 66.7% had HFpEF, and 33.3% of patients had HFrEF; 2. No differences in patients' symptoms in different HF phenotypes were observed; 3. HF and both HF phenotypes share some clinical and biochemical contributing factors.

The frequency of HF in our group of patients is similar to that described by other authors [10, 11, 12]. Antlanger et al. [10] reported on the prevalence of HF of up to 70% among 105 maintenance HD patients, of whom 81% had HFpEF and 19% had HFrEF. In the USA registry data, it was estimated that 44% of HD patients have HF: 10% with HFpEF, 13% with HFrEF [11]. Wang et al. [12] found a slightly lower incidence of HF in 220 patients treated with PD, which was expected for this type of dialysis. The authors found that 86 (39.1%) patients had HF, of which 47 (54.7%) had a HFpEF and 39 (45.3%) had HFrEF.

The clinical diagnosis of HF usually begins with the identification of accompanying symptoms. In dialysis patients it is not easy to identify which symptoms originate from HF and which from ESKD and HD *per se*. Typical HF symptoms, such as paroxysmal nocturnal dyspnea, orthopnea, dyspnea, fatigue, ascites, and lower legs edema, may be intermittent. These symptoms are difficult to distinguish from periodic fluid retention, and chronic renal anemia, so the development of structural heart abnormalities may remain unrecognized in patients with ESKD treated with

dialysis. Even the symptoms reported by patients (and according to NYHA criteria) are not completely reliable for the diagnosis of HF that was in line with previous studies [10, 13, 14]. The presented results have shown that the majority of our patients had no HF symptoms or they were mild, i.e., more than 80% of patients with HFpEF and about 60% of patients with HFrEF had no heart problems or they were mild (NYHA classes 1 and 2). Furthermore, tests and biomarkers used to diagnose CVD and HF in the general population, including Framingham risk model, cannot be performed and reliably interpreted in the dialysis population [15, 16]. However, patients with dialysis-dependent HF should undergo the same evaluation as patients with non-dialysis-dependent HF. Kidney Disease Outcomes Quality Initiative guidelines were recommended to perform a detailed echocardiographic and cardiac examination of all patients who start dialysis and then every three years during the treatment to monitor functional and structural changes in the myocardium even if they are asymptomatic and without overt CVD [17, 18].

Many studies have been conducted to evaluate the factors associated with chronic HF related to dialysis, but the findings have been inconsistent. The association of several traditional risk factors, such as age, diabetes, BMI, blood pressure, serum cholesterol, and mortality and HF have been previously reported [12, 19, 20].

Similarly to the aforementioned studies, we have found that HF phenotypes share some of the contributing factors based on demographic and clinical information. HFrEF was more common in older males, with diabetic nephropathy as underlying kidney disease, and in those with a previous history of ischemic heart disease, with a longer dialysis vintage. On the other hand, HFpEF was more common in males, with lower kT/V and higher pre-dialytic systolic blood pressure. Of these, only the patients' age, diabetic nephropathy, and the use of beta-blockers have been independently associated with HF, which is in accordance with previous data in dialysis patients [12, 19, 20].

Presented results show that HF and both HF phenotypes are associated negatively with triglycerides, meaning that the lower triglycerides – the more likely HF presence. This finding is in accordance with the earlier study conducted in non-chronic kidney disease (CKD) populations with HF. Namely, chronic HF can lead to a catabolic state and cachexia in advanced cases with reduced appetite, malabsorption, and reduced anabolic steroids levels with consequent low cholesterol and triglyceride level. At the molecular level, inflammation, endotoxins accumulation, adrenergic activation, oxidative stress, and tissue injury develop during chronic HF [21]. Also, HF might alter both the production and the storage of triglycerides through liver ischemia. Therefore, low triglycerides are not the cause of HF, but a sign of a disturbed state in the body.

The volume of urea distribution and the OH/ECW ratio as indicators of hypervolemia were selected as predictors of HF and HFrEF in our studied patients. The higher the OH/ECW ratio, the more likely a patient is to have HFrEF. Repeated water retention between dialysis contributes to the development of LVH and both types of HF in dialysis patients [12, 22, 23]. Thus, the control of hypervolemia by ultrafiltration during HD is the mainstay of treatment in the prevention of CV instability [17, 22, 24]. On the other hand, there is evidence that excessive ultrafiltration can adversely affect the hemodynamic stability of the cardiovascular system and trigger a range of inflammatory reactions in patients and thus affect the development of HF, suggesting that continuous volume status assessment in dialysis patients is necessary [20].

Hemoglobin concentration is an independent contributing factor for the development of HF and HFpEF in our analysis, with a negative sign. This is in line with literature data that anemia in CKD patients and those treated with dialysis is a strong predictor of HF [1, 2, 25]. Stable and almost normal hemoglobin, especially after the introduction of erythropoietin-stimulating agents, made it possible to maintain a good oxygen supply to the tissues, which had a protective effect especially on cardiomyocytes and coronary microvascular dysfunction [26].

In addition, iron concentration was selected as independent contributing factor of HFpEF in our study. For each reduction of iron per unit of measure, the probability that a patient will have HFpEF increases by 1.23 times. There is growing evidence that iron treatment has a beneficial effect in the non-CKD population with HF. The explanation lies in the fact that high metabolic needs in cardiomyocytes depend on iron [26]. When observing dialysis patients, maintaining iron balance was important not only for treating anemia, but also for reducing the number of hospitalizations due to HF and nonfatal myocardial infarction [27].

Some limitations of the current study need to be mentioned. This study was cross-sectional and therefore does not provide information on when HF developed. For the same reason, it was not possible to draw conclusions about causality, but about the association of HF and various examined factors.

CONCLUSION

Our cross-sectional study showed that more than half of the patients on maintenance HD met the criteria for HF. As it is not easy to distinguish common HF symptoms from intermittent complications that accompany HD, it is recommended that a complete CV investigation be performed in accordance with the KDIGO guidelines. In addition to immutable factors such as patients age and sex and diabetic nephropathy, HF should be sought in patients with recurrent hyperhydration, who have poorer parameters of HD adequacy, with lower triglycerides, iron, and anemia.

Conflict of interest: None declared.

REFERENCES

1. Cozzolino M, Mangano M, Stucchi A, Ciceri P, Conte F, Galassi A. Cardiovascular disease in dialysis patients. Nephrol Dial Transplant. 2018;33(suppl_3):iii28–iii34. [DOI: 10.1093/ndt/gfy174] [PMID: 30281132]
2. Rangaswami J, McCullough PA. Heart Failure in End-Stage Kidney Disease: Pathophysiology, Diagnosis, and Therapeutic Strategies. Semin Nephrol. 2018;38(6):600–17. [DOI: 10.1016/j.semnephrol.2018.08.005] [PMID: 30413254]
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18(8):891–975. [DOI: 10.1002/ejhf.592] [PMID: 27207191]
4. Genovesi S, Boriani G, Covic A, Vernooij RWM, Combe C, Burlacu A, et al.; EUDIAL Working Group of ERA-EDTA. Sudden cardiac death in dialysis patients: different causes and management strategies. Nephrol Dial Transplant. 2021;36(3):396–405. [DOI: 10.1093/ndt/gfz182] [PMID: 31538192]
5. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895–e1032. [DOI: 10.1161/CIR.0000000000001063] Erratum in: Circulation. 2022;145(18):e1033. Erratum in: Circulation. 2022;146(13):e185. [PMID: 35363499]
6. Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; 1994.
7. Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. J Am Soc Nephrol. 1993;4(5):1205–13. [DOI: 10.1681/ASN.V451205] [PMID: 8305648]
8. Vigan J, Ahoui S, Hounsou D, Goudoté ACK, Vehounkpe Sacca J. Hypertrophie ventriculaire gauche chez les hémodialysés chroniques du CNHU-HKM de Cotonou [Left ventricular hypertrophy in chronic hemodialysis patients at CNHU-HKM of Cotonou]. Nephrol Ther. 2018;14(1):29–34. French. [DOI: 10.1016/j.nephro.2017.06.001] [PMID: 29276083]
9. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233–70. [DOI: 10.1093/ehjci/jev014] Erratum in: Eur Heart J Cardiovasc Imaging. 2016;17(4):412. Erratum in: Eur Heart J Cardiovasc Imaging. 2016;17(9):969. [PMID: 25712077]
10. Antlanger M, Aschauer S, Kopecky C, Hecking M, Kovarik JJ, Werzowa J, et al. Heart Failure with Preserved and Reduced Ejection Fraction in Hemodialysis Patients: Prevalence, Disease Prediction and Prognosis. Kidney Blood Press Res. 2017;42(1):165–76. [DOI: 10.1159/000473868] [PMID: 28395286]
11. Johansen KL, Chertow GM, Foley RN, Gilbertson DT, Herzog CA, Ishani A, et al. US Renal Data System 2020 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2021;77(4 Suppl 1):A7–A8. [DOI: 10.1053/j.ajkd.2021.01.002] [PMID: 33752804]
12. Wang AY, Wang M, Lam CW, Chan IH, Lui SF, Sanderson JE. Heart failure with preserved or reduced ejection fraction in patients treated with peritoneal dialysis. Am J Kidney Dis. 2013;61(6):975–83. [DOI: 10.1053/j.ajkd.2012.12.030] [PMID: 23474006]
13. Smyth B, Chan CT, Grieve SM, Puranik R, Zuo L, Hong D, et al. Predictors of Change in Left-Ventricular Structure and Function in a Trial of Extended Hours Hemodialysis. J Card Fail. 2020;26(6):482–91. [DOI: 10.1016/j.cardfail.2020.03.010] [PMID: 32302717]
14. Malik J, Kudlicka J, Valerianova A, Kovarova L, Kmentova T, Lachmanova J. Diastolic dysfunction in asymptomatic hemodialysis patients in the light of the current echocardiographic guidelines. Int J Cardiovasc Imaging. 2019;35(2):313–7. [DOI: 10.1007/s10554-019-01564-2] [PMID: 30815807]
15. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS, et al. The Framingham predictive instrument in chronic kidney disease. J Am Coll Cardiol. 2007;50(3):217–24. [DOI: 10.1016/j.jacc.2007.03.037] [PMID: 17631213]
16. Savoj J, Becerra B, Kim JK, Fusaro M, Gallieni M, Lombardo D, et al. Utility of Cardiac Biomarkers in the Setting of Kidney Disease. Nephron. 2019;141(4):227–35. [DOI: 10.1159/000495946] [PMID: 30726855]
17. Foundation NK. K / DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45(4 Suppl 3):S1–153. [PMID: 15806502]
18. Aghsaeifard Z, Firouzi R, Alizadeh R. Predisposing factors and uremic pericardial effusion among ESRD patients undergoing dialysis. Ann Med Surg (Lond). 2022;77:103579. [DOI: 10.1016/j.amsu.2022.103579] [PMID: 35444804]
19. Kittiskulnam P, Johansen KL. The obesity paradox: A further consideration in dialysis patients. Semin Dial. 2019;32(6):485–9. [DOI: 10.1111/sdi.12834] [PMID: 31338891]
20. Chirakarnjanakorn S, Navaneethan SD, Francis GS, Tang WH. Cardiovascular impact in patients undergoing maintenance hemodialysis: Clinical management considerations. Int J Cardiol. 2017;232:12–23. [DOI: 10.1016/j.ijcard.2017.01.015] [PMID: 28108129]
21. Rauchhaus M, Koloczek V, Volk H, Kemp M, Niebauer J, Francis DP, et al. Inflammatory cytokines and the possible immunological role for lipoproteins in chronic heart failure. Int J Cardiol. 2000;76(2–3):125–33. [DOI: 10.1016/s0167-5273(00)00224-2] [PMID: 11104867]
22. Aksu U, Aksu D, Gulcu O, Kalkan K, Topcu S, Aksakal E, et al. The effect of dialysis type on left atrial functions in patients with end-stage renal failure: A propensity score-matched analysis. Echocardiography. 2018;35(3):308–13. [DOI: 10.1111/echo.13774] [PMID: 29226431]
23. Zhang L, Zhang X, Xue S. Left Heart Failure Caused by Capacity Overload in Peritoneal Dialysis Patients. Biomed Res Int. 2022;2022:5422333. [DOI: 10.1155/2022/5422333] [PMID: 35607309]
24. Ursi R, Pesce F, Albanese M, Pavone V, Grande D, Ciccone MM, Iacoviello M. Reverse cardiac remodeling after fluid balance optimization in patients with end-stage renal disease. Hemodial Int. 2022;26(3):345–50. [DOI: 10.1111/hdi.13019] [PMID: 35416387]
25. Park H, Desai R, Liu X, Smith SM, Hincapie-Castillo J, Henry L, et al. Medicare Bundled Payment Policy on Anemia Care, Major Adverse Cardiovascular Events, and Mortality among Adults Undergoing Hemodialysis. Clin J Am Soc Nephrol. 2022;17(6):851–60. [DOI: 10.2215/CJN.14361121] [PMID: 35589388]
26. Zhang H, Zhabyeyev P, Wang S, Oudit GY. Role of iron metabolism in heart failure: From iron deficiency to iron overload. Biochim Biophys Acta Mol Basis Dis. 2019;1865(7):1925–37. [DOI: 10.1016/j.bbadis.2018.08.030] [PMID: 31109456]
27. Macdougall IC, White C, Anker SD, Bhandari S, Farrington K, Kalra PA, et al; PIVOTAL Investigators and Committees. Intravenous Iron in Patients Undergoing Maintenance Hemodialysis. N Engl J Med. 2019;380(5):447–58. [DOI: 10.1056/NEJMoa1810742] Erratum in: N Engl J Med. 2019 Jan 14. [PMID: 30365356]

Фенотипови хроничне срчане инсуфицијенције код болесника лечених хемодијализом – искуство једног центра

Марија Добричић[1], Весна Пакић[1], Александра Арсеновић[1], Весна Пејовић[1], Александра Кузмановић[1], Миодраг Милић[1], Вишња Лежаић[2]

[1]Специјална болница за интерне болести, Лазаревац, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Увод/Циљ Срчана инсуфицијенција (СИ) главни је узрок морбидитета и морталитета болесника лечених хемодијализом (ХД).

Циљ ове студије пресека спроведене у једном центру био је да испита: 1) учесталост и карактеристике фенотипова СИ код ХД болесника; 2) повезаност СИ са традиционалним и нетрадиционалним факторима ризика за кардиоваскуларне болести.

Методе Укључили смо свих 96 болесника лечених ХД у Специјалној болници за интерне болести, Лазаревац, Србија, и утврдили преваленцију СИ са очуваном ејекционом фракцијом (ЕФ) – *SIpEF* (по критеријумима Европског кардиолошког друштва из 2016) и СИ са смањеном и умерено смањеном ЕФ – *SIrEF* + *SImrEF* – заједно у групи *SIrEF* (ЕФ < 50%) применом стандардизоване пост-ХД трансторакалне ехокардиографије. Процењивани су клинички, рутински лабораторијски и параметри запреминског статуса (биоимпедансном спектроскопијом).

Резултати Шездесет три од 96 испитаних болесника (65,6%) имало је СИ, од тога 42 *SIpEF* (66,7%), а 21 *SIrEF* (33,3%). *SIrEF* је била чешћа код старијих мушкараца, са дијабетичком нефропатијом као основном болешћу бубрега, са дужим периодом дијализе и код оних са претходном исхемијском болешћу срца. *SIpEF* је била чешћа код мушкараца, са нижим квалитетом ХД (*kT*/*V*) и вишим предијализним систолним крвним притиском. У мултиваријантној регресионој анализи *SIrEF* је била повезана са дијабетичком нефропатијом, хиперволемијом (позитивно) и триглицеридима (негативно), док је *SIpEF* била повезана негативно са хемоглобином, гвожђем и триглицеридима.

Закључак У циљу контроле болесника лечених ХД са СИ, поред одговарајуће терапије лековима, саветује се контрола волемије и одржавање концентрације триглицерида, хемоглобина и гвожђа приближно у границама нормале.

Кључне речи: срчана инсуфицијенција; хемодијализа; придружени фактори

DOI: https://doi.org/10.2298/SARH211221110N
UDC: 616.347-085.357

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Use of thyroid hormones in hypothyroid and euthyroid patients – a THESIS questionnaire survey of Serbian physicians

Biljana Nedeljković-Beleslin[1], Roberto Attanasio[2], Laszlo Hegedüs[3], Endre V. Nagy[4], Roberto Negro[5], Enrico Papini[6], Petros Perros[7], Jasmina Ćirić[1], Miloš Žarković[1]

[1]University of Belgrade, Faculty of Medicine, University Clinical Centre of Serbia, Clinic of Endocrinology, Diabetes, and Metabolic Disorders, Belgrade, Serbia;
[2]Associazione Medici Endocrinologi, Scientific Committee, Milan, Italy;
[3]Odense University Hospital, Department of Endocrinology and Metabolism, Odense, Denmark;
[4]University of Debrecen, Faculty of Medicine, Department of Medicine, Division of Endocrinology, Debrecen, Hungary;
[5]Vito Fazzi Hospital, Division of Endocrinology, Lecce, Italy;
[6]Regina Apostolorum Hospital, Department of Endocrinology and Metabolism, Rome, Italy;
[7]Royal Victoria Infirmary, Department of Endocrinology, Newcastle upon Tyne, United Kingdom

SUMMARY

Introduction/Objective Hypothyroidism is a common disease and treatment with levothyroxine (LT4) is effective. However, variations in management are frequent.
The aim of this study was to identify practices and attitudes of Serbian physicians relating to the treatment of hypothyroidism.

Methods An anonymized questionnaire was distributed electronically to members of the Serbian Thyroid Society, Serbian Association of Endocrine Surgeons, and Section for Endocrinology of the Serbian Medical Society.

Results Out of 170 invitations, 99 responses were received. LT4 was the first choice for the treatment of hypothyroidism in 90% of patients. After starting LT4 replacement therapy most respondents would recheck thyroid-stimulating hormone (TSH) in 4–6 weeks (n = 51, 62%) and in eight weeks (n = 29, 35%). In total, 61% of respondents (n = 60) indicated that they would consider treating euthyroid patients with LT4, the commonest indication being female infertility with high levels of thyroid antibodies (54%, n = 50). More than half respondents (58%, n = 45) would recommend combined LT4 + LT3 therapy for patients on LT4 with normal serum TSH who still complain of symptoms of hypothyroidism. 53% (n = 41/77), reported that the frequency of patients with normal serum TSH who still complain of hypothyroid symptoms is less than 5%.

Conclusion LT4 was the first choice of therapy for the treatment of hypothyroid patients, whereas LT3 + LT4 combination treatment is considered in patients with persistent symptoms of hypothyroidism despite normalization of TSH. The most common indication for thyroid hormone treatment in euthyroid patients was female infertility with high levels of thyroid antibodies. Alternative LT4 formulations like liquid solution or soft-gel capsules –formulations presently not available in Serbia, were largely reserved for specific conditions (interfering drugs, malabsorption, inability to take LT4 in the fasting state, unexplained poor biochemical control of hypothyroidism).

Keywords: THESIS; survey; Serbia; thyroid hormones; hypothyroidism; levothyroxine

INTRODUCTION

Hypothyroidism is a common disease affecting approximately 3% of the European population [1]. The treatment of choice for hypothyroidism is levothyroxine (LT4). For optimal efficacy, the traditional tablet formulation requires that patients avoid concomitant ingestion with food, drinks, and certain medications. Some comorbidities influence the bioavailability of LT4 and may mandate repeated-dose adjustments. In such situations, other formulations, like LT4 oral solution could have an increased absorption rate in comparison to LT4 tablets, and potentially could be a better choice [2]. As 5–10% LT4 treated hypothyroid patients have persistent complaints despite serum thyroid-stimulating hormone (TSH) values within the reference range, the combination of LT3+LT4 therapy has been proposed as an experimental treatment modality [3].

Although numerous papers publications including the European Thyroid Association (ETA) guidelines [4] are available concerning this topic, the choice of therapy is influenced by local/regional conditions and traditions.

In Serbia, LT4 tablets is the only formulation currently available, and the only formulation included in National guidelines on hypothyroidism published by the Serbian Thyroid Society and the Ministry of Health [5]. The health care system in Serbia is mainly public and based on universal health coverage but private healthcare is also available. The majority

Received • Примљено: December 21, 2021
Revised • Ревизија: November 3, 2022
Accepted • Прихваћено: November 16, 2022
Online first: November 22, 2022

Correspondence to:
Biljana NEDELJKOVIĆ BELESLIN
University of Belgrade
Faculty of Medicine
Clinic of Endocrinology, Diabetes and Metabolic Disorders
University Clinical Centre of Serbia
Belgrade
Serbia
biljana_beleslin@yahoo.com

of hypothyroid patients are managed by endocrinologists in secondary care. The Balkan Peninsula and the Serbian region are iodine deficient. Iodine prophylaxis was introduced in 1951 and a recent national survey established that iodine deficiency disorders have been eliminated [6].

LT4 is an effective treatment for hypothyroidism, however, controversies such as the use of combination treatment or unorthodox indications and variations in management exist. This study was part of a larger project investigating thyroid practices across Europe.

The aim was to identify practices and attitudes of Serbian physicians relating to the treatment of hypothyroidism.

METHODS

A total of 99 members of either the Serbian Thyroid Society, Serbian Association of Endocrine Surgeons, or Section for Endocrinology of the Serbian Medical Society participated in a web-based survey investigating the treatment of hypothyroidism. The survey was conducted using Lime-Survey, an open-source online survey tool. Lime-Survey was hosted on servers belonging to the Faculty of Medicine, University of Belgrade. The Treatment of Hypothyroidism in Europe by Specialists: An International Survey (THESIS) questionnaire was translated and adapted to Serbian by a bilingual clinician and further checked by two senior physicians fluent in English. The survey contained 25 questions, eight related to the demographic and professional characteristics of the responder, and 17 related to hypothyroidism treatment. Survey responses were collected anonymously and stored electronically. The survey platform automatically blocked repeated submissions from the same computer. A total of 170 physicians were invited, and 99 responded and participated in the survey following two reminders (response rate 58%). According to the latest Health Statistical Yearbook of the Republic of Serbia, from 2019, the total number of practicing endocrinologists and endocrine surgeons is 184 and 10, respectively [7]. The survey opened on 25 September 2020 and closed on 26 November 2020.

Statistical analysis

Statistical analysis was performed using multinomial regression for nominal variables, ordinal logistic regression for ordinal data and logistic regression for binomial data. For table analysis, χ^2 and Fisher exact test were used. Statistical significance (alpha error) was at 0.05 level. R statistical environment was used for the analyses.

Ethical approval

Responses on the online platform were collected anonymously. Respondents agreed to fill out the survey voluntarily, were aware that they could at any point leave the survey and did not receive any incentives. Personal identifiable data were not collected. Institutional board review was not necessary as the survey was anonymous.

RESULTS

The demographic and professional characteristics of the participants

The demographic and professional characteristics of the participants are presented in Table 1. Most of the physicians were women aged 40–60 years, with 20–40 years of medical practice. The vast majority of respondents were endocrinologists and were employed at university centers. Importantly, nearly all respondents managed hypothyroid patients in their routine practice. Twenty-seven (27%) of 99 respondents were not members of any endocrine society. Twenty-seven (27%) were members of the ETA, two (2%) of the American Thyroid Association, and 66 (66%) of the other national societies. Some of the respondents were members of multiple societies.

Table 1. Characteristics of respondents

Gender	n (%)
Male	30 (30.3%)
Female	69 (69.7%)
Age (years)	**n (%)**
20–30	4 (4%)
31–40	19 (19.2%)
41–50	34 (34.3%)
51–60	33 (33.3%)
61–70	9 (9.1%)
70 +	0
Years of medical practice	**n (%)**
< 20	40 (40.4%)
21–40	58 (58.6%)
> 40	1 (1%)
Specialization*	**n (%)**
Endocrinology	65 (66%)
Internal medicine	53 (54%)
Pediatric Endocrinology	4 (4%)
Nuclear Medicine	1 (1%)
Surgery	6 (6%)
Other	0
Place of employment*	**n (%)**
University Centre	71 (72%)
Regional hospital	15 (15%)
Private clinic	19 (19%)
General Practice	1 (1%)
Basic researcher	4 (4%)
Treats thyroid patients	**n (%)**
Daily	65 (68%)
Weekly	29 (30%)
Rarely	2 (2%)
Missing	3 (3%)
Number of patients with hypothyroidism treated	**n (%)**
10–50 / year	9 (9.4%)
51–100 / year	23 (24%)
> 100 / year	62 (64.6%)
rarely	2 (2%)
Missing	3 (3%)

*Total is greater than the number of respondents because some respondents choose multiple answers

First choice of therapy for hypothyroidism

LT4 was the primary choice of therapy for the treatment of hypothyroid patients for most respondents in this survey (Table 2). Generally, they reported that for most

Table 2. First choice of therapy for the treatment of hypothyroid patients

Thyroid hormone	Responses, n (%)
LT4	88 (90%)
LT3	2 (2%)
Desiccated thyroid extract	1 (1%)
LT4 and LT3 combination	7 (7%)
Missing	1

Table 3. Responses on indications for thyroid hormone treatment in euthyroid subjects

Indications	Responses, n (%)	Total responses, (n)
Unexplained fatigue	29 (32%)	92
Obesity resistant to life-style interventions	21 (23%)	92
Severe hypercholesterolemia, as a complementary treatment	26 (28%)	92
Depression resistant to anti-depressant medications	22 (24%)	92
Female infertility with a high level of thyroid antibodies	50 (54%)	92
Simple goiter growing over time	25 (27%)	92
No, treatment is never indicated for these patients	36 (39%)	92

of their patients they have control over the type of LT4 brand that they prescribe (n = 82; 92% responders, 89 responses). Thirty-three percent of physicians (n = 28 out of 86) thought that LT4 tablets are least liable to variable absorption compared to 27% (n = 23 out of 86) who selected soft-gel capsules, and 11% (n = 9 out of 86) liquid solution. Twenty-six respondents (30%) did not expect significant differences between the preparations.

Monitoring thyroid hormone treatment

After starting LT4 replacement therapy most respondents would recheck TSH in 4–6 weeks (n = 51, 62%) and in eight weeks (n = 29, 35%). Only 1% (n = 1) would recheck TSH after two weeks, and 1% (n = 1) based their choice of interval on clinical assessment. Even after switching to a different formulation or changing from one manufacturer's LT4 tablet to another most respondents would recheck TSH in 4–6 weeks (n = 34, 42%, 82 responses) and in eight weeks (n = 22, 27%, 82 responses). However, a number of physicians would not recheck TSH (n = 14, 17%, 82 responses) or would recheck TSH according to clinical judgment (n = 12, 15%, 82 responses).

Treating patients with dietary supplements

Dietary supplements were deemed to be acceptable in addition to thyroid hormones mainly in patients with hypothyroidism due to autoimmune thyroiditis (n = 57, 70%, 82 responses).

Treating euthyroid subjects with thyroid hormones

In euthyroid patients, almost 40% (n = 36 out of 92 responses) of respondents would never recommend LT4. The most common indication for thyroid hormone treatment in euthyroid patients was female infertility with a high level of thyroid antibodies (54%, n = 50 out of 92 responses). For all other indications, the distribution of those who would recommend thyroid hormone was similar (23–31%). The results are presented in Table 3.

Using different LT4 formulations

Table 4 summarizes the preferences of the respondents regarding the administration of LT4 as a tablet, soft-gel capsule, and liquid solution. Soft-gel capsule and liquid solution are presently not available in Serbia. In all clinical scenarios, the liquid solution was the last choice.

Combination treatment with LT4 + LT3

Regarding the possible indications for combined LT4 + LT3 treatment, more than half respondents would recommend combined LT4 + LT3 therapy to patients with normal serum TSH who still complain of symptoms suggestive of hypothyroidism (Table 5).

Table 4. Responses on the choice of LT4 formulations in different clinical scenarios.

Scenario	Formulation	Total responses, (n)
A patient who self-reports intolerance to various foods raising the possibility of celiac disease, malabsorption, lactose intolerance, or intolerance to common excipients	Tablets 24 (28%) Soft-gel capsules 29 (34%) Liquid solution 11 (13%) No major changes with the different formulations 22 (26%)	86
A patient established on generic LT4 who has unexplained poor biochemical control of hypothyroidism*	Tablets 46 (56%) Soft-gel capsules 16 (20%) Liquid solution 8 (10%) No major changes with the different formulations 12 (15%)	82
A patient with poor biochemical control who is unable (due to a busy lifestyle) to take LT4 fasted and separate from food/drink	Tablets 17 (21%) Soft-gel capsules 31 (38%) Liquid solution 14 (17%) No major changes with the different formulations 20 (24%)	82
A patient established on LT4 who has good biochemical control of hypothyroidism but continues to have symptoms	Tablets 37 (45%) Soft-gel capsules 17 (21%) Liquid solution 4 (5%) No major changes with the different formulations 24 (30%)	82

Persistence of hypothyroid symptoms despite normal serum TSH

About half of the respondents (53%) considered that the frequency of patients with normal serum TSH who still complain of hypothyroid symptoms is less than 5% and that this has not changed in the last five years (49%).

Physicians with hypothyroidism in relation to their own treatment

Five respondents (7%) indicated that they had hypothyroidism. One experienced excessive

Table 5. Possible indications for combined LT4 + LT3 treatment

Possible indications	Responses, n (%)*	Total responses, n
For a short period, in patients recovering from protracted hypothyroidism	17 (22%)	78
In patients with normal serum TSH who still complain of symptoms suggestive of hypothyroidism	45 (58%)	
In hypothyroid patients with normal serum TSH who complain of unexplained weight gain	10 (12%)	
Due to the low quality of available evidence, combined therapy should never be used	24 (31%)	

TSH – thyroid-stimulating hormone

Table 6. Perceptions about the persistence of hypothyroid symptoms despite normal serum thyroid-stimulating hormone

Frequency	Responses, n (%)	Total responses, n
< 5%	41 (53%)	78
6–10%	17 (22%)	
11–30%	7 (9%)	
> 30%	0	
Not sure	13 (17%)	
Trends		
I am seeing more such cases	8 (10%)	78
I am seeing fewer such cases	13 (17%)	
No change	38 (49%)	
Not sure	19 (24%)	

tiredness and none of them tried combination treatment with LT4 + LT3 or desiccated thyroid extract. Out of 69 non-hypothyroid physicians, 51 (74%) would not try combination treatment with LT4 + LT3 or desiccated thyroid extract if they experienced persistent symptoms on LT4. However, out of 51 physicians who would not treat themselves 32 (62.7%) would treat their patients with the LT4 + LT3 combination.

Correlations between baseline characteristics and responses

Multivariate analysis of answers based on the respondents' age, gender, specialization, and years of medical practice did not influence physicians' answers while the place of employment and number of patients treated per year showed some trends.

Physicians treating a high volume of hypothyroid patients (over 100 patients per year) tended to monitor the serum TSH at eight weeks rather than to 4–6 weeks after initiation of LT4 treatment compared to other physicians ($p = 0.047$, OR = 2.9).

University-based physicians (57%) were less inclined than other physicians (90%) to use combined LT4 + LT3 to treat persistent symptoms in patients with normal TSH ($p < 0.01$, OR = 0.1).

By multivariate analysis using the place of employment and number of patients treated, the use of LT4 + LT3 to treat obesity was less likely by university-based physicians ($p < 0.01$ OR = 0.04) and by physicians treating a large number of patients (over 100, $p < 0.01$, OR = 0.08), than the rest of the responders. Using the same multivariate analysis, university-based physicians strongly agreed with the statement that LT4 + LT3 combination should never be used ($p < 0.01$, OR = 7.6), compared to other physicians.

Endocrinologists employed at university centers agreed with the statement that chronic fatigue syndrome was the cause of the persistence of hypothyroid symptoms despite normal serum TSH (OR = 7.3), while those who treated more than 50 thyroid patients per year disagreed with this statement (OR = 0.09).

Only 1 out of 10 endocrinologists employed at university hospitals considered "normal serum TSH in hypothyroid patients who complain of unexplained weight gain" as possible indications for combined LT4 + LT3 treatment.

A total of 43% of endocrinologists employed at university hospitals would never use LT4 + LT3 therapy due to the low quality of available evidence (OR = 6.2).

DISCUSSION

The current study was the first of its kind among Serbian endocrinologists.

The typical Serbian endocrinologist respondent is female, 40–60 years old with 20–40 years of medical practice. Most endocrinologists are employed at a university center and are members of the national endocrine society.

Almost all guidelines indicate that LT4 is the only recommended option for the treatment of hypothyroidism. The ETA recommendations commented on the possibility of LT4 + LT3 combination therapy also, but rather as a short-term trial or last option in patients who do not respond sufficiently to LT4 treatment [4]. Attitudes of Serbian physicians are in line with these recommendations. LT4 is the first choice of therapy for 90% of Serbian physicians. At variance with evidence-based recommendations, 7% of the physicians would use the LT4 + LT3 combination as the first choice, although this formulation is not available on the Serbian market.

After the start of the LT4 replacement therapy, most respondents would recheck TSH in 4–6 weeks (62%) and in eight weeks (35%). The volume of patients seen significantly influenced the choice of monitoring interval, as physicians treating with more than 100 patients per year tend to use an eight-week monitoring interval ($p = 0.047$, OR = 2.9, compared to physicians with a lower-case load who monitor their patients at shorter intervals). Similarly, after a change of the LT4 manufacturer, most respondents would check TSH in 4–6 weeks (42%) and in eight weeks (27%). On the other hand, 17% would not check TSH at all, or according to clinical judgement (15%). The longer interval between thyroid function tests preferred by respondents with the high number of hypothyroid patients can be explained that by the assumption that in a busy practice prolonging the monitoring interval also reduces the clinician's workload (either perceptually or really). However, we could not confirm a similar trend after the LT4 manufacturer change scenario. A significant percentage of physicians (32%) would not routinely check TSH

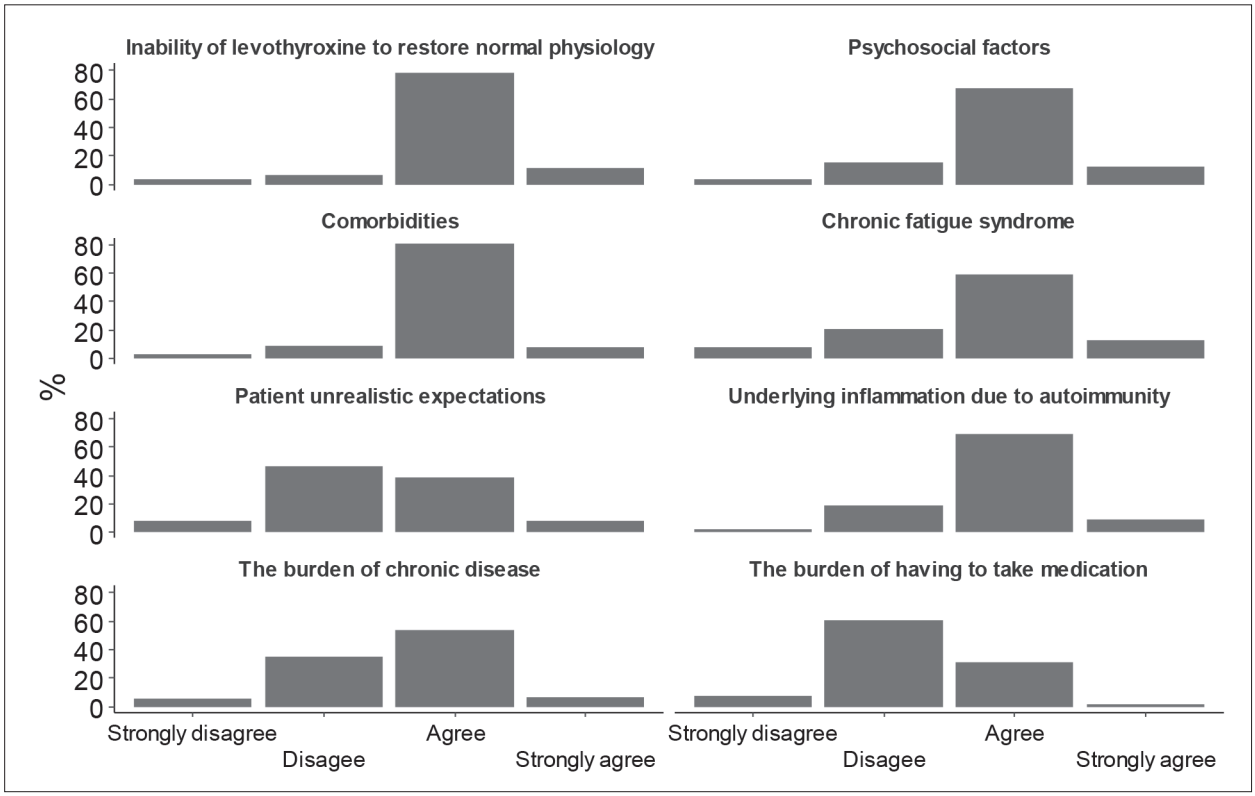


Figure 1. Distributions of a degree of agreement with the explanations for the persistence of hy-pothyroid symptoms despite normal serum thyroid-stimulating hormone; counts on the y-axis

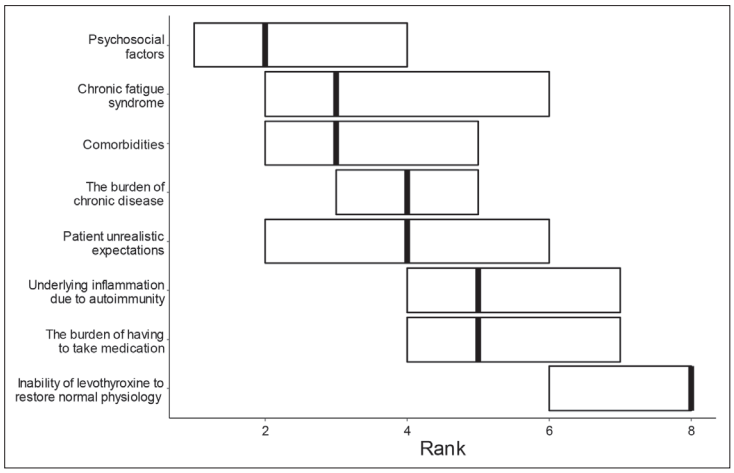


Figure 2. Physician's ranking of the explanations for the persistence of hypothyroid symp-toms despite normal serum thyroid-stimulating hormone (1 is the most likely and 8 is the least likely explanation); the bold line represents the median and boxes the 95% confidence limits

after a change in the formulation of LT4, probably based on confidence in the bioequivalence of the preparations.

More than half respondents (58%) would recommend combined LT4 + LT3 therapy to patients with normal serum TSH who still complain of symptoms suggestive of hypothyroidism. On the other hand, 31% reported no indication for combined treatment due to the low quality of available evidence for efficacy. Of the latter, the majority worked at the university clinic ($p < 0.001$, OR = 7.64). However, 21 out of 99 respondents did not answer this question. Working at the university clinic was the only factor we could identify for not answering this question ($p = 0.035$, OR = 3.55). Even if we assume that all missing responses from university-affiliated physicians are negative, the conclusion remains unchanged: respondents working at university clinics consider that there is no indication for combined treatment ($p = 0.002$, OR = 6.50).

This approach of the majority of Serbian respondents appears not consistent with the ETA guidelines that recommend only a short trial of treatment for patients who complain of hypothyroid like symptoms after the attainment of biochemical euthyroidism.

Among Serbian physicians' dietary supplements are a popular adjunct to the treatment of hypothyroidism mainly in patients with hypothyroidism due to autoimmune thyroiditis (70%). Only 8.5% of physicians responded that supplements should never be used. Despite lack of evidence, many ETA members recommend selenium supplementation in Hashimoto's thyroiditis [8].

Physician perceptions of persistence of hypothyroid symptoms despite normal serum TSH in Serbia are different to the previously published data of THESIS study from other European countries. In Serbia, 53% of the physicians think that the prevalence of patients with normal TSH and persistent symptoms of hypothyroidism is less than 5%. Also, 49% of Serbian physicians think that there has been no change in number the prevalence of such patients over recent years and 17% think it is decreasing. This pattern is more similar to Romanian and Bulgarian data and different to the Danish data implying that regional differences

in patient perception of symptoms and/or physicians' approach to patient complaints [9]. Also, this survey was conducted during the COVID-19 pandemic, when most physicians were working in the COVID hospitals. That could have influenced physicians' perceptions of their current and previous experiences.

Almost 40% of respondents would never recommend LT4 treatment for euthyroid patients. The most common indication for thyroid hormone treatment in euthyroid patients was female infertility with high levels of thyroid antibodies (54%). Such practice is in contrast with the available evidence – a large prospective study and a recently published randomized clinical trial refuted any benefit of LT4 treatment for female infertility with a high level of thyroid antibodies [10, 11]. Surprisingly, all other indications were also selected in significant percentages (23–31%) which are not in line with current recommendations and differ from the results of other THESIS publications [12, 13, 14]. Such an approach to patients that implies unnecessary treatment with LT4 carries the risk of over-replacement which can have detrimental long-term physical and psychological consequences [15]. It is interesting to note that physicians affiliated with university hospitals were significantly less likely to treat euthyroid patients for non-evidence-based indications (fatigue OR = 0.35, obesity OR = 0.29, hyperlipoproteinemia OR = 0.25, depression OR = 0.33), except for female infertility with high levels of thyroid antibodies and goiter increasing in size. Therefore, the only risk factor for the use of LT4 for some non-evidence-based indications was working in a non-university hospital. However, we could not identify other or universal risk indicators for this physician behavior. Furthermore, we did not explore patient preferences that could significantly influence physicians' behavior.

The development of new oral formulations as liquid preparation and soft gel capsules represents the most recent advance regarding LT4 therapy. They are mainly indicated for specific conditions, like malabsorption, interfering drugs, inability to take LT4 in the fasting state or unexplained poor biochemical control of hypothyroidism [16]. However, Serbian endocrinologists still preferred tablets and thought that there were no major changes with the different formulations. The liquid solution was the least chosen formulation for all clinical scenarios as presented in Table 4. This is most probably due to a fact that tablets from only two manufacturers are available in Serbia. Considering that soft-gel capsules and liquid solution are more expensive, and they are not available in Serbia, Serbian endocrinologists do not recommend and do not have experience with them.

Interest in measuring satisfaction and quality of life (QOL) with regards to healthcare has grown in recent years and is considered an important patient-reported outcome measure [17, 18]. Population studies have confirmed that 5–30% of patients with a diagnosis of hypothyroidism treated with LT4 alone continue to have symptoms compared to controls even when the serum is within the normal reference range [19, 20, 21].

Most physicians agreed that the main reasons for the persistence of hypothyroid symptoms despite normal serum TSH include psychosocial factors, the inability of LT4 to restore normal physiology, presence of underlying inflammation due to autoimmunity, comorbidities, and chronic fatigue syndrome.

Major determinants of Serbian physician opinions and preferences are practice volume and practice settings. Physicians working in the university setting and at high volume practices had different opinions and preferences compared to other physicians.

From the patients' point of view, an online survey by the British Thyroid Foundation [22] showed that there was no association between satisfaction or QOL with a type of thyroid hormone replacement treatment for hypothyroidism. Patient expectations, poor experiences with healthcare professionals and lack of information from the general practitioner on hypothyroidism had a major impact on satisfaction and QOL.

Limitations of the survey

Since the survey was conducted during the COVID-19 pandemic the number of physicians who participated in this survey may not be representative especially of those employed at regional hospitals. Also, those who responded were about 50% of the total number of relevant clinicians in Serbia.

CONCLUSION

Serbian physicians preferred LT4, as the first choice of therapy for the treatment of hypothyroid patients. LT3 + LT4 combination treatment is mainly considered in patients with persistent symptoms of hypothyroidism who are biochemically euthyroid. In a biochemically euthyroid patient, the most common indication for thyroid hormone treatment was female infertility with a high level of thyroid antibodies. Alternative LT4 formulations, like liquid solution or soft-gel capsules, were recommended for patients with suspected or proven malabsorption, use of interfering drugs, lifestyle issues and unexplained poor biochemical control of hypothyroidism.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Conflict of interest: None declared.

REFERENCES

1. Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab. 2014;99(3):923–31. [DOI: 10.1210/jc.2013-2409] [PMID: 24423323]
2. Nagy EV, Perros P, Papini E, Katko M, Hegedüs L. New Formulations of Levothyroxine in the Treatment of Hypothyroidism: Trick or Treat? Thyroid. 2021;31(2):193–201. [DOI: 10.1089/thy.2020.0515] [PMID: 33003978]
3. Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MP. 2012 ETA Guidelines: The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism. Eur Thyroid J. 2012;1(2):55–71. [DOI: 10.1159/000339444] [PMID: 24782999]
4. Pearce SH, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S, et al. 2013 ETA Guideline: Management of Subclinical Hypothyroidism. Eur Thyroid J. 2013;2(4):215–28. [DOI: 10.1159/000356507] [PMID: 24783053]
5. Trbojević B, Žarković M, Artiko V, Beleslin B, Ćirić J, Ćirić S, et al. Nacionalni vodič dobre kliničke prakse za poremećaj rada štitaste žlezde. Beograd: Ministarstvo zdravlja Republike Srbije; 2011.
6. Iodine Global Network (IGN) – Serbia [Internet]. [cited 2022 May 19]. Available from: https://www.ign.org/serbia.htm
7. Jovanović V, Ivanović I, Krstić M, Medarevć A, Tomasević S, editors. Health Statistical Yearbook of Republic of Serbia 2019. Belgrade: Institute of Public Health of Serbia "Dr Milan Jovanović Batut"; 2020.
8. Winther KH, Papini E, Attanasio R, Negro R, Hegedüs L. A 2018 European Thyroid Association Survey on the Use of Selenium Supplementation in Hashimoto's Thyroiditis. Eur Thyroid J. 2020;9(2):99–105. [DOI: 10.1159/000504781] [PMID: 32257959]
9. Riis KR, Frølich JS, Hegedüs L, Negro R, Attanasio R, Nagy EV, et al. Use of thyroid hormones in hypothyroid and euthyroid patients: A 2020 THESIS questionnaire survey of members of the Danish Endocrine Society. J Endocrinol Invest. 2021;44(11):2435–44. [DOI: 10.1007/s40618-021-01555-y] [PMID: 33774809]
10. Plowden TC, Schisterman EF, Sjaarda LA, Zarek SM, Perkins NJ, Silver R, et al. Subclinical Hypothyroidism and Thyroid Autoimmunity Are Not Associated With Fecundity, Pregnancy Loss, or Live Birth. J Clin Endocrinol Metab. 2016;101(6):2358–65. [DOI: 10.1210/jc.2016-1049] [PMID: 27023447]
11. Dhillon-Smith RK, Middleton LJ, Sunner KK, Cheed V, Baker K, Farrell-Carver S, et al. Levothyroxine in Women with Thyroid Peroxidase Antibodies before Conception. N Engl J Med. 2019;380(14):1316–25. [DOI: 10.1056/NEJMoa1812537] [PMID: 30907987]
12. Negro R, Attanasio R, Nagy EV, Papini E, Perros P, Hegedüs L. Use of Thyroid Hormones in Hypothyroid and Euthyroid Patients; the 2019 Italian Survey. Eur Thyroid J. 2020;9(1):25–31. [DOI: 10.1159/000502057] [PMID: 32071899]
13. Borissova AMI, Boyanov MA, Attanasio R, Hegedüs L, Nagy E, Negro R, et al. Use of Thyroid Hormones in Hypothyroid and Euthyroid Patients: a THESIS Questionnaire Survey of Bulgarian Physicians. Journal Endocrinologia. 2020;25(4):299–309.
14. Niculescu DA, Attanasio R, Hegedüs L, Nagy E, Negro R, Papini E, et al. Use of Thyroid Hormones in Hypothyroid and Euthyroid Patients: a THESIS Questionnaire Survey of Romanian Physicians. Acta Endocrinol (Buchar). 2020;16(4):462–9. [DOI: 10.4183/aeb.2020.462] [PMID: 34084238]
15. Brandt F, Thvilum M, Almind D, Christensen K, Green A, Hegedüs L, et al. Hyperthyroidism and psychiatric morbidity: evidence from a Danish nationwide register study. Eur J Endocrinol. 2013;170(2):341–8. [DOI: 10.1530/EJE-13-0708] [PMID: 24282192]
16. Fallahi P, Ferrari SM, Ruffilli I, Ragusa F, Biricotti M, Materazzi G, et al. Advancements in the treatment of hypothyroidism with L-T4 liquid formulation or soft gel capsule: an update. Expert Opin Drug Deliv. 2017;14(5):647–55. [DOI: 10.1080/17425247.2016.1227782] [PMID: 27552635]
17. Batbaatar E, Dorjdagva J, Luvsannyam A, Savino MM, Amenta P. Determinants of patient satisfaction: a systematic review. Perspect Public Health. 2017;137(2):89–101. [DOI: 10.1177/1757913916634136] [PMID: 27004489]
18. Jackson JL, Chamberlin J, Kroenke K. Predictors of patient satisfaction. Soc Sci Med. 2001;52(4):609–20. [DOI: 10.1016/s0277-9536(00)00164-7] [PMID: 11206657]
19. Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM. Psychological well-being in patients on 'adequate' doses of l-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol (Oxf). 2002;57(5):577–85. [DOI: 10.1046/j.1365-2265.2002.01654.x] [PMID: 12390330]
20. Wekking EM, Appelhof BC, Fliers E, Schene AH, Huyser J, Tijssen J, et al. Cognitive functioning and well-being in euthyroid patients on thyroxine replacement therapy for primary hypothyroidism. Eur J Endocrinol. 2005;153(6):747–53. [DOI: 10.1530/eje.1.02025] [PMID: 16322379]
21. Panicker V, Evans J, Bjoro T, Asvold BO, Dayan CM, Bjerkeset A. A paradoxical difference in relationship between anxiety, depression and thyroid function in subjects on and not on T4: findings from the HUNT study. Clin Endocrinol. 2009;71(4):574–80. [DOI: 10.1111/j.1365-2265.2008.03521.x] [PMID: 19751298]
22. Mitchell A, Hegedüs L, Žarković M, Hickey JL, Perros P. Patient satisfaction and quality of life in hypothyroidism: An online survey by the British Thyroid Foundation. Clin Endocrinol (Oxf). 2021;94(3):513–20. [DOI: 10.1111/cen.14340] [PMID: 32978985]

Употреба тироидних хормона код хипотироидних и еутироидних болесника – анкета лекара у Србији *THESIS*

Биљана Недељковић-Белеслин[1], Роберто Атаназио[2], Ласло Хегедиш[3], Ендре В. Нађ[4], Роберто Негро[5], Енрико Папини[6], Петрос Перос[7], Јасмина Ћирић[1], Милош Жарковић[1]

[1]Универзитет у Београду, Медицински факултет, Универзитетски клинички центар Србије, Клиника за ендокринологију, дијабетес и болести метаболизма, Београд, Србија;
[2]Италијанско удружење клиничких ендокринолога, Научни комитет, Милано, Италија;
[3]Универзитетска болница Оденсе, Одељење за ендокринологију и метаболизам, Оденсе, Данска;
[4]Универзитет у Дебрецину, Медицински факултет, Одељење медицине, Одсек за ендокринологију, Дебрецин, Мађарска;
[5]Болница „Вито Фаци", Одсек за ендокринологију, Леће, Италија;
[6]Болница „Ређина Апостолорум", Одељење за ендокринологију и метаболизам, Рим, Италија;
[7]Болница краљице Викторије, Одељење за ендокринологију, Њукасл на Тајну, Уједињено Краљевство

САЖЕТАК

Увод/Циљ Хипотиреоза је често обољење које се ефикасно лечи левотироксином (ЛТ4), мада постоје извесне контроверзе везане за терапију.

Циљ рада је био испитивање ставова лекара у Србији према терапији хипотиреозе.

Методе Анонимна анкета је електронским путем послата члановима Српског тироидног удружења, Српског удружења ендокриних хирурга и члановима Ендокринолошке секције Српског лекарског друштва.

Резултати Од укупно 170 лекара којима је анкета упућена, 99 је одговорило. ЛТ4 је био прва линија лечења хипотиреозе за већину учесника анкете (90%). После започињања супституције ЛТ4 већина учесника би поновила хормон штитне жлезде (ТСХ) за 4–6 недеља (*n* = 51; 62%) или осам недеља (*n* = 29; 35%), 61% учесника анкете (*n* = 60) лечило би еутироидне болеснике са ЛТ4, а најчешћа индикација је био женски инфертилитет са високим нивоом антитироидних антитела (54%, *n* = 50). Више од половине учесника (58%, *n* = 45/77) препоручила би комбиновану терапију ЛТ4 + ЛТ3 болесницима на ЛТ4 са нормалним вредностима ТСХ који и даље имају симптоме хипотироидизма. Укупно 53% учесника (*n* = 41/77) сматра да је учесталост болесника са нормалним ТСХ који се и даље жале на симптоме хипотироидизма мања од 5%, а 49% има утисак да се то није променило за последњих пет година.

Закључак ЛТ4 је био прва линија лечења хипотиреозе, док би комбиновану терапију ЛТ3 + ЛТ4 већина учесника препоручила болесницима са перзистентним симптомима хипотиреозе упркос нормализованом нивоу ТСХ. Најчешћа индикација за лечење хормона штитне жлезде код еутироидних болесника је био женски инфертилитет са високим нивоом антитироидних антитела. Алтернативне формулације ЛТ4, попут течног раствора или гел-капсула које нису доступне у Србији, у анкети су углавном биле резервисане за специфична стања (лекови који ометају апсорпцију, стварна или сумња на малапсорпцију, немогућност узимања ЛТ4 наште, необјашњива лоша биохемијска контрола хипотироидизма).

Кључне речи: *THESIS*; анкета; Србија; тироидни хормони; хипотиреоза; левотироксин

DOI: https://doi.org/10.2298/SARH220524090M
UDC: 616.728.3-001.5-073

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Magnetic resonance imaging *vs.* arthroscopy in diagnosing anterior cruciate ligament and meniscus injuries – is there a difference

Milan Mirković[1], Aleksandar Crnobarić[1], Sanja Mirković[2], Andreja Baljozović[1,3], Vladan Stevanović[1,3], Miodrag Glišić[1,3], Aleksandar Jevtić[1,3], Nemanja Slavković[1,3], Zoran Baščarević[1,3]

[1]Banjica Institute of Orthopedics, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Sport and Physical Education, Belgrade, Serbia;
[3]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY

Introduction/Objective The knee joint is prone to injuries caused by direct or indirect trauma. The meniscus and ligament injuries, cannot be completely diagnosed with clinical examination; therefore, we use additional non-invasive and invasive diagnostic methods such as magnetic resonance imaging (MRI) and arthroscopy.
The aim was to compare the accuracy of MRI and objective knee findings based on arthroscopic examination in case of meniscus and anterior cruciate ligament injuries.

Methods The study involved 50 patients treated with elective surgery which mandatory involved arthroscopic visualization of the knee structures. We compared the MRI findings, obtained from different institutions, and arthroscopic knee findings for all the patients involved in the study.

Results There were 50 patients included in the study with mean age of 31 years.
MRI showed that Anterior cruciate ligament was damaged in 41 patients, while arthroscopy confirmed damage in 43 patients. Medial meniscus was damaged in 31 patients on MRI and in 27 on arthroscopic examination. Lateral meniscus was injured in 35 patients on MRI and arthroscopy showed damage in 32 patients. Using χ^2 test we found no significant difference between MRI and arthroscopy as diagnostic methods. Wilcoxon signed-rank test shows similar results between MRI and arthroscopy findings.

Conclusion A comparative analysis of MRI and arthroscopy diagnostic value in case of anterior cruciate ligament, medial meniscus and lateral meniscus injuries have shown that there is no significant difference between these two methods.

Keywords: magnetic resonance imaging; arthroscopy; meniscus; anterior cruciate ligament

INTRODUCTION

The knee joint is the largest and most complex joint in the human body. On the front side, the knee joint is not protected by a thicker muscular covering, and, due to this structural weakness, this joint is prone to injury by direct trauma and rotation. Twisting injuries are usually presented as a tear of the meniscus and ligaments [1]. Meniscal injuries are usually longitudinal and accompanied with anterior cruciate ligament (ACL) injuries in 55–65% of the cases. Meniscus and ligament injuries cannot be completely diagnosed by clinical examination; therefore, we use additional non-invasive and invasive diagnostic methods such as magnetic resonance imaging (MRI) and arthroscopy [2]. MRI has proved to be a quick and non-invasive diagnostic method, complementing clinical examination [3]. MRI has become a popular and practical tool on the basis of which we make the final conclusion about the ACL and meniscus condition and the choice of arthroscopy [4]. Arthroscopy can be used for the diagnosis and treatment, but it is at the same time an invasive method [1]. Arthroscopic examination lets us evaluate, visualize, and confirm if the diagnosis based on clinical examination and MRI is correct [4]. Pain with blockade after a twisting knee injury is a typical symptomatology. The anamnesis is usually clear. The tear is usually longitudinal pericapsular or, in some cases, bucket handle type. It happens to young people, especially athletes [5].

Injuries to the medial meniscus (MM) are much more common than to the lateral meniscus (LM). It occurs mostly when lower leg is in semi-flexion and fixed with the foot, followed by a sudden abduction and external rotation of the lower leg. In that moment, there is a strong torsional force on the meniscus being pinched between condyles [6].

Injuries to the LM are much less frequent; they are mostly presented as longitudinal tears, and the mechanism of injury is defined as a varus and internal rotation, most commonly referred to a fall on the bent leg [7].

ACL injury occurs by an indirect mechanism in case of twisting, flexion, and in cases of contact and deceleration. There is the pain feeling that something is broken ("cracked") in the knee, functional disability of the knee and acute painful knee effusion in the next few hours, up to 24 hours [8].

Received • Примљено: May 24, 2022
Revised • Ревизија: August 13, 2022
Accepted • Прихваћено: August 30, 2022
Online first: September 1, 2022

Correspondence to:
Zoran BAŠČAREVIĆ
Banjica Institute of Orthopedics
Mihaila Avramovića 28
11000 Belgrade, Serbia
zoran.bascarevic@iohbb.edu.rs

The aim of this work is to compare MRI and arthroscopic examination in meniscal and ACL injuries diagnosis.

METHODS

This retrospective study was conducted at the Banjica Institute for Orthopedic Surgery in Belgrade, Serbia from March 1, 2015 to July 1, 2015. The study involved 50 patients treated by elective arthroscopic knee surgery with preoperative MRI findings. Only patients with injured knee were included in the study. Exclusion criteria were previous arthroscopic surgery, absence of MRI and degenerative pathology. All MRI findings were interpreted by the leading author. We compared the MRI findings in terms of ACL, MM, and LM damage, obtained from different institutions, and arthroscopic findings for all the patients involved in the study. All surgeries were conducted in regional anesthesia by the same surgical team. Statistical data analysis was performed by χ^2 test and Wilcoxon signed-rank test. This study was done in accordance with standards of the institutional committee on ethics.

RESULTS

There were 49 males and one female included in the study with the mean age of 31 years (24–43 years).

MRI showed that ACL was damaged in 41 patients, while it was preserved in nine. The arthroscopy confirmed that ACL was damaged in 43 patients, while it was preserved in seven. Regarding MM, MRI showed damage in 31 patients, while in 19 it was preserved. The arthroscopic examination confirmed damage in 27 patients, while in 23 patients the finding on the MM was normal. LM was injured in 35 patients, while in 15 it was preserved, according to MRI findings. The arthroscopy confirmed LM damage in 32 patients, while no changes were observed in 18. Results of two compared diagnostic procedures are presented in Table 1.

Table 1. Results of magnetic resonance imaging (MRI) and arthroscopy (ASC) diagnostics in knee injuries

Part of the knee	Damaged/ preserved	MRI	ASC	p*	p**
ACL	Damage	41	43	0.317	0.585
	Preserved	9	7		
MM	Damage	31	27	0.248	0.417
	Preserved	19	23		
LM	Damage	35	32	0.366	0.523
	Preserved	15	18		

ACL – anterior cruciate ligament; MM – medial meniscus; LM – lateral meniscus;
*Wilcoxon signed-rank test;
**χ^2 test

The χ^2 test and Wilcoxon signed-rank test showed that there were not statistically significant differences between the two diagnostic methods for all three types of injury ($p > 0.05$), as presented in Table 1.

DISCUSSION

After clinical examination of a knee injury, additional diagnostics is usually required. In this study, we compared the results obtained by MRI and arthroscopy in meniscal and ACL knee injuries. Both methods have their limitations.

MRI offers precise insight in both intraarticular and extraarticular structures of the knee, while arthroscopy is mainly focused on intraarticular structures. Knee arthroscopy does not routinely recognize injuries of some soft tissue structures, e.g., superficial medial collateral ligament complex, structures of the posterolateral corner, or the extensor mechanism. Arthroscopy is inferior in the assessment of traumatic and infiltrative bone marrow abnormalities, which commonly follow meniscal injuries. MRI is also the preferred method for the diagnosis of synovial lesions [9].

MRI does not provide a dynamic assessment of soft-tissue knee structures like in arthroscopy. Meniscal tears and chondral defects can be assessed both by MRI and arthroscopic probing. The probing is especially useful in the postoperative meniscus to distinguish tear from postoperative signal or healing changes in a repaired tear [10].

Our results showed that ACL injury on arthroscopy was slightly more often positive than on MRI, while for MM and LM it was reversed as shown in Figure 1. One of the explanations is that decreased sensitivity of MRI in diagnosing ACL injury may be attributed to difficulties of displaying the ligament fully on the sagittal plane due to its anatomical obliquity passage across the joint, as depicted by some studies [11]. Diagnostic accuracy of ligamentous injuries has been improved by dynamic arthroscopic evaluation. Although MRI is very sensitive and specific in the diagnosis of complete ACL tears, the functional status and presence of partial tears may be better assessed by arthroscopy. The degree of the medial and lateral joint gap with valgus or varus stress during arthroscopy serves as an indicator of the severity of collateral ligaments injury. Also, dynamic posterior drawer test during the procedure with the knee flexed to 90° can assess posterior cruciate ligament incompetence [12].

It is necessary to be aware of some anatomical structures in the knee that may not be well visualized by MRI

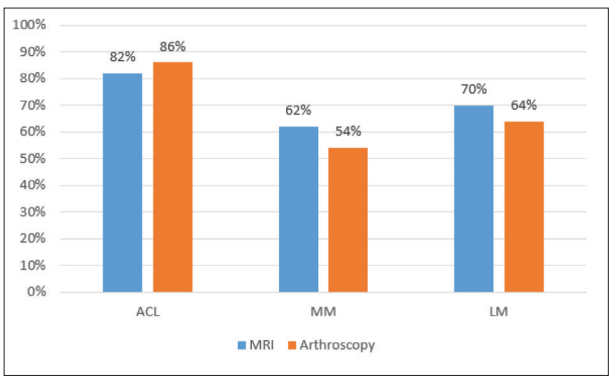


Figure 1. The comparison of anterior cruciate ligament (ACL), medial meniscus (MM), and lateral meniscus (LM) injuries found by magnetic resonance imaging (MRI) and arthroscopy

nor by arthroscopy. For example, the posterior horn of the MM that plays an important role in limiting anterior tibial translation may sometimes be difficult to evaluate with the standard anterior viewing portals [13].

In our study, we found that MRI and arthroscopy are equally valuable diagnostic tools, because the number of diagnosed injuries was approximately the same by both methods, for each type of knee injury. The obtained results are in accordance with the other studies in all parameters of testing [14, 15].

Diagnostic correlation between MRI and arthroscopy based on Wilcoxon signed-rank test showed that the p value was higher for LM than for ACL and MM. These results are comparable to a recent study by Duong et al. [16], who found 88% *vs*. 86% accuracy for lateral and medial meniscal lesions, respectively. In our study, a higher number of injuries to the LM compared to the medial one were observed using both diagnostic methods. One explanation could be the relatively small sample size, which is also comparable to the results form Duong et al. [16]. We believe that with an increase in the sample, the ratio of these injuries would be closer to literature data, which is also one of the limitations of the study.

The disadvantage of our research could be that not all MRI examinations were performed by the same technique.

CONCLUSION

Differences in accuracy between MRI and arthroscopy as diagnostic methods for ACL, MM and LM injuries should not be expected. The correlation between the two methods is higher for the LM than for the MM and the ACL.

Conflict of interest: None declared.

REFERENCES

1. Schnaiter JW, Roemer F, McKenna-Kuettner A, Patzak HJ, May MS, Janka R, et al. Diagnostic Accuracy of an MRI Protocol of the Knee Accelerated Through Parallel Imaging in Correlation to Arthroscopy. Rofo. 2018;190(3):265–72. [DOI: 10.1055/s-0043-119038] [PMID: 28950384]
2. Zheng T, Song G, Li Y, Zhang Z, Ni Q, Cao Y, et al. Clinical, Radiographic, and Arthroscopic Outcomes of Surgical Repair for Radial and Avulsed Lesions on the Lateral Meniscus Posterior Root During ACL Reconstruction: A Systematic Review. Orthop J Sports Med. 2021;9(3):2325967121989678. [DOI: 10.1177/2325967121989678] [PMID: 33796590]
3. Greif DN, Baraga MG, Rizzo MG, Mohile NV, Silva FD, Fox T, et al. MRI appearance of the different meniscal ramp lesion types, with clinical and arthroscopic correlation. Skeletal Radiol. 2020;49(5):677–89. [DOI: 10.1007/s00256-020-03381-4] [PMID: 31982971]
4. Hogea GB, Pătraşcu JM Jr, Săndesc MA, Bredicean AC, Nussbaum LA, Hogea LM, et al. The utility of indirect imagistic signs in the diagnosis of anterior cruciate ligament ruptures. Rom J Morphol Embryol. 2018;59(3):741–5. [PMID: 30534812]
5. Bronstein RD, Schaffer JC. Physical Examination of the Knee: Meniscus, Cartilage, and Patellofemoral Conditions. J Am Acad Orthop Surg. 2017;25(5):365–74. [DOI: 10.5435/JAAOS-D-15-00464] [PMID: 28406879]
6. Popović Z. Oboljenja kolena. In: Vukašinović Z. et al., editors. Specijalna ortopedija. 1st ed. Beograd: IOHB „Banjica"; 2004. p. 336–56.
7. Chien A, Weaver JS, Kinne E, Omar I. Magnetic resonance imaging of the knee. Pol J Radiol. 2020;85:e509–e531. [DOI: 10.5114/pjr.2020.99415] [PMID: 33101555]
8. Lecouvet F, Van Haver T, Acid S, Perlepe V, Kirchgesner T, Vande Berg B, et al. Magnetic resonance imaging (MRI) of the knee: Identification of difficult-to-diagnose meniscal lesions. Diagn Interv Imaging. 2018;99(2):55–64. [DOI: 10.1016/j.diii.2017.12.005] [PMID: 29396088]
9. Wang W, Li Z, Peng HM, Bian YY, Li Y, Qian WW, et al. Accuracy of MRI Diagnosis of Meniscal Tears of the Knee: A Meta-Analysis and Systematic Review. J Knee Surg. 2021;34(2):121–29. [DOI: 10.1055/s-0039-1694056] [PMID: 31390675]
10. Rizk B, Brat H, Zille P, Guillin R, Pouchy C, Adam C, et al. Meniscal lesion detection and characterization in adult knee MRI: A deep learning model approach with external validation. Phys Med. 2021;83:64–71. [DOI: 10.1016/j.ejmp.2021.02.010] [PMID: 33714850]
11. Machagge H, Mrita F, Muhamedhussen M, Haonga B, Mcharo CN. Evaluation of Accuracy of Clinical Examination and MRI on Diagnosing Anterior Cruciate Ligament and Meniscal Tears in Comparison to Diagnostic Arthroscopy among Patients Attending at Muhimbili Orthopedic Institute. Open J Orthop. 2021;11(12):353–70. [DOI: 10.4236/ojo.2021.1112034]
12. Alaia EF, Alaia MJ, Gyftopoulos S. MRI-Arthroscopy Correlation of Knee Anatomy and Pathologic Findings: A Teaching Guide. AJR Am J Roentgenol. 2018;211(6):1291–7. [DOI: 10.2214/AJR.18.19726] [PMID: 30332292]
13. DePhillipo NN, Cinque ME, Chahla J, Geeslin AG, Engebretsen L, LaPrade RF. Incidence and Detection of Meniscal Ramp Lesions on Magnetic Resonance Imaging in Patients with Anterior Cruciate Ligament Reconstruction. Am J Sports Med. 2017;45(10):2233–7. [DOI: 10.1177/0363546517704426] [PMID: 28463534]
14. Kulkarni OP, Pundkar GN, Sonar SB. A comparative study of MRI versus arthroscopic findings in ACL and meniscal injuries of the knee. Int J Res Orthop. 2018;4:198–202. [DOI: 10.18203/issn.2455-4510]
15. Singh N, Hanekom H, Suleman FE. The accuracy of magnetic resonance imaging diagnosis of non-osseous knee injury at Steve Biko Academic Hospital. SA J Radiol. 2019;23(1):1754. [DOI: 10.4102/sajr.v23i1.1754] [PMID: 31754541]
16. Duong TD, Tran DT, Do BNT, Tran HT, Le SM, Vu TT. Diagnostic value of clinical tests and Mri for meniscal injury in patients with anterior cruciate ligament injury: Case series study. Int J Surg Case Rep. 2021;88:106492. [DOI: 10.1016/j.ijscr.2021.106492] [PMID: 34655974]

Дијагностика повреде менискуса и предњег укрштеног лигамента колена магнетном резонанцом у односу на артроскопију – има ли разлике

Милан Мирковић[1], Александар Црнобарић[1], Сања Мирковић[2], Андреја Баљозовић[1,3], Владан Стевановић[1,3], Миодраг Глишић[1,3], Александар Јевтић[1,3], Немања Славковић[1,3], Зоран Башчаревић[1,3]

[1]Институт за ортопедију Бањица, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Универзитет у Београду, Факултет спорта и физичког васпитања, Београд, Србија

САЖЕТАК

Увод/Циљ Зглоб колена подложан је повредама узрокованим директном или индиректном силом. Повреде менискалних и лигаментарних структура не могу бити потпуно сагледане клиничким прегледом, те су неопходне инвазивне и неинвазивне дијагностичке методе попут магнетне резонанце (МР) и артроскопије.

Циљ овог рада је поређење прецизности налаза МР и објективног стања у колену утврђеног артроскопијом у случају повреде медијалног и латералног менискуса, као и предњег укрштеног лигамента.

Методе У истраживање смо укључили 50 болесника лечених елективним артроскопским процедурама. Код свих болесника упоређивали смо налазе МР, рађене у различитим установама, са налазима виђеним у колену уз помоћ артроскопа.

Резултати Студија је обухватила 50 болесника просечне старости 31 годину. МР је показала повреду предњег укрштеног лигамента код 41 болесника, док је оштећење потврђено артроскопијом код њих 43. Медијални менискус је био оштећен код 31 болесника на МР снимку, док је артроскопски верификовано 27 оштећења. Латерални менискус повређен је код 35 болесника на МР снимку, а артроскопски је оштећење уочено код њих 32. Тестом χ^2 није утврђена статистички значајна разлика између ове две методе у дијагностичком смислу. Примена Вилкоксоновог теста предзнака, као и анализа варијансе указали су на исти резултат.

Закључак Упоредном анализом дијагностичке вредности МР и артроскопије код повреда предњег укрштеног лигамента, медијалног и латералног менискуса утврдили смо да нема значајних разлика у дијагностичком смислу између ове две методе.

Кључне речи: магнетна резонанца; артроскопија; менискус; предњи укрштени лигамент

DOI: https://doi.org/10.2298/SARH211119094L
UDC: 616.517:616.25

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Association of body mass index with clinical variants of psoriasis

Olivera Levakov, Zorica Gajinov, Branislava Gajić, Ljuba Vujanović, Milana Ivkov-Simić, Zoran Golušin

University Clinical Centre of Vojvodina, Novi Sad, Serbia;
University of Novi Sad, Faculty of Medicine, Department of Dermatology, Novi Sad, Serbia

SUMMARY

Introduction/Aim Psoriasis is a common, chronic, immune-mediated, inflammatory and proliferative skin disease in which both genetic and environmental influences have a role in its pathogenesis. The relationship between psoriasis and obesity is probably bidirectional.
The aim of this study was to evaluate the association between psoriasis and obesity, whether a quantitative graduation of overweight using Body Mass Index (BMI) shows direct correlation with various clinical variants of psoriasis, disease duration and having positive family history of psoriasis.

Methods This prospective, observational descriptive cross-sectional study included 120 psoriatic patients who were referred to Clinic of Dermatovenereology at the University Clinical Centre of Vojvodina. Clinical variants of psoriasis were determined. Age, gender, duration of the disease, BMI and family history of psoriasis were measured and compared.

Results In total, 53.3% males and 46.7% females were included in this study. The mean age was 49.5 ± 15.5 years. The most present clinical variants of psoriasis were psoriasis vulgaris (55%) and psoriatic arthritis (30%). Most of the patients (42.5%) were overweight, 23.3% were obese, and 1.7% were morbidly obese. The mean BMI was high (27.7 ± 5.2). Mean duration of the disease was 15.6 ± 14.9 years. Positive family history of psoriasis was found in 33 (27.5%) patients.

Conclusion There was no correlation between the BMI and gender of the patients, psoriasis clinical variants, duration of the disease and positive family history of psoriasis. The slight positive correlation was found between BMI and age of psoriatic patients. That requires further studies that include physical activities questionnaire, considering that lack of physical activities in older patients might be an explanation.

Keywords: psoriasis; body mass index; BMI

INTRODUCTION

Psoriasis is a common, chronic, immune-mediated, inflammatory, and proliferative skin disease in which both genetic and environmental influences have a role in its pathogenesis [1]. It affects approximately 125 million people worldwide [2], and usually occurs with bimodal age distribution, with peaks in the third and sixth decade. Between 60% and 90% of patients have a family history of the disease [3, 4]. Psoriasis is systemic inflammatory disease accompanied with various comorbidities and exert major impact on both physical and emotional quality of life that is comparable with other major illnesses [5] as with that of cardiovascular and cancer patients [3]. About one third of psoriasis patients develop psoriatic arthritis (PsA), chronic inflammatory arthropathy associated with skin and nail psoriasis, belonging to the spondyloarthritis spectrum [6]. Nineteen percent of the psoriasis patients with arthritis suffer from operational inabilities that impact their quality of life greatly [3].

Obesity is defined as increase in body fat that exceeds the normal level. Usual tool used for estimation of body fat is Body Mass Index (BMI) and represents weight-to-height ratio. It is defined as the weight in kilograms divided by the square of the height in meters (kg/m^2) [1, 7]. In adults, BMI ≥ 25 is defined as overweight, and BMI ≥ 30 as obesity. It has become one of the leading health issues of the 21 century [8, 9]. The relationship between psoriasis and obesity is bidirectional. The question is – which comes first [3, 10, 11]?

Obesity may exacerbate the clinical manifestation of psoriasis or trigger the disease and present in early adulthood may promote the risk of developing PsA [1, 12]. It has been associated with a decreased response to systemic and biologic therapies [10, 11]. Both psoriasis and obesity could cause metabolic alterations that could be the main and triggering effects [13, 14, 15]. Chronic subclinical inflammation plays the major role in obesity and psoriasis, explained as "proinflammatory state" [16]. Adipose tissue is a large endocrine and secretory organ that produces adipokines and pro-inflammatory cytokines. In obesity, adipocytes are in a state of upregulation of pro-inflammatory adipokines, leptin and resistin, and stimulation of pro-inflammatory cytokine production by macrophages, and downregulation of anti-inflammatory adipokines [16]. Numerous studies revealed higher prevalence of obesity in psoriatic patients than in general population. There is two-fold increased risk for psoriasis in obese patients comparing to normal weight

Received • Примљено: November 19, 2021
Revised • Ревизија: May 16, 2022
Accepted • Прихваћено: September 6, 2022
Online first: September 14, 2022

Correspondence to:
Olivera LEVAKOV
University Clinical Centre of Vojvodina
University of Novi Sad
Faculty of Medicine
Department of Dermatology
Hajduk Veljkova 1
21137 Novi Sad
Serbia
olivera.levakov@mf.uns.ac.rs

subjects [10, 17]. A meta-analysis of 16 observational studies found a pooled odds ratio to be 1.66 for the correlation between psoriasis and obesity [5, 18]. Several studies have been reported the association between psoriasis and obesity measuring BMI [1, 10, 19]. In several cross-sectional studies has been noted that increased BMI coincides with a greater degree of psoriasis disease severity [5, 20, 21, 22]. Also, a positive correlation between the increased BMI and the severity of psoriasis expressed as psoriasis area and severity score has been determined [13, 21].

The main objective of this study was to determine the relation between BMI and psoriasis clinical variants, duration of psoriasis and positive family history for psoriasis in psoriasis patients.

METHODS

This prospective, observational descriptive cross-sectional study included 120 adult psoriasis patients, according to the order of referral to the Clinic of Dermatovenereology at the University Clinical Centre of Vojvodina in Novi Sad, Serbia, between January 2019 and February 2020. Exclusion criteria included the history of diabetes or hypothyroidism, or refusal to take part in the study and sign the informed consent. The study was approved by the institutional ethics committee. Patient clinical and demographic data were recorded in a checklist. All measurements were performed under fasting condition in the morning using a scale and a measuring type. To determine waist circumference measuring tape was placed at the uppermost part of the hip bone around the abdomen without causing compression on the skin. BMI (kg/m^2) classification in five categories was used, according to World Health Organization classification [7]: underweight (BMI < 18.50 kg/m^2), normal range (BMI 18.50–24.99 kg/m^2), overweight (BMI ≥ 25 kg/m^2), obese (BMI ≥ 30 kg/m^2), morbidly obese (BMI ≥ 40 kg/m^2).

Statistical analysis

SPSS Statistics for Windows, Version 23.0. (IBM Corp., Armonk, NY, USA) was used. χ^2 test was used for comparison of categorical data, t-test for comparison of continuous data and Pearson's correlation test for correlation analysis. The degree of correlation was measured by a Pearson's correlation coefficient and degree of correlation was interpreted according to the recommendation of the British Journal of Medicine [23].

RESULTS

Of 120 adult psoriasis patients included in this study 64 were males (54.3%) and 56 females (46.7%). The mean age was 49.5 ± 15.5 years. Age distribution of patients is presented in Figure 1.

Psoriasis clinical variants: Plaque psoriasis (vulgaris) (PV) was the most frequent clinical variant in total sample,

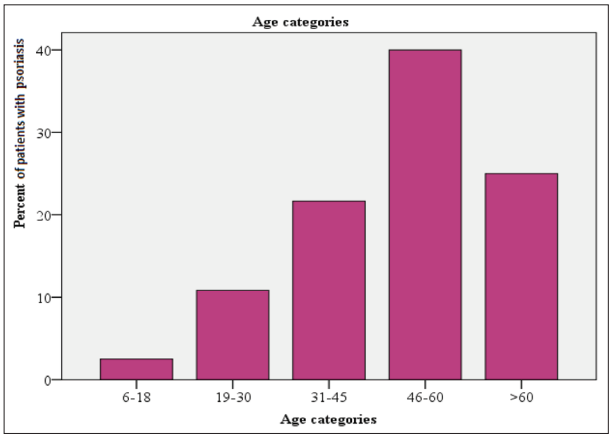


Figure 1. Percentage of psoriasis patients in each age category

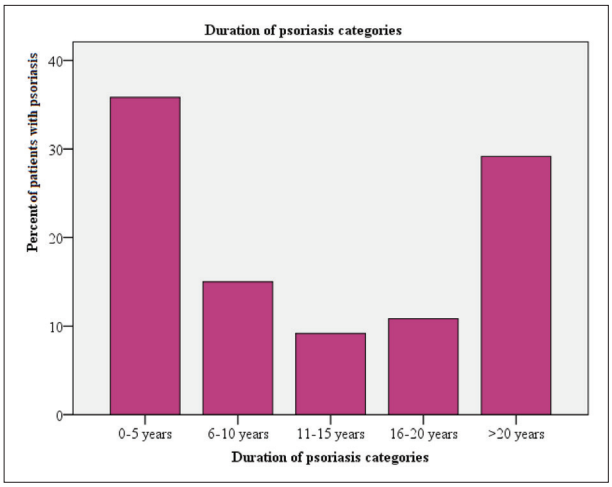


Figure 2. Percentage of psoriasis patients in each category of psoriasis duration

in 66 (55%) patients, and PsA was diagnosed in 36 (30%) patients. 10 (8.3%) patients presented with guttate psoriasis, three (2.5%) patients presented with palmo-plantar psoriasis, two (1.7%) patients with erythrodermic psoriasis, two (1.7%) patients with scalp psoriasis as the only manifestation of psoriasis, and one patient (0.8%) with generalized pustular psoriasis.

Duration of psoriasis was categorized in five-year intervals. Shortest duration of psoriasis, between 0–5 years was in 43 patients (35.8%); 18 (15%) patients were in the group in which the duration of psoriasis ranged from 6–10 years; 11 (9.2%) patients were in the third group where the duration was from 11–15 years; 13 (10.8%) patients were in the fourth group in which the duration of psoriasis was from 16–20 years and 35 (29.2%) patients had psoriasis over 20 years (fifth group) (Figure 2).

Body mass index in psoriasis patients – differences between gender, psoriasis clinical types and duration of psoriasis

In total sample of 120 patients, 51 (42.5%) of patients were overweight, 28 (23.3%) were obese and 2 (1.7%) were morbidly obese. The mean BMI was high (27.7 ± 5.2). The mean BMI in men was 28.4 kg/m^2 (SD 4.72, std error

Table 1. Frequency of different categories of body mass index in male and female patients with psoriasis

Parameters			Body mass index category					Total	p
			< 18.5	18.5–24.99	> 24.99	> 29.99	> 39.99		
Sex	m	n	0	16	30	17	1	64	0.283
		%	0	25	46.9	26.6	1.6	100	
	f	n	2	21	21	11	1	56	
		%	3.6	37.5	37.5	19.6	1.8	100	
Total		n	2	37	51	28	2	120	
		%	1.7	30.8	42.5	23.3	1.7	100	

Table 2. Body mass index in patient with various psoriasis clinical variants

Types	n	Mean	Standard deviation	Minimum	Maximum	p
Psoriasis vulgaris	66	27	4.4	18.3	37	
Guttate psoriasis	10	26.5	5.5	20.4	38.2	
Palmoplantar psoriasis	3	28.2	6.1	22.8	34.7	
Pustular psoriasis	1	34.1	.	34	34	
Erythrodermic psoriasis	2	25.7	1.6	24.6	26.8	0.456
Scalp psoriasis	2	25.6	8.9	19.4	31.9	
Psoriatic arthritis	36	29.4	6	20.5	49.3	
Total	120	27.7	5.1	18.2	49.3	

Table 3. Correlation of body mass index and duration of psoriasis

Parameters			Body Mass Index category					Total	p
			< 18.5	18.5–24.99	> 24.99	> 29.99	> 39.99		
Duration of psoriasis categories	0–5 years	n	1	16	18	8	0	43	0.233
		%	2.3	37.2	41.9	18.6	0	100	
	6–10 years	n	1	8	5	3	1	18	
		%	5.6	44.4	27.8	16.7	5.6	100	
	11–15 years	n	0	3	4	4	0	11	
		%	0	27.3	36.4	36.4	0	100	
	16–20 years	n	0	2	4	7	0	13	
		%	0	15.4	30.8	53.8	0	100	
	> 20 years	n	0	8	20	6	1	35	
		%	0	22.9	57.1	17.1	2.9	100	
Total		n	2	37	51	28	2	120	
		%	1.7	30.8	42.5	23.3	1.7	100	

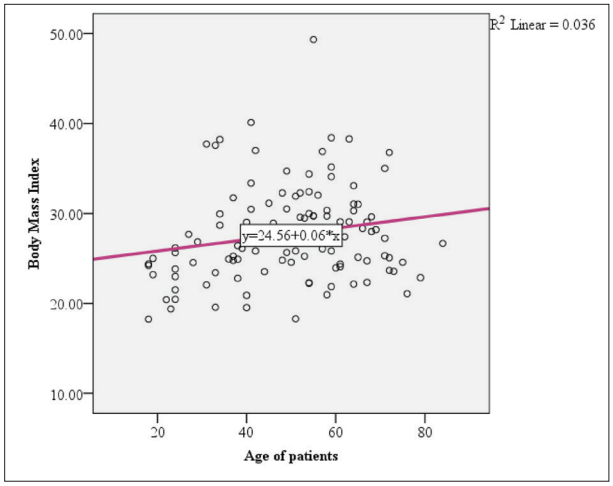


Figure 3. Correlation between body mass index and the age of patients

of mean 0.59) and in women 26.89 kg/m^2 (SD 5.54, std error of mean 0.74) and this difference is not statistically significant (t-test, p = 0.109). Neither the difference in frequencies of patient in each of BMI categories between man and women were statistically significant (χ^2 test, p = 0.283) (Table 1).

Albeit one pustular psoriasis patient has higher BMI than all other patients, due to small number of patients in pustular, erythrodermic and scalp psoriasis groups, these differences did not reach the statistical significance in this study. Also, BMI of patients with PsA was higher than BMI of patients with plaque psoriasis, but this did not reach statistical significance also (t-test, p = 0.456) (Table 2).

The BMI was not correlating with duration of psoriasis (p-value 0.059) (Table 3), and with age of the patients (p-value was 0.038) (Figure 3).

Correlation between BMI and patient age was low, and no correlation of BMI with duration of psoriasis could have been demonstrated (Table 4).

Positive family history of psoriasis was found in 33 (27.5%) patients. Mean BMI was similar in both groups, with and without positive family history of psoriasis, and BMI was not correlating with positive family history of psoriasis (t = -0.255, p = 0.799) (Table 5).

DISSCUSION

High BMI as an indicator of obesity has a negative impact on manifestation and severity of psoriasis. Obesity at an early age increases the risk of developing PsA. Prevention and early treatment of obesity may decrease the risk of PsA development and help in psoriasis management [1].

In our study, the observed higher BMI in patients with PSA confirmed results from the literature [1].

The mean BMI was high (27.7 ± 5.2), similar to prospective hospital based cross-sectional study that was

Table 4. Correlation of body mass index and the age of patients and the duration of psoriasis

Correlation		Body mass index
Age of patients	Pearson correlation	0.190*
	Sig. (2-tailed)	0.038
Duration of psoriasis	Pearson correlation	0.059
	Sig. (2-tailed)	0.525

Table 5. Body mass index in patients with and without family history of psoriasis

Parameters	Family history of psoriasis	n	Mean	Standard Deviation	Standard Error Mean
Body Mass Index	No	87	27.6241	5.28947	0.56709
	Yes	33	27.8936	4.85408	0.84499

conducted by Elobeid HE, et al. [1] in Sudan in which the mean BMI was 25.34, as well as in retrospective case control study in Japan conducted by Naito and Imafuku [24] in which the mean BMI was 22.22 ± 3.98 kg/m^2.

No significant statistical difference was found regarding BMI and gender of the patients. The mean BMI in men was 28.40 kg/m^2 and 26.89 kg/m^2 in women similar as in study that was conducted in Japan in which the mean BMI in male psoriatic patients was 22.33 ± 3.78 kg/m^2, and 22.09 ± 4.17 kg/m^2 in women with the difference that in the Japanese study patients were not overweight [24]. Different results were obtained in study conducted in Sudan in which the BMI of more than half of the patients with high BMI (54%) was higher in female patients [1].

In our study, the slight positive correlation between BMI and age of psoriatic patients was found which was opposite comparing to results obtained in study that was conducted in Sudan in which the BMI was not correlating with the age of the patients [1]. In a Japanese study, female psoriatic patients aged 20–39 years had significantly higher BMI compared to controls represented by patients with other dermatological diseases, and in contrast male psoriatic patients were 40 years and older and had a mean BMI higher than control groups [24].

In our study, the most prevalent clinical variant was PV in 66 (55%) patients, 36 (30%) of patients had PsA, followed by 10 (8.3%) patients presented with guttate psoriasis.

The results were slightly different in study conducted in India by Appukkuttan et al. [25] where the most common clinical variant was PV (86.1%), followed by pustular psoriasis (3.7%), psoriasis with pustulation (2.8%), and guttate psoriasis (1.85%).

There was no association between BMI and psoriasis clinical variants. The mean BMI was highest in the group of patients with PsA (29.4), following BMI in group with PV (27.0), and group with guttate psoriasis (26.5).

Concerning the distribution of the BMI of psoriasis clinical variants in the study by Elobeid et al. [1], most of the patients had PV among which 23 patients were with normal BMI (28.40%), 21 were overweight (25.93%), 11 were obese (13.58%), five were underweight (6.17%), and two were morbidly obese 2.47%, comparing to our patients with PV among which 23 were with normal BMI (34.84%), 26 were overweight (39.39%), 14 were obese (21.21%), and two patients were underweight (3.03%).

In our study, six patients with PsA had normal BMI (16.66%), 19 were overweight (52.7%), nine were obese (25%), and two (5.55%) patients were morbidly obese (BMI ≥ 40).

Regarding the correlation of BMI and duration of the disease the results were similar to the results of Sudanese cross-sectional study conducted on 81 psoriatic patients in which the BMI was not correlating with the duration of the disease [1]. The same finding was observed in a study conducted in India [26].

The association between family history of psoriasis and BMI was not found in our study which was different comparing to the results by Bayaraa et al. [27] study conducted in Fukoka, Japan. They surveyed whether patients with familial psoriasis were obese at the onset of psoriasis and found that patients with familial psoriasis had lower BMI than those with no familial psoriasis [27].

Study limitations include the fact that BMI evaluates excess weight rather than excess fat [28], consequently it poorly distinguishes between fat mass and bone or lean mass [29]. Waist circumference is recommended as additional measurement for fat distribution regarding its high correlation with visceral fat [30]. This study was performed at the University hospital, and that can be the reason why patients with mild skin psoriasis are under-represented. Apart from psoriasis, numerous other behavioral and lifestyle factors can contribute to obesity, but these could not have been investigated in detail in the current study.

CONCLUSION

In the current study, more than a half of psoriasis patients are overweight or obese, which is in accordance with most psoriasis studies. There was no association between the BMI and gender of the patients, psoriasis clinical variants, duration of the disease and positive family history of psoriasis. The slight positive correlation was found between BMI and age of psoriatic patients. That requires further studies that include physical activities questionnaire, considering that the lack of physical activities in older patients might be an explanation.

ACKNOWLEDGMENT

Prior publication: Poster presentation at the 26th International Conference on Human Metabolic Health-Diabetes, Obesity and Endocrinology (June 22–23, Abu Dhabi, UEA), and printed as an abstract in the Journal of Diabetes and Metabolism, ISSN: 2155-6156

Conflict of interest: None declared.

REFERENCES

1. Elobeid HE, Alfarouk K, Aljarbou AN, Elhassan GO, Muddathir AK, Ramadan ARMA, et al. Correlation between the Body Mass index and Psoriasis in Dermatology and Venereology Teaching Hospital in Khartoum. AJDV. 2017;6(2):30–9. [DOI: 10.5923/j.ajdv.20170602.03]
2. Drvar DL, Vlahinić T, Maleš Ž, Turčić P, Čeović R. A modern approach to the treatment of plaque psoriasis. Acta Pharm. 2019;69(4):511–23. [DOI: 10.2478/acph-2019-0047] [PMID: 31639088]
3. Sobhan M, Farshchian M. Associations between body mass index and severity of psoriasis. Clin Cosmet Investig Dermatol. 2017;10:493–8. [DOI: 10.2147/CCID.S147236] [PMID: 29200884]
4. Young M, Aldredge L, Parker P. Psoriasis for the primary care practitioner. J Am Assoc Nurse Pract. 2017;29(3):157–78. [DOI: 10.1002/2327-6924.12443] [PMID: 28233460]
5. Takeshita J, Grewal S, Langan SM, Mehta NN, Ogdie A, Van Voorhees AS, et al. Psoriasis and comorbid diseases: Epidemiology.

J Am Acad Dermatol. 2017;76(3):377–90. [DOI: 10.1016/j.jaad.2016.07.064] [PMID: 28212759]
6. Costa L, Caso F, Ramonda R, Del Puente A, Cantarini L, Darda MA, et al. Metabolic syndrome and its relationship with the achievement of minimal disease activity state in psoriatic arthritis patients: an observational study. Immunol Res. 2015;61(1–2):147–53. [DOI: 10.1007/s12026-014-8595-z] [PMID: 25395342]
7. WHO contributors. BMI classification. (Accessed 4 September 2021).
8. Budu-Aggrey A, Brumpton B, Tyrrell J, Watkins S, Modalsli EH, Celis-Morales C, et al. Evidence of a causal relationship between body mass index and psoriasis: A mendelian randomization study. PLoS Med. 2019;16(1):e1002739. [DOI: 10.1371/journal.pmed.1002739] [PMID: 30703100]
9. The NHS Information Centre. Statistics on Obesity, Physical Activity and Diet: England. 2017. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/613532/obes-phys-acti-diet-eng-2017-rep.pdf. [cited 2019 July 9].
10. Barrea L, Nappi F, Di Somma C, Savanelli MC, Falco A, Balato A, et al. Environmental Risk Factors in Psoriasis: The Point of View of the Nutritionist. Int J Environ Res Public Health. 2016;13(5):743. [DOI: 10.3390/ijerph13070743] [PMID: 27455297]
11. Carrascosa JM, Rocamora V, Fernandez-Torres RM, Jimenez-Puya R, Moreno JC, Coll-Puigserver N, et al. Obesity and psoriasis: inflammatory nature of obesity, relationship between psoriasis and obesity, and therapeutic implications. Actas Dermosifiliogr. 2014 Jan–Feb;105(1):31–44. English, Spanish. [DOI: 10.1016/j.ad.2012.08.003] [PMID: 23177976]
12. Aljohani R. Metabolic Syndrome and Its Components in Psoriatic Arthritis. Open Access Rheumatol. 2022;14:7–16. [DOI: 10.2147/OARRR.S347797] [PMID: 35210876]
13. Kong Y, Zhang S, Wu R, Su X, Peng D, Zhao M, et al. New insights into different adipokines in linking the pathophysiology of obesity and psoriasis. Lipids Health Dis. 2019;18(1):171. [DOI: 10.1186/s12944-019-1115-3] [PMID: 31521168]
14. Rodríguez-Cerdeira C, Cordeiro-Rodríguez M, Carnero-Gregorio M, López-Barcenas A, Martínez-Herrera E, Fabbrocini G, et al. Biomarkers of Inflammation in Obesity-Psoriatic Patients. Mediators Inflamm. 2019:7353420. [DOI: 10.1155/2019/7353420] [PMID: 31275060]
15. Baran A, Flisiak I, Jaroszewicz J, Świderska M. Serum adiponectin and leptin levels in psoriatic patients according to topical treatment. J Dermatolog Treat. 2015;26(2):134–8. [DOI: 10.3109/09546634.2014.915917] [PMID: 24754531]
16. Wong Y, Nakamizo S, Tan KJ, Kabashima K. An Update on the Role of Adipose Tissues in Psoriasis. Front Immunol. 2019;10:1507. [DOI: 10.3389/fimmu.2019.01507] [PMID: 31316526]
17. Ramírez J, Azuaga-Piñango AB, Celis R, Cañete JD. Update on Cardiovascular Risk and Obesity in Psoriatic Arthritis. Front Med (Lausanne). 2021;8:742713. [DOI: 10.3389/fmed.2021.742713] [PMID: 34692732]
18. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and obesity: a systematic review and meta-analysis of observational studies. Nutr Diabetes. 2012;2(12):e54. [DOI: 10.1038/nutd.2012.26] [PMID: 23208415]
19. Dalamaga M, Papadavid E. Can we better strategize our choice of pharmacotherapy for patients with co-morbid psoriasis and obesity? Expert Opin Pharmacother. 2019;20(11):1303–8. [DOI: 10.1080/14656566.2019.1603294] [PMID: 31002541]
20. Norden A, Rekhtman S. Risk of psoriasis according to body mass index: A retrospective cohort analisys. JAAD. 2021;86(5):1020–6. [DOI: 10.1016/j.jaad.2021.06.012]
21. Alizadeh N, Azimi S, Hoseinzadeh S. Body mass index and severity of psoriasis: a cross-sectional study. Iranian Journal of Dermatology. 2021;24(1):46–52. [DOI: 10.22034/ijd.2020.232580.1107]
22. Duarte GL, Porto da Silva L. Correlation between psoriasis' severity and waist-to-height ratio. An Bras Dermatol. 2014;89(5):846–7. [DOI: 10.1590/abd1806-4841.20142854]
23. Sedgwick P. Pearson's Correlation Coefficient. BMJ. 2012;345:e4483. [DOI: 10.1136/bmj.e4483]
24. Naito R, Imafuku S. Distinguishing features of body mass index and psoriasis in men and women in Japan: A hospital-based case-control study. J Dermatol. 2016;43(12):1406–11. [DOI: 10.1111/1346-8138.13439] [PMID: 27178353]
25. Appukkuttan AS, Haridasan RK, Jose BA. Histopathological Features and Clinical Variants of Biopsy Confirmed Psoriasis Cases in a Tertiary Care Setting in Kerala. J Evolution Med Dent. 2020;9(33):2372–6. [DOI: 10.14260/jemds/2020/514]
26. Praveenkumar U, Ganguly S, Ray L, Nanda SK, Kuruvila S. Prevalence of Metabolic Syndrome in Psoriasis Patients and its Relation to Disease Duration: A Hospital Based Case-Control Study. J Clin Diagn Res. 2016;10(2):WC01–5. [DOI: 10.7860/JCDR/2016/17791.7218] [PMID: 27042565]
27. Bayaraa B, Arima H, Imafuku S. Body mass index in psoriatic patients with or without familial psoriasis. J Dermatol. 2020;47(4):402–4. [DOI: 10.1111/1346-8138.15233] [PMID: 31953878]
28. Israel E, Hassen K, Markos M, Wolde K, Hawulte B. Central Obesity and Associated Factors Among Urban Adults in Dire Dawa Administrative City, Eastern Ethiopia. Diabetes Metab Syndr Obes. 2022;15:601–14. [DOI: 10.2147/DMSO.S348098] [PMID: 35241919]
29. Bunn J, Eustace D, Miskech T, Manor J, Jiroutek M. Fitness and Fatness: Body Mass Index versus Percent Body Fat. J Clin Exerc Physiol. 2019;8(4):131–7. [DOI: 10.31189/2165-6193-8.4.131]
30. Ross R, Neeland IJ, Yamashita S, Shai I, Seidell J, Magni P, et al. Waist circumference as a vital sign in clinical practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. Nat Rev Endocrinol. 2020;16(3):177–89. [DOI: 10.1038/s41574-019-0310-7] [PMID: 32020062]

Повезаност индекса телесне масе са клиничким варијантама псоријазе

Оливера Леваков, Зорица Гајинов, Бранислава Гајић, Љуба Вујановић, Милана Ивков-Симић, Зоран Голушин

Клинички центар Војводине, Нови Сад, Србија;
Универзитет у Новом Саду, Медицински факултет, Одељење за дерматологију, Нови Сад, Србија

САЖЕТАК

Увод/Циљ Псоријаза је честа, хронична, имунски посредована, инфламаторна и пролиферативна болест коже у чијој патогенези играју улогу и генетика и утицај средине. Повезаност између псоријазе и гојазности је вероватно двосмерна. Циљ ове студије је да се процени повезаност псоријазе и гојазности, односно да ли квантитативно градирање прекомерне тежине уз помоћ индекса телесне масе (ИТМ) показује директну корелацију са различитим клиничким варијантама псоријазе, трајањем болести и позитивном породичном анамнезом на псоријазу.

Методе У ову проспективну, опсервациону дескриптивну студију је укључено 120 болесника са псоријазом упућених на Клинику за кожно-венеричне болести Универзитетског клиничког центра Војводине. Одређене су клиничке варијанте псоријазе. Узети су подаци о годинама, полу, трајању болести, ИТМ, и подаци о породичној анамнези на псоријазу, након чега су урађени обрада и поређење.

Резултати Укупно 53,3% мушкараца и 46,7% жена било је укључено у студију. Просек година је био 49,5 ± 15,5. Најзаступљеније клиничке варијанте су биле вулгарна псоријаза (55%) и псоријатски артритис (30%). Већина болесника (42,5%) била је са прекомерном тежином, 23,3% болесника било је гојазно и 1,7% морбидно гојазно. Просечан ИТМ је био висок (27,7 ± 5,2). Просечна дужина трајања болести је била 15,6 ± 14,9 година. Позитивну породичну анамнезу на псоријазу имала су 33 (27,5%) болесника.

Закључак Није утврђена корелација између ИТМ и пола болесника, клиничких варијанти псоријазе, трајања болести и позитивне породичне анамнезе на псоријазу. Дискретна позитивна корелација је утврђена између ИТМ и старости болесника. Такав закључак захтева даља испитивања која би садржала и упитник о физичкој активности, с обзиром на то да мањак физичке активности код старијих болесника може бити објашњење.

Кључне речи: псоријаза; индекс телесне масе; ИТМ

DOI: https://doi.org/10.2298/SARH220725097T
UDC: 616.36-008; 616.348/.35-006.6-06

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Factors contributing to survival in hepatic dysfunction due to colorectal cancer

Fatih Tay, Mustafa Büyükkör, Ayşe Ocak Duran

Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Medical Oncology, Ankara, Turkey

SUMMARY

Introduction/Objective Colorectal cancer (CRC) is currently the third most common cancer in incidence in the United States and accounts for about 8.5% of all cancer related deaths. Our study aim was to determine the parameters that contribute to the survival of CRC patients with hepatic dysfunction, attention to the positive effects on survival when the most appropriate clinical approaches.

Methods Patients with CRC, diagnosed with hepatic dysfunction, and who were followed up in our inpatient service in the last two years were included in our study. Survival rates were analyzed starting from after the development of hepatic failure.

Results A total of 57 patients were included in the study, 44 (77.2%) were colon carcinoma, and 13 (22.8%) were rectal carcinoma patients, and 14 (24.56%) were female. Bile duct dilatation (BD) was detected in 19 (33%) of 57 patients with imaging methods. The median OS was calculated as 4 *vs*. 1.4 months in patients with BD compared to patients without BD ($p < 0.001$). Survival times were significantly higher in patients with BD compared to those without dilatation, and in patients without renal failure compared to those with renal failure.

Conclusion In cancer patients with hepatic dysfunction, those with additional renal failure had shorter survival times and a worse prognosis. The longer survival of patients with BD was attributed to the optimal timing of the percutaneous transhepatic cholangiography insertion, close clinical and inflammation marker follow-ups, and early prevention of external biliary drainage, therefore preventing a possible septic complication early on.

Keywords: colorectal cancer; hepatic dysfunction; percutaneous transhepatic biliary drainage; survivability

INTRODUCTION

About 149,500 new colorectal cancer (CRC) cases are diagnosed each year in the United States, of which 104,270 are colon cancer, and the remainder are rectal cancer [1]. According to Globocan 2020 data, CRC is ranked third after breast and lung cancer according to the frequency of new cases and second after lung cancer in mortality rates [2].

In the evaluation of liver function, aspartate aminotransferase (AST), serum albumin, and prothrombin time are measured, cellular damage is evaluated with alanine aminotransferase (ALT) concentrations, and bile cholestasis is assessed with alkaline phosphatase (ALP), gamma-glutamyl-transferase (GGT), and bilirubin levels. Serum bilirubin levels are a specific indicator of severe liver injury and an essential indicator of loss of liver function [3]. Therefore, in our study, when determining liver dysfunction, we considered the elevation of bilirubin (simultaneous total and direct bilirubin) as the main antecedent parameter and accepted it as the first parameter to be evaluated in patient selection. Then, the clinical reflections of the changes in all other liver function tests were evaluated.

The mechanism by which cancer causes liver dysfunction is multifactorial. This may occur through a direct reduction in liver volume, or it may occur with the development of intrahepatic or extrahepatic biliary obstruction [3]. It has also been reported that some cancer-related immunological factors may increase cholestasis and inflammatory liver damage. Development of liver dysfunction secondary to metastatic CRC is considered a poor prognosis and reduces median survival to only a few weeks [4].

Our study aimed to determine the parameters that contribute to the survival of CRC patients with hepatic dysfunction, regardless of the development of liver metastasis, and to draw the patients' attention to the positive effects on survival when the most appropriate clinical approaches and optimal treatment are performed with the earliest timing.

METHODS

The patients aged 18 years and older who were hospitalized and followed up with liver dysfunction and diagnosed with CRC at our health center in the last two years were included in the study. The study was conducted in accordance with the Declaration of Helsinki. Patient information was recorded by retrospectively scanning the hospital database. Patients who did not

Received • Примљено: July 25, 2022
Revised • Ревизија: September 23, 2022
Accepted • Прихваћено: September 29, 2022
Online first: October 5, 2022

Correspondence to:
Fatih TAY
Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital
06200 Yenimahalle
Ankara
Turkey
dr.fatihtay@gmail.com

meet the inclusion criteria as well as those who withdrew their voluntary consent during the study were excluded.

The study's ethics committee approval was obtained from the ethics committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital with the number 2022-02/1669, dated 23.02.2022.

In the analyzes, the effects of hemogram, serum glucose, ALT and AST, total bilirubin, direct bilirubin, ALP, GGT, albumin, international normalized ratio, blood urea nitrogen, and creatinine parameters, as well as bile duct dilatation (BD), sex, and age parameters on survival after the development of hepatic dysfunction were calculated.

Statistical analyzes were performed using the Statistical Package for the Social Sciences program SPSS for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). Normality analyzes were performed for the distribution of numerical variables. Continuous quantitative variables were reported using the median (interquartile range) (min–max) for non-parametrically distributed and mean (SD) for parametrically distributed variables. Qualitative categorical variables were reported using Pearson's χ^2 or Fisher exact test. Survival analyses were performed with Cox regression analysis, while survival curves were created using the Kaplan–Meier method. A p-value of < 0.05 was considered significant.

RESULTS

A total of 57 patients were included in the study by scanning the retrospective database. Of these, 44 (77.2%) were colon carcinoma, and 13 (22.8%) were rectal carcinoma patients, and 14 (24.56%) were female.

The performance statuses were evaluated using the Eastern Cooperative Oncology Group (ECOG) performance status. There were 33 (57.9%) patients with ECOG ≤ 2 and 24 (42.1%) patients with ECOG ≥ 3.

When the age distributions were categorized as over 50 years old and 50 years old and below, the median overall survival (OS) in the > 50 years *vs.* ≤ 50 age group was higher, with a value close to significance of 4.1 *vs.* 1.5 months, respectively (p = 0.08) (Table 1).

The R-value (R factor), an additional factor in determining the possible type of liver injury in patients, was calculated based on serum ALT and ALP levels. Values of five and above were considered hepatocellular damage, while values of two and below were considered as cholestatic damage. The median R factor was 1 (1–3). While 55 (96.5%) of our patients had cholestatic damage, hepatocellular damage was present in two (3.5%).

When albumin values were similarly categorized as < 3 g/dL and ≥ 3 g/dL, the median OS was 2.1 *vs.* 1.4 months in the group with albumin above 3 mg/dL (p = 0.015) (Table 1).

In our patients, no pathology supporting chronic renal failure was present in the pre-hepatic dysfunction, both in the past laboratory findings and in the current urinary system ultrasound imaging. When the kidney functions were evaluated, the median OS was 2.72 *vs.* 1.41 months in the group with serum blood urea nitrogen values of 15 mg/dl and below and in the group with over 15 mg/dl (p = 0.016). In the group with creatinine values below 1.5 mg/dl, OS was calculated as 2.2 *vs.* 0.98 months compared to 1.5 mg/dl and above (p < 0.001) (Table 1).

Table 1. Survival analyzes of demographic characteristics and laboratory parameters

Parameters	Median OS (95% CI)	p value
Age, median		
≤ 50	4.1 (0.1–11.25)	0.08
> 50	1.5 (1.19–1.95)	
Sex		
Male	1.7 (0.91–2.5)	0.470
Female	1.3 (1.1–1.4)	
Glucose		
< 126	1.7 (0.85–2.5)	0.799
≥ 126	1.5 (1.2–1.8)	
Alanine transaminase		
< 40	1.5 (0.74–2.4)	0.443
≥ 40	1.6 (1.1–2.1)	
Aspartate transaminase		
< 40	1.3 (0.45–2.2)	0.108
≥ 40	1.7 (1.2–2.1)	
Alkaline phosphatase		
< 140	1.5 (1.2–1.9)	0.948
≥ 140	1.7 (1–2.4)	
Gamma-glutamyl transferase		
< 340	2.7 (1.11–4.34)	0.036
≥ 340	1.6 (1.12–2.04)	
Albumin		
< 3	1.4 (1.1–1.6)	0.015
≥ 3	2.1 (1–3.2)	
International normalized ratio		
< 1.5	1.5 (1–2)	0.61
≥ 1.5	1.3 (0.66–2)	
Blood urea nitrogen		
< 15	2.72 (0.43–5.02)	0.016
≥ 15	1.41 (1.09–1.73)	
Creatinine		
< 1.5	2.2 (1.31–3.09)	< 0.001
≥ 1.5	0.98 (0.84–1.12)	
Hemoglobin		
< 11	1.4 (1.1–1.7)	0.211
≥ 11	1.9 (1.1–2.6)	
Bile duct dilatation		
Present	4 (0.01–8.59)	< 0.001
Absent	1.4 (1.19–1.63)	
Kaplan–Meier survival analysis		

BD was detected in 19 (33%) of 57 patients with imaging methods. In the evaluations made according to the patients who developed BD and therefore had percutaneous transhepatic cholangiography (PTC) and those who did not have PTC, it was determined that 16 (84.2%) of 19 patients underwent PTC procedure. The median OS was calculated as 4 *vs.* 1.4 months in patients with BD compared to patients without dilatation (p < 0.001) (Tables 1 and 2, Figure 1).

The patients were followed closely regarding coagulopathy, another consequence of liver failure, and

Table 2. Survival analyzes of laboratory parameters (univariate and multivariate analyzes)

Parameters	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Direct bilirubin	0.89 (0.803–0.999)	0.47	1.105 (0.956–1.278)	0.177
Gamma-glutamyl transferase	1.00 (1.000–1.001)	0.37	1.001 (1.000–1.002)	0.002
Blood urea nitrogen	1.02 (1.012–1.047)	0.001	1.032 (1.012–1.053)	0.002
Hemoglobin ≥ 11	0.56 (0.321–1.003)	0.51	0.761 (0.412–1.406)	0.384
Bile duct dilatation, present	3.26 (1.650–6.477)	0.001	0.197 (0.077–0.506)	0.001
HALP score	0.933 (0.827–1.054)	0.250	0.932 (0.819–1.050)	0.281
Cox Regression Analysis				

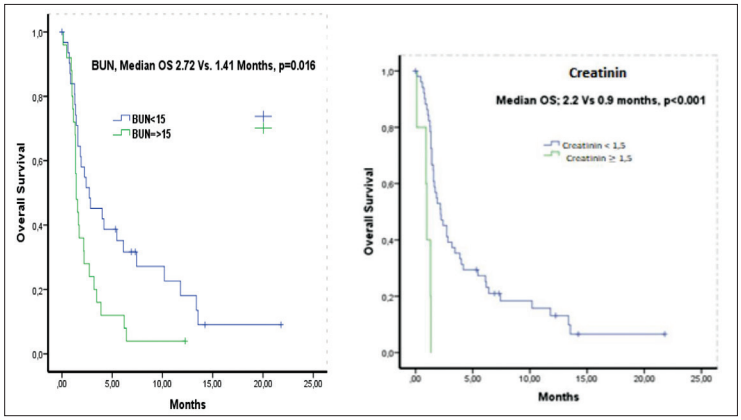


Figure 1. Overall survival related to blood urea nitrogen and creatinine in hepatic dysfunction

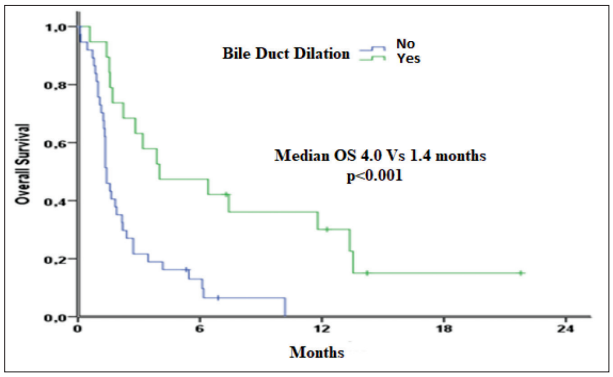


Figure 2. Overall survival in bile duct dilation

Table 3. Correlation of numerical variables

Parameters		Direct bilirubin	Total bilirubin	Gamma-glutamyl transferase	Lymphocyte	Neutrophil	Platelets
Direct bilirubin	r	1					
	p						
Total bilirubin	r	0.948**	1				
	p	**< 0.001**					
Gamma-glutamyl transferase	r	0.018	-0.021	1			
	p	0.892	0.877				
Lymphocyte	r	0.004	-0.005	0.317*	1		
	p	0.975	0.970	**0.016**			
Neutrophil	r	-0.172	-0.204	0.268*	0.180	1	
	p	0.202	0.127	**0.044**	0.181		
Platelets	r	0.338*	0.322*	0.439**	0.289*	0.379**	1
	p	**0.010**	**0.014**	**< 0.001**	**0.029**	**0.004**	
Spearman correlation analysis							

anti-vascular endothelial growth factor therapy [5]. However, no thrombosis or bleeding was reported.

When the patients with BD were evaluated according to their subgroups, the median serum ALT levels were calculated as 110 in the dilated group and 36 in the non-dilated group ($p = 0.06$). Other significant variables in bile dilatation were total and direct bilirubin values ($p < 0.001$, Table 1).

In the Spearman correlation analysis performed between numerical variables, the correlation of serum cholestasis enzymes with platelet, neutrophil, and lymphocyte values was evaluated. It was determined that platelet values had a significant positive correlation with bilirubin (total and direct bilirubin) and GGT, and neutrophil and lymphocyte values were also positively correlated with GGT (Table 3).

The HALP score (calculated by serum hemoglobin (g/dL) × albumin (g/L) × lymphocyte (10^9/L) / platelet (10^9/L) method) was calculated for all patients. The median value was calculated as 1.78 (0.23–16.6). The Cox regression analysis for the calculated HALP score is given in Table 2.

DISCUSSION

Survival in hepatic dysfunction due to cancer is expressed in weeks. Therefore, early identification of factors affecting this survival, initiation of treatment with optimal timing, or early interventions for treatment will increase survival times. Liver biopsy is the gold standard test for detecting liver damage and fibrosis. On the other hand, reasons such as the high cost, the risk of complications such as bleeding, the pathology results being time consuming, the lack of a practical evaluation method, and the fact that 24 (42.1%) of our patients with liver dysfunction consisted of patients with ECOG performance status of three and above, etc. have led to the need to search for methods that can provide rapid results and have an impact on the clinic. For this purpose, some laboratory parameters and clinical findings were evaluated in our patients.

PTC was not implanted in any of our 38 patients who developed hepatic dysfunction but did not have dilated BD. However, PTC was inserted in 16 (84.2%) of our 19 patients with BD. The longer survival of patients with BD was attributed to the fact that PTC fitted with optimal timing, close clinical and inflammation marker follow-ups, and early external biliary drainage could

be provided, and therefore, a possible septic picture that could develop was prevented early.

In some studies, the development of sinusoidal obstruction syndrome (SOS) has been shown in patients treated with oxaliplatin-containing regimens [6, 7, 8]. In another study, surgery-confirmed SOS was found in 24 of 60 patients who received neo-adjuvant oxaliplatin-based chemotherapy for over 12 weeks [9, 10]. In our study, SOS was diagnosed with the revised European Society for Blood and Marrow Transplantation criteria by the presence of two of the following findings in addition to a total bilirubin value ≥ 2: painful hepatomegaly, ≥ 5% weight gain, and ascites [11]. SOS was detected in a total of eight patients. All patients with SOS had received oxaliplatin-based treatment. Some reports state adding bevacizumab to the neoadjuvant oxaliplatin-based regimen may reduce the incidence and severity of oxaliplatin-related hepatic sinusoidal injury [10–13]. Of the 57 patients in our study, 16 received combined treatment with bevacizumab. Four (50%) of our patients with SOS had received bevacizumab.

Side effects of regimens containing irinotecan are more frequently associated with steatosis and steatohepatitis [14]. Publications are stating that patients with steatohepatitis have an overall survival difference of approximately three months compared to those without [15]. A total of 36 (63.1%) patients received irinotecan treatment at any step. In our study, a total of 32 (56.14%) patients had grade 1 and higher steatosis. Of these patients, 21 had received irinotecan treatment.

We determined that young age is an important parameter of survival. Therefore, patients with poor nutritional support should be considered when evaluating the significant survival difference in albumin values of three and above.

Hypoalbuminemia usually indicates severe liver injury with decreased albumin synthesis [16]. Therefore, serum albumin level is included in the Child–Turcotte–Pugh classification, a scoring system with prognostic significance in patients with liver cirrhosis [17]. Serum albumin is also decreased in nephrotic syndrome, as a negative acute phase reactant, in widespread systemic inflammation, and in severe nutritional disorders.

Hypoalbuminemia is aggravated as albumin synthesis is also affected by the addition of hepatic dysfunction to these clinical conditions, which are very common in many cancer patients. It was thought that the lower survival rate in patients with hypoalbuminemia was primarily related to liver dysfunction and poor nutritional support in these patients.

Hepatorenal syndrome is a state usually accompanied by acute renal failure in patients with acute or chronic liver disease. Although it is usually seen in patients with advanced cirrhosis, it can also be seen in portal hypertension due to metastatic tumors [18–21]. Since our study was retrospective, although hepatorenal syndrome was not diagnosed by considering the diagnostic criteria, it was shown that adding hepatic dysfunction to renal failure reduces patient survival.

Some publications show that the HALP score can be used as a prognostic marker. In a study by Topal et al. [22], an indirect relationship between the HALP score and tumor budding in patients with CRC was shown. Another analysis by Yalav et al. [23] found an independent prognostic factor for survival in patients with CRC who underwent curative resection. Our study determined that the HALP score did not make a statistically significant contribution in terms of survival. Therefore, it was thought that there is a need for studies on this subject with more patients and including patients at all stages.

CONCLUSION

Although liver function tests have an important place in cancer patients, early detection of liver dysfunction prolongs the survival of patients. A significant proportion of hepatic dysfunction in CRC patients develops with cholestatic occlusive damage. Therefore, in cases with dilated biliary tract, PTC should not be delayed and should be seen as a priority. Drug toxicities and even non-metastatic liver damage should also be considered since many of these patients receive multiple drug therapies.

Conflict of interest: None declared.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7–30. [DOI: 10.3322/caac.21492] [PMID: 30207593]
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–49. [DOI: 10.3322/caac.21660] [PMID: 33538338]
3. Field KM, Dow C, Michael M. Part I: Liver function in oncology: biochemistry and beyond. Lancet Oncol. 2008;9(11):1092–101. [DOI: 10.1016/S1470-2045(08)70279-1] [PMID: 19012858]
4. Lin S, D'Cunha R. A Review of Regulatory Guidance for Conducting Hepatic Impairment Studies: A Case Study in Oncology. J Oncol Cancer Res. 2018;2(1):14–22. [DOI: 10.28967/jocr.2018.01.18004]
5. Tosetti G, Farina E, Caccia R, Sorge A, Berzuini A, Valenti L, et al. Preprocedural prophylaxis with blood products in patients with cirrhosis: Results from a survey of the Italian association for the study of the liver (AISF). Dig Liver Dis. 2022;54(11):1520–6. [DOI: 10.1016/j.dld.2022.03.017] [PMID: 35474168]
6. Shimagaki T, Sugimachi K, Mano Y, Onishi E, Iguchi T, Uehara H, et al. Simple systemic index associated with oxaliplatin-induced liver damage can be a novel biomarker to predict prognosis after resection of colorectal liver metastasis. Ann Gastroenterol Surg. 2022;6(6):813–22. [DOI: 10.1002/ags3.12580] [PMID: 36338597]
7. Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, et al. Chemotherapy Regimen Predicts Steatohepatitis and an Increase in 90-Day Mortality After Surgery for Hepatic Colorectal Metastases. J Clin Oncol. 2006;24(13):2065–72. [DOI: 10.1200/JCO.2005.05.3074] [PMID: 16648507]
8. Zhao J, van Mierlo KMC, Gómez-Ramírez J, Kim H, Pilgrim CHC, Pessaux P, et al. Systematic review of the influence of chemotherapy-associated liver injury on outcome after partial hepatectomy for colorectal liver metastases. Br J Surg. 2017;104(8):990–1002. [DOI: 10.1002/bjs.10572] [PMID: 28542731]
9. Costa G, Cavinato L, Masci C, Fiz F, Sollini M, Politi LS, et al. Virtual Biopsy for Diagnosis of Chemotherapy-Associated Liver Injuries and Steatohepatitis: A Combined Radiomic and Clinical Model in Patients with Colorectal Liver Metastases. Cancers (Basel).

2021;13(12):3077. [DOI: 10.3390/cancers13123077] [PMID: 34203103]
10. Robinson SM, Wilson CH, Burt AD, Manas DM, White SA. Chemotherapy-Associated Liver Injury in Patients with Colorectal Liver Metastases: A Systematic Review and Meta-analysis. Ann Surg Oncol. 2012;19(13):4287–99. [DOI: 10.1245/s10434-012-2438-8] [PMID: 22766981]
11. Mohty M, Malard F, Abecassis M, Aerts E, Alaskar AS, Aljurf M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives—a position statement from the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant. 2015;50(6):781–9. [DOI: 10.1038/bmt.2015.52] [PMID: 25798682]
12. van der Pool AE, Marsman HA, Verheij J, Ten Kate FJ, Eggermont AM, Ijzermans JN, et al. Effect of bevacizumab added preoperatively to oxaliplatin on liver injury and complications after resection of colorectal liver metastases. J Surg Oncol. 2012;106(7):892–7. [DOI: 10.1002/jso.23142] [PMID: 22552819]
13. Jácome AA, Oliveira FA, Lino F, Lima JPSN. Effect of Adding Bevacizumab to Chemotherapy on Pathologic Response to Preoperative Systemic Therapy for Resectable Colorectal Liver Metastases: A Systematic Review and Meta-analysis. Clin Colorectal Cancer. 2021;20(3):265–72. [DOI: 10.1016/j.clcc.2021.05.006] [PMID: 34158251]
14. Mahli A, Saugspier M, Koch A, Sommer J, Dietrich P, Lee S, et al. ERK activation and autophagy impairment are central mediators of irinotecan-induced steatohepatitis. Gut. 2018;67(4):746–56. [DOI: 10.1136/gutjnl-2016-312485] [PMID: 28053052]
15. Han J, Zhang J, Zhang C. Irinotecan-Induced Steatohepatitis: Current Insights. Front Oncol. 2021;11:4165. [DOI: 10.3389/fonc.2021.754891] [PMID: 34707997]
16. Kumar A, Kumar JB, Goud BM. Liver Function Tests: Biochemical Overview for Clinical Correlation. Indian J Med Biochem. 2021;25(1):31–7. [DOI:10.5005/jp-journals-10054-0171]
17. El-Khateeb E, Darwich AS, Achour B, Athwal V, Rostami-Hodjegan A. Review article: time to revisit Child-Pugh score as the basis for predicting drug clearance in hepatic impairment. Aliment Pharmacol Ther. 2021;54(4):388–401. [DOI: 10.1111/apt.16489] [PMID: 34218453]
18. Campion D, Rizzi F, Bonetto S, Giovo I, Roma M, Saracco GM, et al. Assessment of glomerular filtration rate in patients with cirrhosis: Available tools and perspectives. Liver Int. 2022;42(11):2360–76. [DOI: 10.1111/liv.15198] [PMID: 35182100]
19. Londono MC, Cardenas A, Guevara M, Quinto L, de Las Heras D, Navasa M, et al. MELD score and serum sodium in the prediction of survival of patients with cirrhosis awaiting liver transplantation. Gut. 2007;56(9):1283–90. [DOI: 10.1136/gut.2006.102764] [PMID: 17452425]
20. Gonwa TA, Wadei HM. The challenges of providing renal replacement therapy in decompensated liver cirrhosis. Blood Purif. 2012;33(1–3):144–8. [DOI: 10.1159/000334149] [PMID: 22269395]
21. Mindikoglu AL, Pappas SC. New Developments in Hepatorenal Syndrome. Clin Gastroenterol Hepatol. 2018;16(2):162–177.e1. [DOI: 10.1016/j.cgh.2017.05.041] [PMID: 28602971]
22. Topal U, Guler S, Teke Z, Karakose E, Kurtulus I, Bektas H. Diagnostic Value of Preoperative Haemoglobin, Albumin, Lymphocyte and Platelet (HALP) Score in Predicting Tumour Budding in Colorectal Cancer. J Coll Physicians Surg Pakistan. 2022;32(6):751–7. [DOI: 10.29271/jcpsp.2022.06.751] [PMID: 35686407]
23. Yalav O, Topal U, Unal AG, Eray IC. Prognostic significance of preoperative hemoglobin and albumin levels and lymphocyte and platelet counts (HALP) in patients undergoing curative resection for colorectal cancer. Ann Ital Chir. 2021;92:283–92. [PMID: 34312330]

Фактори који доприносе преживљавању болесника са дисфункцијом јетре услед колоректалног карцинома

Фатих Тај, Мустафа Бујукор, Ајше Оџак Дуран

Болница „Абдурахман Журтаслан“ за обуку и истраживање онкологије у Анкари, Одељење за медицинску онкологију, Анкара, Турска

САЖЕТАК

Увод/Циљ Колоректални карцином (КРК) тренутно је трећи најчешћи рак у Сједињеним Државама и чини око 8,5% свих смртних случајева повезаних са раком.

Циљ наше студије био је да се идентификују параметри који доприносе преживљавању болесника са КРК са дисфункцијом јетре, обраћајући пажњу на позитивне ефекте на преживљавање у најприкладнијим клиничким приступима.

Методе Наша студија је обухватила болеснике са КРК којима је дијагностикована дисфункција јетре традиционалним тестовима функције јетре и који су праћени у нашој болници у последње две године. Стопе преживљавања анализиране су од почетка отказивања јетре.

Резултати У студију је укључено укупно 57 болесника, 44 болесника (77,2%) имала су карцином дебелог црева, 13 њих (22,8%) били су болесници са КРК, а 14 (24,56%) жене. Откривена је дилатација жучних канала код 19 (33%) од 57 болесника са сликовним методама. Медијан ОС је израчунат као 4 наспрам 1,4 месеца код болесника са дилатацијом жучних канала у поређењу са болесницима без дилатације ($p < 0,001$). Време преживљавања је било значајно веће код болесника са дилатацијом билијарног тракта у поређењу са онима без дилатације, и код болесника без бубрежне инсуфицијенције у поређењу са онима са отказивањем бубрега.

Закључак Код болесника оболелих од рака са дисфункцијом јетре, они са додатном бубрежном инсуфицијенцијом имали су краће време преживљавања и лошију прогнозу. Дуже преживљавање болесника са дилатацијом жучних канала било је због оптималног времена перкутане трансхепатичке холангиографије, пажљивог клиничког праћења и контроле маркера упале и ране превенције спољне дренаже жучних путева, што омогућава спречавање могућих септичких компликација у ранојој фази.

Кључне речи: колоректални карцином; дисфункција јетре; перкутана трансхепатична билијарна дренажа; преживљавање

DOI: https://doi.org/10.2298/SARH220609092M
UDC: 616.24-002.828:582.282.123.4

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Incidental finding of pulmonary tumorlet in a case of surgically treated bronchiectatic cavity superimposed by aspergilloma

Dejan Moskovljević[1], Nikola Čolić[2], Anđela Dimkić-Milenković[3], Jelena Marković[4], Vladimir Milenković[1]

[1]University Clinical Center of Serbia, Clinic for Thoracic Surgery, Belgrade, Serbia;
[2]University Clinical Center of Serbia, Center for Radiology and Magnetic Resonance Imaging, Belgrade, Serbia;
[3]University Clinical Center of Serbia, Clinic for Burns, Plastic and Reconstructive Surgery, Belgrade, Serbia;
[4]University Clinical Center of Serbia, Department of Thoracopulmonary Pathology, Pathohistology Service, Belgrade, Serbia

SUMMARY

Introduction Intracavitary aspergilloma is the consequence of a saprophytic infection of the lung with cavitary disease. Pulmonary tumorlet are nodular proliferations of the neuroendocrine cells less than 5 mm in diameter. Both aspergilloma in the bronchiectatic cavity of the lung and pulmonary tumorlet has rare been seen.

Case outline We present a 71-year-old woman with a medical history of recurrent pneumonia complicated with cough and hemoptysis. Computed tomography (CT) scan of the chest showed pulmonary soft tissue mass in the right lower lobe of the lung 42 × 50 mm in diameter. Direct microscopy of the specimens of bronchioalveolar lavage showed spores of *Aspergillus*. Galactoman Ag test was also positive. Right lower lobectomy and mediastinal lymph node sampling was performed via thoracotomy. Pathohistological findings showed aspergilloma with the presence of pulmonary tumourlet and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) in the lymphovascular spaces. Five years follow up showed no abnormalities on the CT scan, and the patient remained alive without medical problems.

Conclusion The concomitant occurrence of bronchiectasis, aspergilloma, and precancerous lesions such as pulmonary tumourlet and DIPNECH is rare and further increases the risk of developing malignant tumors as well as recurrent infections. Therefore, surgical treatment can prevent the development of premalignant lesions and the occurrence of recurrent infections accompanied by dyspnea and hemoptysis as the main symptoms. The question of the connection between pulmonary tumourlet and chronic inflammatory lung diseases is raised. We hope that future researches will provide answers to this question.

Keywords: bronchyectasis; aspergilloma; pulmonary tumourlet; DIPNECH

INTRODUCTION

Aspergillus is a genus of mold which includes about 200 species, including *Aspergillus fumigaus*, *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus terreus* and *Aspergillus nidulans*, which are most common human pathogens [1]. Spreading of the disease depends of the patients immunological and respiratory systems. *Aspergillus* causes infectious as well as allergic diseases [2]. Chronic pulmonary aspergillosis (CPA) is often seen in patients with lung diseases that cause structural damage to lung parenchyma, and have the whole spectrum of progressive disease manifestations caused by *Aspergillus* species [3]. Chronic cavitary pulmonary aspergillosis is a slow destructive type of CPA [4]. Aspergillosis is most often seen in patients with common chronic lung disease or in immunocompromised patients. *Aspergillus* species, a saprophytic fungus, can colonize pulmonary cavities caused by tuberculosis, sarcoidosis, echinococcosis and bronchiectasis [5]. Also, it is well known to complicate malignant diseases [6]. Fungus ball, intracavitary mycetoma, aspergilloma, is the consequence of a saprophytic infection of the lung with cavitary disease. Cough and hemoptysis are the most common symptom [7]. Furthermore, pulmonary tumourlet, defined as nodular proliferations of neuroendocrine cells less than 5 mm in diameter, are a rare pathology [8]. In most cases they are detected incidentally, the most common in bronchiectatic cavity or in areas of lung destruction that are removed surgically. The coexistence of a pulmonary neuroendocrine tumourlet and aspergilloma has rarely been seen [9].

The aim of this case report was to present a rare case of surgically treated pulmonary bronchiectatic cavity superimposed with aspergilloma and an incidental finding of pulmonary tumourlet.

CASE REPORT

A 71-year-old woman with a medical history of recurrent episodes of pneumonia followed by hemoptysis and cough, with expectoration of

Received • Примљено: June 9, 2022
Revised • Ревизија: July 29, 2022
Accepted • Прихваћено: September 1, 2022
Online first: September 5, 2022

Correspondence to:
Vladimir MILENKOVIĆ
University Clinical Center of Serbia
Clinic for Thoracic Surgery
Dr Koste Todorovića 26
11000 Belgrade
Serbia
vlada1309@gmail.com

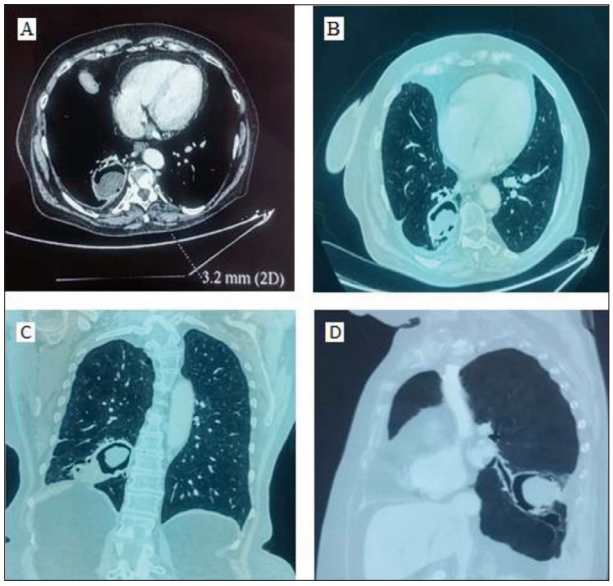


Figure 1. The aspergilloma in the intrapulmonary cavity; A – soft tissue window, axial section; B – lung parenchymal window, axial section; C – lung parenchyma window, coronal section; D – lung parenchyma window, sagittal section

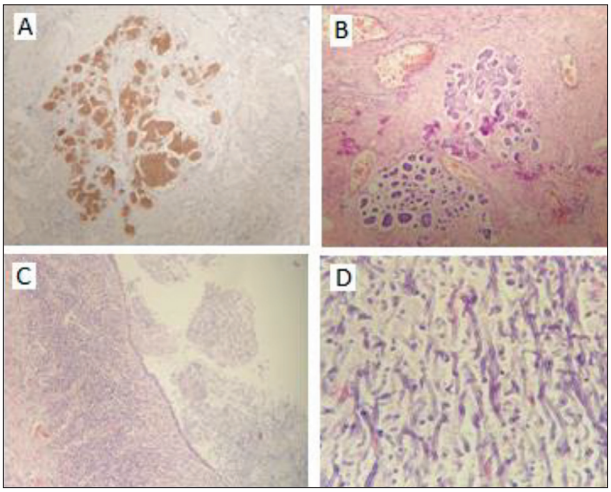


Figure 2. A – hematoxylin-eosin staining of bonchiectatic wall filled with fungus ball, mass consisted of fungal hyphae and necrotic fragments; bronchial wall is infiltrated by inflammatory cells, consisted mainly from lymphocytes, plasma cells and eosinophil leukocytes, lined by metaplastic squamous epithelial cells; magnification 100 ×; B – branching elongated hyphae of *Aspergillus*; periodic-acid-Schiff stain; magnification 400 ×; C – diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; magnification 200 ×; D – neuroendocrine marker CD 56 expression in neuroendocrine cell hyperplasia; magnification 200 ×

brown-yellow sputum, was admitted to our department. The patient had a medical history of smoking, chronic obstructive pulmonary disease, arterial hypertension and mastectomy due to breast cancer. The results of spirometry, diffusion of carbon monoxide (CO) and laboratory were normal. Chest computed tomography (CT) scan is the golden standard for diagnosing of the lung diseases. It showed pulmonary soft tissue mass in the right lower lobe of the lung, oval cavitation approximately 42 × 50 mm in diameter, presence of "air in the form of a crescent sign," and the communication with subsegmental branches of the apicobasal segmental bronchus. Chronic pneumonitis and traction bronchiectasis, with no pathologic enlargement of the lymph nodes was also seen (Figure 1). Direct microscopy of the specimens of bronchoalveolar lavage identified spores of *Aspergillus*. Galactoman Ag test was positive. The patient was initially treated with antimicrobic therapy for two weeks before surgery. Right lower lobectomy and mediastinal lymph node sampling was performed via thoracotomy.

Pathological examination of the specimen showed intrapulmonary cavity in the right lower lobe, 45 mm in diameter. Intracavitary material was brown, necrotic, compatible with aspergilloma. Aspergilloma composed of numerous hyphae of *Aspergillus* was seen on the sections of the lung parenchyma along the bronchial wall. Hyphae were visualized by immunohistochemical methods periodic acid-Schiff and Grocott. Signs of vascular invasion by tumour cells, round, bright cytoplasm, in predominantly organoid arrangement, were observed in the vascular spaces. Group of uniform tumor cells were detected in a microscopic focus and measured less than 5 mm. Immunohistochemical staining for CD56, TTF-1, synaptophysin and cytokeratin were positive, while napsin A, CD34, p40, LCA were negative. Ki67 level was 2–3% in these cells. Lymph nodes specimens showed no metastatic tumor cells. The specimen contained a several areas of pulmonary tumorlet and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH). Final pathohistological findings corresponded to aspergilloma with the presence of pulmonary tumorlet and DIPNECH in the lymphovascular spaces (Figure 2).

Five-year follow up showed no abnormalities on the chest CT scan, and the patient was without medical problems.

We confirm that we have read the journal's position on issues involving ethical publication and affirm that this work is consistent with those guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

DISSCUSION

Aspergilloma occurs as a consequence of saprophytic infection of the previously formed cavity of the lung parenchyma. Cough and hemoptysis are the most common symptoms. After the formation of aspergilloma, the effect of antimicrobial drugs is drastically reduced. In such situations, surgical treatment may be the only choice [7]. Pulmonary tumorlet, which represents nodular proliferations of neuroendocrine cells, are rare and do not exceed 5 mm in diameter [8]. These proliferations occur most often as a consequence of Kulchitsky cells hyperplasia in various lung diseases. They often occur in several places. Hyperplastic foci of these cells larger than 5 mm in diameter represents carcinoid tumors [8, 10, 11, 12]. They are most often detected on surgical material after lung

resections due to diseases that cause destruction of the lung parenchyma. There are several subgroups of neuroendocrine tumors with common characteristics: pulmonary tumorlet, DIPNECH, carcinoid tumors [10]. Concomitant occurrence of neuroendocrine tumors and aspergilloma is rare [9]. They are most often asymptomatic and occur in other lung diseases characterized by destruction of the lung parenchyma and the presence of a chronic inflammatory process. Cellular atypia and cell necrosis are rare, while mitotic activity is usually absent [11]. Recently published studies consider pulmonary tumorlet and DIPNECH precancerous lesions. However, proliferation to carcinoid tumors is rare [12, 13]. Nodal metastases are very rare and usually occurs in hilar lymph nodes [14].

It most often appears between the ages of 60 and 70, and it is four times more likely in men than in women (1:4). Dyspnea is the most common symptom. Small nodules up to 5 mm in diameter on a chest CT scan in patients with dyspnea without clear causes may raise the suspicion of the presence of pulmonary tumorlet and DIPNECH. Positron emission tomography/computed tomography in those cases is not the best diagnostic choice due to their size [8]. There are still no clear guidelines for monitoring and selecting the treatment for pulmonary tumorlet and DIPNECH. Also, prevention measures for their occurrence have not been determined yet. However, risk groups should be advised to quit smoking, practice physical activity, avoid exposure to certain physical and chemical substances such as asbestos, arsenic, tar, chromium, nickel, etc. Avoiding alcohol consumption is also advised [9]. Octreotide, 18F-DOPA amino acid analogs, inhaled corticosteroids, and beta agonists were part of the studies examining their effect in the treatment of neuroendocrine tumors and precancerous lesions such as pulmonary tumorlet and DIPNECH [8, 13]. Chronic inflammatory lung diseases, granulomatous lung diseases and bronchiectasis are the most common lung diseases in which pulmonary tumorlet occurs [10]. In our case, the presence of pulmonary tumorlet and aspergilloma in the bronchiectatic cavity were identified at the same time.

The question of the connection between pulmonary tumorlet and chronic inflammatory lung diseases is raised. The presence of bronchiectasis, aspergilloma, and precancerous lesions, such as pulmonary tumorlet and DIPNECH further increase the risk of developing malignant tumors as well as recurrent infections. So far, no consensus has been reached on the timing and type of surgery in patients with aspergilloma. Despite no comparative studies of antifungal therapy in patients preparing for surgery, voriconazole remains the first option, as it has been related to reduced mortality [15–19]. The presence of chronic inflammation and the negative effect of the infection on the remaining part of the lung parenchyma further complicate recovery after surgery. Therefore, surgical treatment can prevent the development of premalignant lesions and the occurrence of recurrent infections accompanied by dyspnea and hemoptysis as the main symptoms. We hope that the future researches will provide answers to those questions.

Conflict of interest: None declared.

REFERENCES

1. Nilsson JR, Restrepo CS, Jagirdar J. Two cases of endobronchial carcinoid masked by superimposed aspergillosis: A review of the literature of primary lung cancers associated with Aspergillus. Ann Diagn Pathol. 2013;17(1):131–6. [DOI: 10.1016/j.anndiagpath.2011.06.005] [PMID: 22079170]
2. Rasheed A, McCloskey A, Foroutan S, Waheed A, Rodgers A, Seraj SM, et al. Pulmonary Aspergilloma in a Young Immunocompetent Female: A Rare Clinical Dilemma. Cureus. 2022;14(2):e22724. [DOI: 10.7759/cureus.22724] [PMID: 35371658]
3. Bongomin F, Asio LG, Baluku JB, Kwizera R, Denning DW. Chronic Pulmonary Aspergillosis: Notes for a Clinician in a Resource-Limited Setting Where There Is No Mycologist. J Fungi (Basel). 2020;6(2):75. [DOI: 10.3390/jof6020075] [PMID: 32498415]
4. S Kumar S, Ray A, Vikram NK, Vyas S. Unusual case of chronic cavitary pulmonary aspergillosis presenting as spontaneous pneumothorax in an immunocompromised man. BMJ Case Rep. 2021;14(8):e241655. [DOI: 10.1136/bcr-2021-241655] [PMID: 34340987]
5. Goyal RC, Tyagi R, Garg B, Mishra A, Sood N. Pulmonary Hydatid Disease with Aspergillosis - An Unusual Association in an Immunocompetent Host. Turk Patoloji Derg. 2019;35(2):166–9. [DOI: 10.5146/tjpath.2017.01396] [PMID: 29630082]
6. Nivoix Y, Velten M, Letscher-Bru V, Moghaddam A, Natarajan-Amé S, Fohrer C, et al. Factors associated with overall and attributable mortality in invasive aspergillosis. Clin Infect Dis. 2008;47(9):1176–84. [DOI: 10.1086/592255] [PMID: 18808352]
7. Harmouchi H, Sani R, Issoufou I, Lakranbi M, Ouadnouni Y, Smahi M. Pulmonary aspergilloma: from classification to management. Asian Cardiovascular and Thoracic Ann. 2020;28(1):33–8. [DOI: 10.1177/0218492319895113] [PMID: 31799858]
8. Kallianos A, Velentza L, Zarogoulidis P, Baka S, Kosmidis C, Labaki S, et al. Progressive dyspnea due to pulmonary carcinoid tumorlets. Respir Med Case Rep. 2017;21:84–5. [DOI: 10.1016/j.rmcr.2017.03.024] [PMID: 28417065]
9. Yazgan S, Gursoy S, Turk F, Dinc ZA. Conjuction of a Fungus Ball and a Pulmonary Toumorlet in a Brochiectatic Cavity. Korean J Thorac Cardiovasc Surg. 2018;51:138–41. [DOI: 10.5090/kjtcs.2018.51.2.138] [PMID: 29662813]
10. He P, Gu X, Wu Q, Lin Y, Gu Y, He J. Pulmonary carcinoid tumorlet without underlying lung disease: analysis of its relationship to fibrosis. J Thorac Dis. 2012;4(6):655–8. [DOI: 10.3978/j.jssn.2072-1439.2012.06.11] [PMID: 23205296]
11. Churg A, Warnock ML. Pulmonary tumorlet. A form of peripheral carcinoid. Cancer. 1976;37(3):1469–77. [DOI: 10.1002/1097-0142(197603)37:3<1469::aid-cncr2820370332>3.0.co;2-h] [PMID: 177168]
12. Hendifar AE, Marchevsky AM, Tuli R. Neuroendocrine Tumors of the Lung: Current Challenges and Advances in the Diagnosis and Management of Well-Differentiated Disease. J Thorac Oncol. 2017;12(3):425–36. [DOI: 10.1016/j.jtho.2016.11.2222] [PMID: 27890494]
13. Wirtschafter E, Walts AE, Liu ST, Marchevsky AM. Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia of the Lung (DIPNECH): Current Best Evidence. Lung. 2015;193(5):659–67. [DOI: 10.1007/s00408-015-9755-1] [PMID: 26104490]
14. D'Agati VD, Perzin KH. Carcinoid tumorlets of the lung with metastasis to a peribronchial lymph node: report of a case and review of the literature. Cancer. 1985;55(10):2472–6. [DOI: 10.1002/1097-0142(19850515)55:10<2472::aid-cncr2820551027>3.0.co;2-y] [PMID: 3986742]
15. Akram W, Ejaz MB, Mallhi TH, Syed Sulaiman SAB, Khan AH. Clinical manifestations, associated risk factors and treatment outcomes of Chronic Pulmonary Aspergillosis (CPA): Experiences from a tertiary care hospital in Lahore, Pakistan. PLoS One. 2021;16(11):e0259766. [DOI: 10.1371/journal. pone.0259766] [PMID: 34767589]
16. Bongomin F, Asio LG, Baluku JB, Kwizera R, Denning DW. Chronic Pulmonary Aspergillosis: Notes for a Clinician in a Resource-

Limited Setting Where There Is No Mycologist. J Fungi (Basel). 2020;6(2):75. [DOI: 10.3390/jof6020075] [PMID: 32498415]
17. Mir T, Uddin M, Khalil A, Lohia P, Porter L, Regmi N, et al. Mortality outcomes associated with invasive aspergillosis among acute exacerbation of chronic obstructive pulmonary disease patient population. Respir Med. 2022;191:106720. [DOI: 10.1016/j.rmed.2021.106720] [PMID: 34959147]
18. Molinos-Castro S, Pesqueira-Fontán PM, Rodríguez-Fernández S, Rodríguez-Framil M, Barbeito-Castiñeiras G, Gayol-Fernández MC, et al. Clinical factors associated with pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. Enferm Infecc Microbiol Clin (Engl Ed). 2020;38(1):4–10. [DOI: 10.1016/j.eimc.2019.06.007] [PMID: 31405617]
19. Guziejko K, Klukowska K, Budzińska U, Mróz RM. Case Report: Chronic Pulmonary Aspergillosis-An Unusual Long-Term Complication of Lung Cancer Treatment. Front Med (Lausanne). 2022;8:777457. [DOI: 10.3389/fmed.2021.777457] [PMID: 35096873]

Узгредни налаз плућних туморлета у случају хируршки лечене бронхиектатичне шупљине насељене аспергиломом

Дејан Московљевић[1], Никола Чолић[2], Анђела Димкић-Миленковић[3], Јелена Марковић[4], Владимир Миленковић[1]

[1]Универзитетски клинички центар Србије, Клиника за грудну хирургију, Београд, Србија;
[2]Универзитетски клинички центар Србије, Центар за радиологију и магнетну резонанцу, Београд, Србија;
[3]Универзитетски клинички центар Србије, Клиника за опекотине, пластичну и реконструктивну хирургију, Београд, Србија;
[4]Универзитетски клинички центар Србије, Одељење торакопулмоналне патологије, Служба патохистологије, Београд, Србија

САЖЕТАК

Увод Интракавитарни аспергилом је последица сапрофитне инфекције плућа са кавитарном болешћу. Плућни туморлети су нодуларне пролиферације неуроендокриних ћелија пречника мањег од 5 *mm*. Ретки су случајеви истовременог откривања аспергилома у бронхоектатичној шупљини плућа и плућних туморлета.

Приказ болесника У раду је приказан случај болеснице старосне доби 71 годину, са понављаним упалама плућа које су праћене кашљем и хемоптизијама. Компјутеризована томографија грудног коша показала је мекоткивну масу пречника 42 × 50 *mm* у доњем десном плућном режњу. Узорци бронхоалвеоларне лаваже су показали споре аспергилуса (директна микроскопија). Тест *Galactoman Ag* је такође био позитиван. Урађени су десна доња лобектомија и узорковање медијастиналних лимфних чворова приступом кроз торакотомију. Патохистолошки налаз је показао бронхоектатичну шупљину у плућима са аспергилом и присуством плућних туморлета у лимфоваскуларним просторима. После пет година праћења компјутеризована томографија грудног коша није показала абнормалности и болесница је била без здравствених тегоба.

Закључак Истовремена појава бронхиектазије, аспергилома као и преканцерозних лезија као што су плућни туморлети и дифузна идиопатска хиперплазија неуроендокриних ћелија плућа (*DIPNECH*) ретка је и додатно повећава ризик од развоја малигних тумора и рекурентних инфекција. Хируршким лечењем може се спречити развој малигних тумора и појава рекурентних инфекција праћених диспнејом и хемоптизијама као главним симптомима. Поставља се питање повезаности преканцерозних лезија плућа и хроничних инфламаторних болести. Надамо се да ће будућа истраживања дати одговоре на ово питање.

Кључне речи: бронхиектазије; аспергилом; плућни туморлети; *DIPNECH*

DOI: https://doi.org/10.2298/SARH210218106T
UDC: 616.137-007.251; 616.137-089.819-06

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Antegrade dissection of external iliac artery after failed attempt of common femoral artery chronic total occlusion angioplasty

Slobodan Tanasković[1,2], Miodrag Ilić[1], Đorđe Radak[3,4], Predrag Gajin[1,2], Vladimir Kovačević[5], Srđan Babić[1,2], Nenad Ilijevski[1,2]

[1]Dedinje Cardiovascular Institute, Vascular Surgery Clinic, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]Dedinje Cardiovascular Institute, Scientific Board, Belgrade, Serbia;
[4]Serbian Academy of Sciences and Arts, Belgrade, Serbia;
[5]Dedinje Cardiovascular Institute, Clinic for Radiology, Belgrade, Serbia

SUMMARY

Introduction Endovascular treatment of chronic total occlusion (CTO) represents a true challenge even for experienced interventional radiologists. We are presenting a case of hidden antegrade dissection of the external iliac artery (EIA) after a failed attempt to recanalize CTO of the common femoral artery (CFA).

Case outline A 52-year-old male patient was admitted for multidetector computed tomography (CT) angiography. Left common iliac artery (CIA) stenting was performed, followed by "crossover" attempt of recanalization of right CFA CTO that failed. The next day, left femoral superficial artery angioplasty was performed and after one month, angioplasty of the left popliteal and the bellow-knee arteries. A month later, the patient was readmitted for surgical reconstruction of the CFA. After desobstruction, excellent inflow was obtained and a Dacron graft was inserted. A few hours postoperatively, Fogarty catheter thrombectomy was performed. The next morning, pulsations were weakened again and CT angiography showed antegrade dissection of the EIA. Stenting of the EIA was performed with two stents and a favorable outcome was achieved. After a detailed analysis of the CT, hidden thrombosed antegrade dissection of the EIA was noted in the lateral view, which was not seen in the posterior/anterior view and was presented as fibrous plaque with mural thrombosis. Dissection occurred after failed attempt of CFA recanalization and was clinically silent until flow was established triggering opening of the false lumen and the release of thrombotic masses.

Conclusion In patients with failed angioplasty of CTO of the CFA and CT characteristics of fibrous plaque proximal to the site of attempted angioplasty, thrombosed antegrade dissection should be considered.

Keywords: iliac artery dissection; common femoral artery; chronic total occlusion; thrombosis

INTRODUCTION

Common femoral artery (CFA) chronic total occlusion (CTO) represents a true challenge even for experienced and skilled interventional radiologist. In case of extensive, complex and long occlusive lesions of the CFA and iliac arteries, surgical treatment is still a preferable treatment option [1–4]. However, the progress of endovascular therapy as a less invasive procedure in the last two decades has resulted in numerous publications showing good results of endovascular treatment of the CFA stenosis and occlusion, with a low rate of post-procedural morbidity and mortality [5–9]. Herein, we present an interesting case of a hidden thrombosed antegrade dissection of the external iliac artery (EIA) after unsuccessful CTO angioplasty of the CFA evident only after surgical revascularization.

CASE REPORT

A 52-year-old male patient was admitted to our institution for multidetector computed tomography (MDCT) angiography. He complained of rest pain in the left foot with livid ischemia that appeared 10 days prior to admission. He also had claudication in his right leg after 100 m, which was not clinically manifested upon admission due to the inability of walking and the rest pain in the left leg. His past medical history included hypertension and hyperlipidemia. Echocardiography showed regular findings except for dilated left atrium (45 mm). Laboratory findings were within referent values except for creatine kinase, which was elevated – 654 international units (UI)/L. The examination showed absent right femoral pulse, left femoral pulse was palpable with ischemia on the third and fourth finger of the left foot. Ankle brachial indexes on the left leg were 0.37 on both the posterior tibial artery and anterior tibial artery and 0.62 on the posterior and 0.75 on the anterior tibial artery of the right leg. MDCT arteriography (64-slice device, GE HealthCare, Chicago, IL, USA) showed a significant left common iliac artery (CIA) stenosis, occlusion of the right CIA at transition to the CFA, left superficial femoral artery (SFA) subocclusion, and significant stenosis of the left popliteal artery.

Received • Примљено: February 18, 2021
Revised • Ревизија: September 5, 2022
Accepted • Прихваћено: October 26, 2022
Online first: November 2, 2022

Correspondence to:
Slobodan TANASKOVIĆ
Vascular Surgery Clinic
Dedinje Cardiovascular Institute
1 Heroja Milana Tepića Street
Belgrade 11000, Serbia
drslobex@yahoo.com
drslobex@gmail.com

Firstly, left CIA stenting was performed by the antegrade approach from the left groin, followed by a "crossover" simultaneous attempt of recanalization of the right CFA CTO, which failed due to heavily calcified lesions, and CFA surgical treatment was indicated. Right CFA CTO angioplasty was attempted via the crossover approach with 55-cm-long SheatLess guiding system (Asahi-Intecc®, Tokyo, Japan) along with Shinobi 0.014 guidewire (Cordis, Fremont, CA, USA). The following day, by a left retrograde approach, SFA angioplasty was performed with stent placement. A month later, the patient was readmitted for planned right CFA surgical reconstruction. On admission, he still complained on ischemic pain in the left leg and control MDCT angiography showed regular findings after left CIA and SFA stenting (Figure 1), but also significant popliteal artery stenosis beneath the stent. Bearing in mind persisting pain in the left foot, the left popliteal artery, the posterior, and the anterior tibial artery angioplasty was performed with favorable outcome, and right CFA reconstruction was delayed for the next hospitalization.

After one month, the patient was readmitted for right CFA CTO surgical reconstruction based on the previous MDCT findings. Intraoperatively, extensive exposure of the right CFA was performed, and the CFA, the SFA, the deep femoral artery and side branches were clamped. After CFA desobstruction and plaque removal, excellent inflow was obtained and Dacron tubular graft was inserted between the EIA and the femoral arteries. The clamps were removed and distal pulsations were regular. In the evening, femoral pulsations were attenuated and the patient was sent back to the operating room. Inflow was present but weakened, Fogarty catheter was introduced and thrombectomy was performed without any difficulties, followed by improved inflow. The next morning, pulsations in the right groin were weakened again and control MDCT angiography was performed. Surprisingly, antegrade dissection of the EIA was noted, starting just above the level of the proximal graft anastomosis and going to the CIA bifurcation (Figure 2). The graft as well as proximal and distal anastomosis were with regular findings. Stenting of the right EIA was performed with placement of two stents and favorable outcome.

Postoperative course was uneventful, ankle brachial indexes were 0.8 on both arteries of the right leg and 1.0 on both arteries of the left leg. The patient was discharged on the sixth postoperative day. After six-months follow-up, vascularization of both legs was well preserved.

This case report was approved by the institutional ethics committee, and written consent was obtained from the patient for the publication of the case report and any accompanying images.

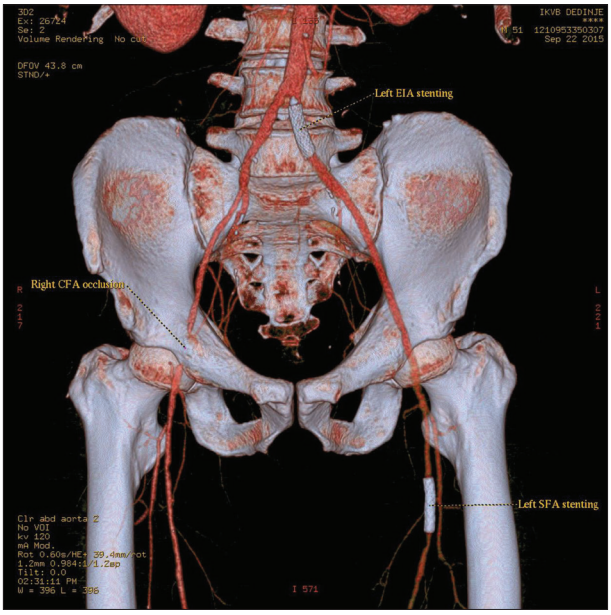


Figure 1. Multidetector computed tomography angiography; regular findings after left common iliac artery and superficial femoral artery (SFA) angioplasty with stent placement and evident right common femoral artery (CFA) occlusion – posterior/anterior view

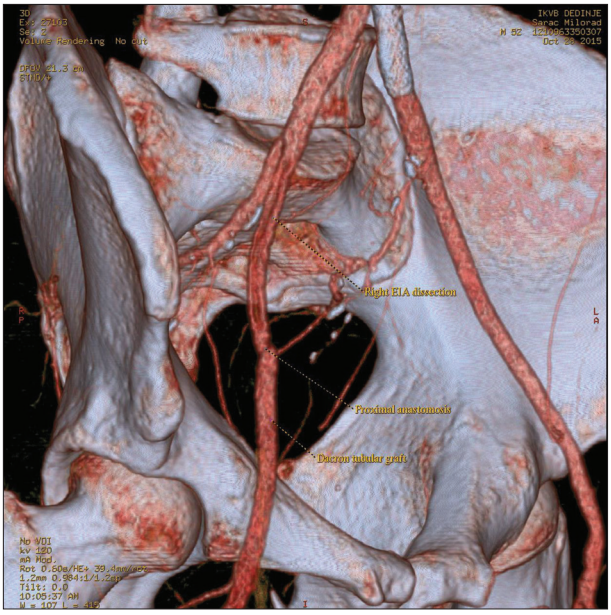


Figure 2. Multidetector computed tomography angiography; antegrade right external iliac artery (EIA) dissection starting just above the proximal anastomosis of the Dacron tubular graft

DISCUSSION

Management of CFA lesions is challenging. Surgical treatment and endarterectomy of CFA lesions has been proved to be a safe and reliable procedure [1–4]. Elsherif et al. [4] reported the outcome of 1134 revascularization procedures due to critical limb ischemia, out of which 66 CFA endarterectomies with favorable outcome. However, improvements in endovascular procedures in recent years have resulted in numerous publications showing good results of the endovascular treatment of CFA lesions [5–10]. In a recent review of seven CFA endarterectomy studies and four CFA endovascular studies, endovascular approach was associated with a lower rate of morbidity and mortality, but also with a higher reintervention rate when compared to surgery [7]. Nakama et al. [11] have recently reported one-year outcomes of thromboendarterectomy and endovascular treatment for CFA lesions in 1193 patients and

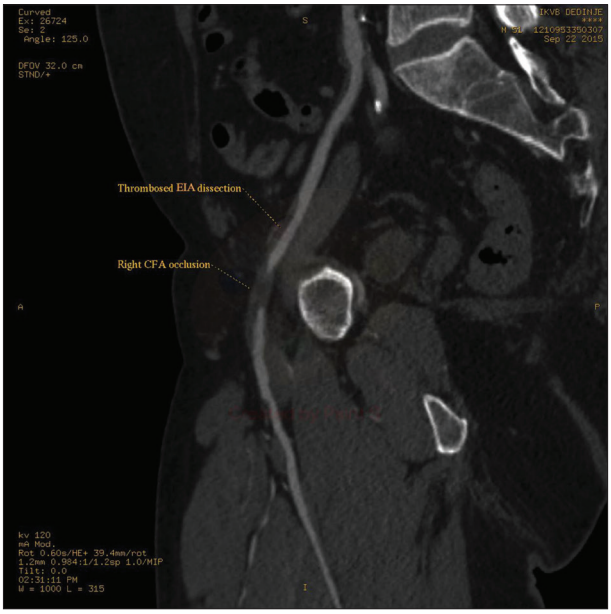


Figure 3. Hidden thrombosed antegrade dissection of the right external iliac artery (EIA) after the angioplasty attempt of the chronic total occlusion of the common femoral artery (CFA) – lateral view

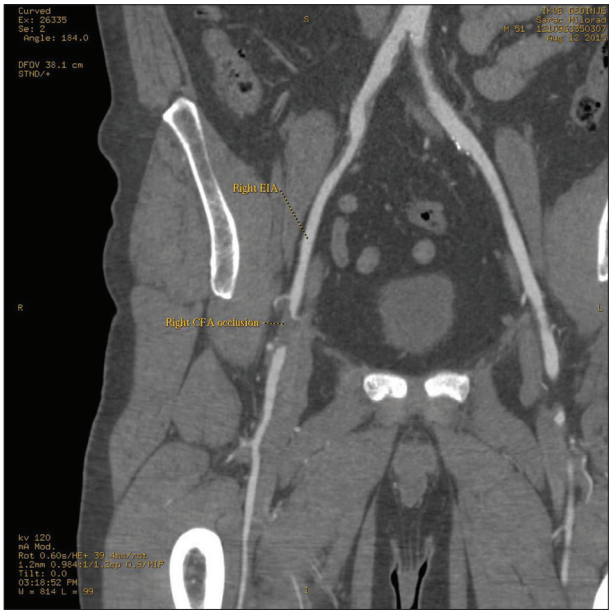


Figure 4. Multidetector computed tomography angiography; chronic total occlusion of the right common femoral artery (CFA) without any signs of thrombosed dissection prior to the angioplasty attempt

found that one-year primary patency rate was significantly higher in the thromboendarterectomy group (96.6% *vs.* 82.3%, $p < 0.001$) but with higher rate of periprocedural complications in the same group of patients.

Results of endovascular treatment of 946 isolated CFA lesions were reported by Siracuse et al. [8] with low rate of periprocedural morbidity and mortality and with dissection rate of 2.9%. Böhme et al. [10] also reported favorable outcomes of CFA angioplasties performed in 250 patients, out of which 64 patients had a CFA occlusion. The overall complications rate was 9.1%, with the primary patency rate of 90.8%, 81.2%, and 72% at six, 12, and 24 months, respectively.

In case of combined CFA lesions and multiple stenoocclusive proximal or distal disease, a hybrid approach, CFA endarterectomy with combined endovascular approach, has been reported with reduced operative risk in patients with high morbidity [12]. A novel approach, stent-assisted angioplasty of CFA lesions showed satisfactory technical success, with low restenosis rate during the follow-up but with high mortality rate [13]. On the other hand, multichannel balloon angioplasty of heavily calcified CFA lesions has been described as well, with good initial results [14].

Although percutaneous angioplasty showed a favorable outcome in the treatment of CFA lesions, post-procedural dissection is still one the major issues after peripheral angioplasty [15, 16, 17]. In the presented case, the CFA CTO angioplasty was attempted by subintimal approach, followed by hidden, clinically silent, thrombosed antegrade dissection of the iliac artery. When we discussed the reasons for unrecognized dissection, we looked in detail and once more processed all previous CT images. After processing images of the control CT angiography, performed after attempted CFA CTO recanalization and the first CIA and SFA angioplasty, we saw an alteration within the EIA wall in the lateral view (Figure 3), which was not visible in the posterior/anterior (PA) view (Figure 1). At first, we thought that this alteration was fibrous atheromatous plaque with mural thrombosis, but then we realized that it was actually thrombosed antegrade dissection (Figure 3). These findings were also not visible on the first CT presentation before the angioplasty attempt (Figure 4); hence, we realized that the dissection occurred in the meantime, after the attempted angioplasty of the CFA. The dissection was clinically silent due to thrombosed false lumen and distal CFA occlusion. After successful surgical revascularization, established flow opened the false lumen, which triggered the release of thrombotic masses, causing early graft thrombosis, successfully treated by Fogarty catheter thrombectomy. Once the flow was established in the true and false lumen, the dissection membrane was clearly visible (Figure 2).

By this case we want to point out three things. Firstly, it is important to emphasize that CT angiography could be misleading in describing thrombosed antegrade iliac artery dissection as fibrous atheromatous plaque with mural thrombosis. CT characteristics were almost identical and the diagnosis was reinforced by the fact that the dissection was clinically silent due to already present distal CFA occlusion. The second thing we wanted to highlight is the importance of the lateral view while processing CT images, as it could reveal hidden minor alterations within the arterial wall that are not visible in the PA view. And thirdly and finally, we wanted to draw attention to the conversion of an asymptomatic, clinically silent, thrombosed antegrade dissection into a manifest dissection associated with thromboembolic events. In case of a unrecognized thrombosed antegrade dissection in patients with CTO, successful surgical revascularization and established flow

could trigger the release of thrombotic mass followed by embolic events and limb-threating ischemia.

In patients with a failed angioplasty of the CFA CTO and CT characteristics of fibrous plaque with mural thrombosis proximal to the site of attempted recanalization, thrombosed antegrade dissection should be considered. Processing CT images in the lateral view could reveal changes within the arterial wall that are not visible in the PA view. Successful surgical revascularization of CTO lesions of the CFA in patients with previously attempted angioplasty could trigger a conversion of a hidden thrombosed to an evident antegrade iliac artery dissection.

Conflict of interest: None declared.

REFERENCES

1. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, HalperinJL, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2006;113(11):e463–654. [DOI: 10.1161/CIRCULATIONAHA.106.174526] [PMID: 16549646]
2. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-society Consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg. 2007;45(Suppl S):S5–67. [DOI: 10.1016/j.jvs.2006.12.037] [PMID: 17223489]
3. Ballotta E, Gruppo M, Mazzalai F, Da Giau G. Common femoral artery endarterectomy for occlusive disease: an 8-year single-center prospective study. Surgery. 2010;147(2):268–74. [DOI: 10.1016/j.surg.2009.08.004] [PMID: 19828166]
4. Elsherif M, Tawfick W, Elsharkawi M, Campell R, Hynes N, Sultan S. Common femoral artery endarterectomy in the age of endovascular therapy. Vascular. 2018;26(6):581–90. [DOI: 10.1177/1708538118772682] [PMID: 29759039]
5. Wong G, Lahsaei S, Aoun J, Garcia LA. Management of common femoral artery occlusive disease: A review of endovascular treatment strategies and outcomes. Catheter Cardiovasc Interv. 2019;93(3):514–21. [DOI: 10.1002/ccd.27983] [PMID: 30537332]
6. Imran HM, Hyder ON, Soukas PA. Efficacy and safety of adjunctive drug-coated balloon therapy in endovascular treatment of common femoral artery disease. Cardiovasc Revasc Med. 2019;20(3):210–4. [DOI: 10.1016/j.carrev.2018.06.018] [PMID: 29970328]
7. Halpin D, Erben Y, Jayasuriya S, Cua B, Jhamnani S, Mena-Hurtado C. Management of Isolated Atherosclerotic Stenosis of the Common Femoral Artery: A Review of the Literature. Vasc Endovascular Surg. 2017;51(4):220–7. [DOI: 10.1177/1538574417702773] [PMID: 28376704]
8. Siracuse JJ, Van Orden K, Kalish JA, Eslami MH, Schermerhorn ML, Patel VI, et al; Vascular Quality Initiative. Endovascular treatment of the common femoral artery in the Vascular Quality Initiative. J Vasc Surg. 2017;65(4):1039–46. [DOI: 10.1016/j.jvs.2016.10.078] [PMID: 28041804]
9. Baumann F, Ruch M, Willenberg T, Dick F, Do DD, Keo HH, et al. Endovascular treatment of common femoral artery obstructions. J Vasc Surg. 2011;53(4):1000–6. [DOI: 10.1016/j.jvs.2010.10.076] [PMID: 21215567]
10. Böhme T, Zeller T, Abboud M, Beschorner U, Noory E. Evaluation of Stent Angioplasty in the Treatment of Arteriosclerotic Lesions of the Common Femoral Artery. J Clin Med. 2022;11(10):2694. [DOI: 10.3390/jcm11102694] [PMID: 35628821]
11. Nakama T, Takahara M, Iwata Y, Fujimura N, Yamaoka T, Suzuki K, et al; CAULIFLOWER Study Investigators. 1-Year Outcomes of Thromboendarterectomy vs Endovascular Therapy for Common Femoral Artery Lesions: CAULIFLOWER Study Results. JACC Cardiovasc Interv. 2022;15(14):1453–63. [DOI: 10.1016/j.jcin.2022.03.010] [PMID: 35863795]
12. Kim JH, So BJ, Byun SJ, Kim KY. The Advantage of Common Femoral Endarterectomy Alone or Combined with Endovascular Treatment. Vasc Specialist Int. 2018;34(3):65–71. [DOI: 10.5758/vsi.2018.34.3.65] [PMID: 30310809]
13. Stricker H, Spinedi L, Limoni C, Giovannacci L. Stent-Assisted Angioplasty (SAA) at the Level of the Common Femoral Artery Bifurcation: Long-Term Outcomes. Cardiovasc Intervent Radiol. 2020;43(4):541–6. [DOI: 10.1007/s00270-020-02413-9] [PMID: 31974742]
14. Nagatomi S, Ichihashi S, Yamamoto H, Iwakoshi S, Taguchi H, Inagaki M, et al. Efficacy of Multichannel Balloon Angioplasty in Calcified Common Femoral Artery Lesions. J Vasc Interv Radiol. 2021;32(2):181–6. [DOI: 10.1016/j.jvir.2020.10.018] [PMID: 33288417]
15. Gray WA, Cardenas JA, Brodmann M, Werner M, Bernardo NI, George JC, et al. Treating Post-Angioplasty Dissection in the Femoropopliteal Arteries Using the Tack Endovascular System: 12-Month Results From the TOBA II Study. JACC Cardiovasc Interv. 2019;12(23):2375–84. [DOI: 10.1016/j.jcin.2019.08.005] [PMID: 31806218]
16. Tan M, Urasawa K, Koshida R, Haraguchi T, Kitani S, Igarashi Y, et al. Comparison of Angiographic Dissection Patterns Caused by Long vs Short Balloons During Balloon Angioplasty of Chronic Femoropopliteal Occlusions. J Endovasc Ther. 2018;25(2):192–200. [DOI: 10.1177/1526602818756610] [PMID: 29429382]
17. Kobayashi N, Hirano K, Yamawaki M, Araki M, Sakai T, Sakamoto Y, et al. Simple classification and clinical outcomes of angiographic dissection after balloon angioplasty for femoropopliteal disease. J Vasc Surg. 2018;67(4):1151–8. [DOI: 10.1016/j.jvs.2017.08.092] [PMID: 29242063]

Антероградна дисекција спољашње илијачне артерије после неуспелог покушаја ангиопластике хроничне тоталне оклузије заједничке феморалне артерије

Слободан Танасковић[1,2], Миодраг Илић[1], Ђорђе Радак[3,4], Предраг Гајин[1,2], Владимир Ковачевић[5], Срђан Бабић[1,2], Ненад Илијевски[1,2]

[1]Институт за кардиоваскуларне болести „Дедиње“, Клиника за васкуларну хирургију, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Институт за кардиоваскуларне болести „Дедиње“, Научно веће, Београд, Србија;
[4]Српска академија наука и уметности, Београд, Србија;
[5]Институт за кардиоваскуларне болести „Дедиње“, Клиника за радиологију, Београд, Србија

САЖЕТАК

Увод Ендоваскуларни третман хроничне тоталне оклузије представља прави изазов чак и за искусне интервентне радиологе. Приказујемо случај скривене антероградне дисекције спољашње илијачне артерије (СИА) после неуспелог покушаја реканализације хроничне тоталне оклузије заједничке феморалне артерије (ЗФА).

Приказ болесника Мушкарац старости 52 године примљен је ради мултидетекторске компјутеризоване томографске ангиографије. Урађен је стентинг леве заједничке илијачне артерије, а после тога и *crossover* покушај реканализације хроничне тоталне оклузије десне ЗФА, који није успео. Следећег дана урађена је ангиопластика леве површне бутне артерије, а после месец дана и ангиопластика поплитеалне и потколених артерија леве ноге. Месец дана касније болесник је поново примљен због хируршке реконструкције ЗФА. После дезопструкције добијен је одличан проток и урађена је интерпозиција дакронског графта. Неколико сати постоперативно урађена је и тромбектомија Фогартијевим катетером. Наредног јутра пулсације у десној препони су поново биле ослабљене и КТ ангиографија је показала антероградну дисекцију СИА. Урађен је стентинг СИА са два стента и са задовољавајућим исходом. После детаљне анализе КТ снимака, верификована је тромбозирана дисекција СИА у латералном прегледу, која није била виђена у постериорно/антериорном прегледу и које је била представљена као фиброзни плак са муралном тромбозом. Дисекција је настала после неуспелог покушаја реканализације ЗФА и била је клинички нема док није успостављен проток који је покренуо отварање лажног лумена и ослобађање тромботичних маса.

Закључак Код болесника са неуспешном ангиопластиком хроничне тоталне оклузије ЗФА и КТ карактеристикама фиброзног плака проксимално од места покушаја ангиопластике, треба помислити и на тромбозирану антероградну дисекцију.

Кључне речи: дисекција илијачне артерије; заједничка феморална артерија; хронична тотална оклузија; тромбоза

DOI: https://doi.org/10.2298/SARH211222079D
UDC: 616.34-007.272; 616.366-003.7-06

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Cholecystoduodenal fistula and gallstone ileus – diagnosis and surgical treatment

Džemail S. Detanac[1], Dženana Detanac[1], Krstina Doklestić[2,3], Džemil Bihorac[1], Safet Muratović[1]

[1]Novi Pazar General Hospital, Novi Pazar, Serbia;
[2]University Clinical Center of Serbia, Clinic for Emergency Surgery, Belgrade, Serbia;
[3]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY
Introduction Gallstone ileus is a complete or partial mechanical bowel obstruction due to gallstone impaction in the bowel lumen and most commonly occurs after stones migrate through the cholecystoenteric fistula.
Case outline We present a patient with signs of gallstone ileus after stone migration through the cholecystoduodenal fistula into the duodenum with hematemesis as the first symptom. Conservative treatment had been started, to which the patient initially responded well. On the eighth day from the onset of the disease, the condition worsened. Signs of the Rigler triad were identified on computed tomography and magnetic resonance imaging of the abdomen. Enterolithotomy was successfully performed by the open surgical method. Postoperative recovery was orderly, without any biliary problems.
Conclusion Physical examination, upper endoscopy, and radiological diagnostic procedures are complementary and necessary in monitoring the dynamics of stone movement and deciding on when to perform surgery.
Keywords: gallstone ileus; cholecystoduodenal fistula; computed tomography; magnetic resonance imaging; surgery

INTRODUCTION

Gallstones are a severe health problem and can be found in 10–15% of the adult population [1]. Most patients are asymptomatic, but complications can be serious and lead to acute cholecystitis, choledocholithiasis, pancreatitis, and gallstone ileus. Of all patients with gallstones, gallstone ileus occurs in 0.3–0.5% and represents 1–4% of all mechanical small bowel obstructions. Statistics show that it is more common in the elderly (over 60 years old) and women. Factors that can lead to gallstone ileus are long-standing cholelithiasis and recurrent episodes of acute cholecystitis [2]. It most often occurs as a result of stone migration through the resulting fistula between the gallbladder and the adhered portion of the gastrointestinal tract. Due to anatomical features, cholecystoduodenal fistula is the most common, but those with stomach, small, and large intestine have also been reported [3]. Nevertheless, mortality remains high (12–27%), probably because of nonspecific symptoms that lead to high misdiagnosis rates and delayed discovery [2]. We present a case of gallstone ileus, the applied diagnostic procedures, as well as the operative method.

CASE REPORT

A 70-year-old male was admitted to the Department of Surgery, Novi Pazar General Hospital, with mild pain in the epigastrium after he vomited contents the color of black coffee, with fresh traces of blood. The pain started two hours before the admission to the hospital. Comorbidities included chronic calculous gallbladder, hypertension, and diabetes, with a BMI of 30.1 kg/m^2. On admission, the patient was normotensive, without signs of melena, with laboratory parameters in the normal respective ranges, with hematemesis on the nasogastric tube. On the performed native radiography of the abdomen, the patient was without pathological changes. He had normal laboratory values. Initial esophagogastroduodenoscopy (EGD) showed the presence of ulcers on the D2 duodenum without signs of active bleeding but indicating erosive gastritis and biliary reflux. Conservative treatment was initiated (proton-pump inhibitors, fluids, and other symptomatic therapy). The patient responded well to the therapy, and was discharged for home treatment on the fourth day of hospitalization, due to the reduced capacity of hospital beds in the non-COVID part of the hospital and the large influx of COVID-19-positive patients.

On the eighth day after the onset of the disease, the patient was admitted to a Gastroenterology Department of the Novi Pazar General Hospital due to nausea, emesis, and severe pain in the epigastrium and periumbilical. The radiograph showed no signs of pneumoperitoneum and hydroaerial levels. Abdominal ultrasound (US) showed collapsed gallbladder with suspected intraluminal gas and pneumobilia

Received • Примљено: December 22, 2021
Revised • Ревизија: July 18, 2022
Accepted • Прихваћено: July 24, 2022
Online first: August 4, 2022

Correspondence to:
Džemail S. DETANAC
Sutjeska BB/AD/3/44
36300 Novi Pazar
Serbia
dzemail.detanac@gmail.com

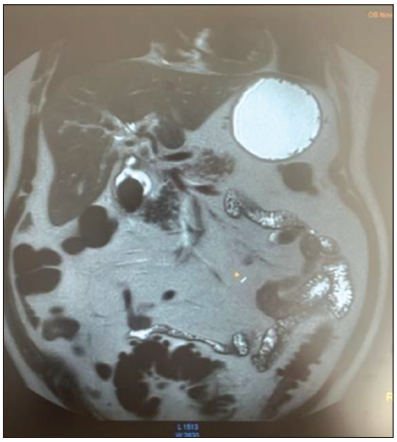


Figure 1. Magnetic resonance imaging – gallstone in the duodenum

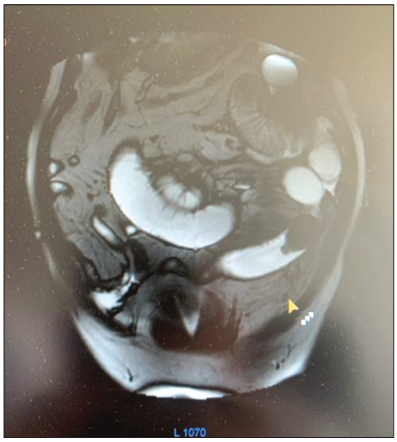


Figure 2. Magnetic resonance imaging – gallstone in the ileum

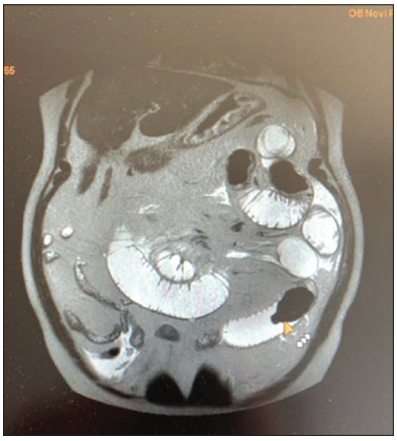


Figure 3. Magnetic resonance imaging – gallstone in the ileum

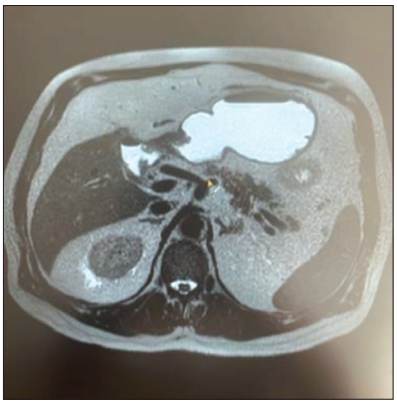


Figure 4. Magnetic resonance imaging – collapsed gallbladder

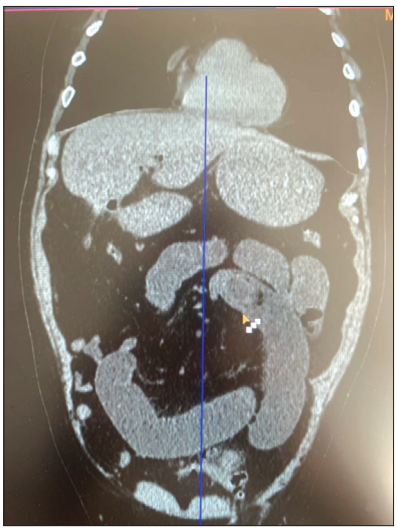


Figure 5. Abdominal computed tomography – gallstone in the ileum

in the biliary tree, no free fluid in the abdominal cavity. EGD was performed and cholecystoduodenal fistula was verified, with calculus in the duodenal lumen, with no signs of bleeding. Both EGDs were performed by the same gastroenterologist. The general condition of the patient was good, with no vomiting. At the first abdominal computed tomography (CT) examination, after the calculus in the gallbladder known to the patient could not be visualized by abdominal US, the gallbladder was found to be contracted, fibrously altered, and without a lumen, and something resembling a calculus was seen in the D2 duodenum. As an additional diagnosis, since CT is insufficient in the visualization of cholesterol calculus, a rapid magnetic resonance imaging (MRI) examination of the abdomen without contrast was performed in the sagittal, coronal and transverse planes in T1W and T2W sequences where a calculus about 50 mm in diameter was observed in the D2 duodenum (Figure 1). Since the general condition of the patient was good, we decided to observe the patient and follow the calculus migration. Next day, abdominal MRI examination was observed again according to the same protocols, when we found migration, of previously seen, calculus in the distal part of the ileum and congestion of the small intestine and signs of ileus (Figures 2–5). Surgery was scheduled and the patient was transferred to the surgery department of the General Hospital in Novi Pazar. After preoperative preparation, we opted for an open surgical approach. Under general anesthesia, the midline laparotomy incision was made. The gallbladder was identified without the possibility of safely identifying the contents of Calot's triangle. The calculus was identified in the lumen of the distal ileum, 60 cm from the ileocecal valve. Enterotomy was performed with calculus extraction. The patient was discharged on the seventh postoperative day without postoperative morbidity. Postoperatively, the patient was monitored for nine months, without signs of complication.

We obtained verbal and written informed consent of the patients to publish the case report. This article was planned in compliance with the Patient Rights Directive and ethical rules by considering the principles of the Declaration of Helsinki.

DISCUSSION

Gallstone ileus does not present with unique symptoms, making diagnosis difficult. It most often occurs as a result of chronic cholecystitis. Inflammation of the gallbladder and surrounding structures leads to adhesions, which in recurrent attacks of infection, due to the pressure of the stone on the wall of the gallbladder, leads to ischemia and the creation of a fistula between the gallbladder and the digestive tube, and the migration of the stone into the digestive tract and its further pathways [3, 4]. The most common type of fistula is the cholecystoduodenal one (up to 70%), while less common are cholecystojejunal, cholecystogastric, and cholecystocolonic fistulae. The stone can

reach the digestive tract through the ampulla of Vater or by iatrogenic transmission (during ERCP or a cholecystectomy), thus leading to intestinal obstruction [5].

More than two-thirds of intraluminal stones will pass spontaneously and be eliminated by stool, while those larger than 2.5 cm pose a risk of intestinal obstruction [6]. The presence of intestinal adhesion, tumor changes, Crohn's disease, etc. can reduce the intestinal lumen and increase the risk of mechanical obstruction.

Gallstone ileus is a geriatric disease because it is most common in the elderly, and since gallstones are more common in women, gallstone ileus is slightly more common in women [5, 7]. As a result of untreated biliary-enteric fistula with cholelithiasis, the literature reports an estimated risk of recurrent gallstone ileus of 5–8% [7].

The symptoms of gallstone ileus are not specific. Physical examination may be nonspecific and completely orderly if the obstruction is not present at the time of the examination. Data from the literature show that patients usually appear four to eight days after the beginning of the disease, most often with signs of nausea, vomiting, abdominal pain, constipation. Only 10–30% of patients with gallstone ileus have symptoms of acute cholecystitis. Partial obstruction or distal migration of the gallstone may be the cause of not reporting to the physician in time [5, 8].

All diagnostic radiological procedures have their place in the diagnosis of gallstone ileus. Plain abdominal radiograph is a quick and easy procedure that works in 40–70% of cases [9]. In order to notice the stone in the lumen of the digestive tract, it must have a high level of calcium. The presence of two signs of Rigler's triad (pneumobilia, ectopic gallstone, and intestinal obstruction) is pathognomonic in up to 50% of cases, but sometimes it is identified only in retrospective observation [4, 5, 8].

US is a highly sensitive diagnostic method for gallstone ileus, and in combination with radiography it is accurate up to 74% [4, 5]. CT has a sensitivity of up to 93% [10, 11].

Our case was an older man whose first symptoms were hematemesis and epigastric pain without signs of ileus and peritoneal irritation. Since duodenal ulcer and erosive gastritis were seen on the initial EGD, and the radiographs were normal, there was no indication for additional diagnostics, and conservative treatment was continued, to which the patient responded well. During the second hospitalization, due to recurrence of symptoms, the second EGD was performed and cholecystoduodenal fistula was verified, with calculus in the duodenal lumen (calculus was not seen on the first EGD), with no signs of bleeding. Additional CT and MRI scans were performed and confirmed a stone in the duodenum. The good general condition of the patient allowed further monitoring of the dynamics of stone movement, and the MRI showed a calculus in the lumen of the small intestine as the cause of intestinal obstruction. Gallstone ileus management is surgical, but there is no consensus as to which of the different surgical techniques is the procedure of choice. The surgical approach can be as follows: a) one-stage procedure – enterolithotomy or enterolithotomy with cholecystectomy and fistula closure; b) two-stage procedure – enterolithotomy with cholecystectomy in the second act. Surgical approaches for managing the gallbladder and cholecystoenteric fistulas remain debated due to worse postoperative outcomes compared to enterolithotomy alone. Spontaneous closures of cholecystoenteric fistula were reported leading to a reduction in the need for surgical intervention in the second stage [4, 12, 13, 14]. Our surgical approach was enterolithotomy alone because surgical management of the gallbladder and cholecystoenteric fistula in high-risk patient was difficult due to severe adhesions and no possibility of safely identifying the contents of Calot's triangle. Postoperatively, the patient was monitored for nine months, with no signs of complications.

In conclusion, gallstone ileus is an infrequent complication of gallstone disease, whose outcome is influenced by timely diagnosis and treatment. Endoscopy, CT, and MRI play a significant role in diagnosing this disease when other methods are unavailable or false negative. Surgical treatment saves lives, and enterotomy with calculus extraction, without gallbladder surgery, and fistula resolution in the same act is a justified and satisfactory approach.

Conflict of interest: None declared.

REFERENCES

1. Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. Gut Liver. 2012;6(2):172–87. [DOI: 10.5009/gnl.2012.6.2.172] [PMID: 22570746]
2. Turner AR, Sharma B, Mukherjee S. Gallstone Ileus. [Updated 2021 Sep 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430834/
3. Tsang CF. A rare case of gallstone ileus-the unanswered question. J Surg Case Rep. 2021;2021(4):rjab164. [DOI: 10.1093/jscr/rjab164] Erratum in: J Surg Case Rep. 2021;2021(6):rjab250. [PMID: 33959256]
4. Nuño-Guzmán CM, Marín-Contreras ME, Figueroa-Sánchez M, Corona JL. Gallstone ileus, clinical presentation, diagnostic and treatment approach. World J Gastrointest Surg. 2016;8(1):65–76. [DOI: 10.4240/wjgs.v8.i1.65] [PMID: 26843914]
5. Mitrovic M, Stanisic N, Perisic Z, Lesevic I, Vasin D, Doklestic K. Emergency abdominal ultrasound as sufficient diagnostic modality in the diagnosis of biliary ileus. Sanamed. 2020;15(3):317–21. [DOI: 10.24125/sanamed.v15i3.476]
6. Vera-Mansilla C, Sanchez-Gollarte A, Matias B, Mendoza-Moreno F, Díez-Alonso M, Garcia-Moreno Nisa F. Surgical treatment of gallstone Ileus: less is more. Visc Med. 2022;38(1):72–7. [DOI: 10.1159/000518451] [PMID: 35291697]
7. Halabi WJ, Kang CY, Ketana N, Lafaro KJ, Nguyen VQ, Stamos MJ, et al. Surgery for gallstone ileus: a nationwide comparison of trends and outcomes. Ann Surg. 2014;259(2):329–35. [DOI: 10.1097/SLA.0b013e31827eefed] [PMID: 23295322]
8. Liisa C, Minna C, Hanna MC, Aina IC, Fuju C. Clinical and radiological diagnosis of gallstone ileus: a mini-review. Emerg Radiol. 2018;25(2):189–96. [DOI: 10.1007/s10140-017-1568-5] [PMID: 29147883]
9. Ploneda-Valencia CF, Gallo-Morales M, Rinchon C, Navarro Muniz E, Bautista-Lopez CA, de la Cerda-Trujillo LF, et al. Gallstone ileus: an overview of the literature. Rev Gastroenterol Mex. 2017;82(3):248–54. [DOI: 10.1016/j.rgmx.2016.07.006] [PMID: 28433486]

10. Tran A, Hoff C, Polireddy K, Neymotin A, Maddu K. Beyond acute cholecystitis-gallstone-related complications and what the emergency radiologist should know. Emerg Radiol. 2022;29(1):173–86. [DOI: 10.1007/s10140-021-01999-y] [PMID: 34787758]
11. Ţanco M, Tofolean IT. A rare and unexpected case of intestinal obstruction-gallstone ileus. Ultrasound Med Biol. 2022;48(suppl 1):S60. [DOI: 10.1016/j.ultrasmedbio.2022.04.171]
12. Ferhatoglu M, Kartal A. Porcelain gallbladder: a case report. Sanamed.2019;14(1):79–81. [DOI: 10.24125/sanamed.v14i1.294]
13. Lee BT, Mahamid A, Ahmad J, Tabrizian P. Cholecystoduodenal fistula resulting in gallstone ileus: A path paved by stone. Clin Case Rep. 2021;9(4):2479–80. [DOI: 10.1002/ccr3.3943] [PMID: 33936721]
14. Gungor F, Atalay Y, Acar N, Gur EO, Kokulu I, Acar T, et al. Clinical outcome of gallstone ileus; a single-centre experience of case series and review of the literature. Acta Chir Belg. 2022;122(1):7–14. [DOI: 10.1080/00015458.2020.1816673] [PMID: 32857668]

Холецистодуоденална фистула и илеус изазван жучним каменом – дијагностика и хируршко лечење

Џемаил С. Детанац[1], Џенана Детанац[1], Крстина Доклестић[2,3], Џемил Бихорац[1], Сафет Муратовић[1]

[1]Општа болница Нови Пазар, Нови Пазар, Србија;
[2]Универзитетски клинички центар Србије, Клиника за ургентну хирургију, Београд, Србија;
[3]Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Увод Илеус изазван жучним каменом је парцијална или комплетна механичка опструкција црева настала као резултат опструкције цревног лумена, а најчешће настаје после миграције камена кроз холецистоентеричну фистулу.

Приказ болесника Приказујемо болесника са знацима билијарног илеуса после миграције камена кроз холецистодуоденалну фистулу у дуоденум са хематемезом као првим симптомом. Започето је конзервативно лечење, на које је болесник иницијално добро реаговао. Осмог дана од почетка болести дошло је до погоршања стања. На урађеној компјутеризованој томографији и магнетној резонанци абдомена идентификовани су знаци Риглерове тријаде. Отвореном хируршком методом успешно је урађена ентеролитотомија. Постоперативни опоравак је био уредан, без забележених билијарних тегоба.

Закључак Физикални преглед, горња ендоскопија и радиолошке дијагностичке методе су комплементарне и неопходне у праћењу динамике кретања камена и одлучивању о томе када ће се извршити хируршки захват.

Кључне речи: илеус изазван жучним каменом; холецистодуоденална фистула; компјутеризована томографија; магнетна резонанца; хирургија

DOI: https://doi.org/10.2298/SARH211231093S
UDC: 616.346-006.6

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Angiosarcoma of the caecum

Dejan Stevanović[1,2], Nebojša Mitrović[1,2], Damir Jašarović[1,2], Aleksandar Lazić[1,2], Branko Lukić[2]

[1]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[2]Zemun Clinical Hospital Center, Department of General Surgery, Belgrade, Serbia

SUMMARY

Introduction Primary angiosarcomas arising from the digestive system are rare, representing less than 1% percent of the malignant sarcomas. Only a few cases have been reported in the literature. Colorectal involvement is exceedingly uncommon and is a harbinger of a poor prognosis with widespread metastasis. Diagnosis is often delayed due to non-specific symptoms and pathology which mimics other tumors.

Case outline A 52-year-old woman was presented to the emergency room in July 2021, complaining of protracted malaise, and rapid fatigue and occasional sweating. Multislice computed tomography (MSCT) of the abdomen and small pelvis revealed the existence of lobular, well vascularized, supravesical lesion, located along the anterior contour of the uterine corpus, in the convolutes of the small intestine. The patient was subjected to operative treatment with curative intent. Intraoperatively, a completely tumor-altered caecum was verified Standard histopathological examination demonstrated a high grade epithelioid angiosarcoma with severe pleomorphism and solid growth pattern. The control MSCT of abdomen and small pelvis which was done 12 months after the operation did not show the existence of any pathological lesions.

Conclusion Both clinical and pathological diagnoses of colorectal angiosarcoma are challenging. Patients are presenting non-specific symptoms, which can lead to mismanagement and late diagnosis. A pathological diagnosis relies on immunohistochemical staining for endothelial markers. In limited tissue biopsies, it can be easily misdiagnosed as poorly differentiated adenocarcinoma or gastrointestinal stromal tumor. For now, surgical treatment with R0 resection seems to be the only effective treatment modality.

Keywords: angiosarcoma; caecum; gastrointestinal angiosarcoma; colonic angiosarcoma

INTRODUCTION

Primary angiosarcomas arising from the digestive system are rare, representing less than 1% percent of the malignant sarcomas [1]. They usually arise in the stomach and small intestine [2], while colorectal involvement is extremely uncommon and is a harbinger of a poor prognosis with diffuse metastasis [1, 3]. Diagnosis is often delayed due to non-specific symptoms, but also due to pathology which mimics other tumors. Management guidelines are very limited due to tumors rarity.

CASE REPORT

A 52-year-old woman presented to the emergency room in July 2021, complaining of protracted malaise, rapid fatigue, and occasional sweating. No other difficulties were listed. The patient was a diabetic with a significant medical history and was hospitalized several times at our Institution, last time three years ago due to myocardial infarction and transient ischemic attack. Since then, the patient has been diagnosed with ischemic heart disease and had been using oral anticoagulant therapy regularly due to the presence of echosonographically-verified thrombus in the apical area of the heart. Also, two years ago she was examined on an outpatient basis by a hematologist in order to perform tests for thrombophilia – genetic analysis on *MTFHR*, *FII* and *FV Leiden* was negative, and homocysteine was in the reference range. She was instructed to conduct tests for antiphospholipid syndrome, which was not done. The family history was positive for malignancies – both parents had liver cancer.

On examination she was slightly hypotensive (90/50 mmHg), tachycardic (110 beats per minute) with normal body temperature of 36.8°C. The abdomen was slightly distended with hyperactive bowel sounds and without any tenderness. Initial blood analysis revealed leukocytosis with "left shift", eosinophilia, moderate to severe microcytic anemia and thrombocytosis (leukocytes 51.6; neutrophiles 40.80 × 10^9/L; eosinophil 8.60 × 10^9/L; erythrocytes 3.60; hemoglobin 84; hematocrit 0.282; Tr 642). Inflammatory parameters were elevated (erythrocyte sedimentation 100/1 h, C-reactive protein 225 mg/L, phenolsulfonphthalein 1418 pg/mL, procalcitonin 0.81 ng/mL). Prothrombin time was prolonged (INR 10.64 s) but considered as a consequence of an inadequate dose of warfarin. Urine analyses were normal. Abdominal ultrasound and plain abdominal radiography were without any pathological finding.

The patient was hospitalized at the Hematology Department for further diagnosis and

Received • Примљено: December 31, 2021
Accepted • Прихваћено: September 3, 2022
Online first: September 6, 2022

Correspondence to:
Branko LUKIĆ
Zemun Clinical Hospital Centar
Vukova 9
11080 Belgrade
Serbia
branko.lukic@live.com

treatment. Due to the positive inflammatory syndrome, antibiotic therapy was administered empirically and prolonged prothrombin time was corrected. Bone marrow aspiration and trepanobiopsy were performed and the pathohistological finding was without signs of myeloproliferative and lymphoproliferative disease. The origin of eosinophilia was then investigated. X-ray of the paranasal cavities and ear-nose-throat examination excluded the existence of nasal polyposis. Stool was negative for parasites and to rule out Churg–Strauss syndrome, samples were sent for immunology (antinuclear antibody test, peripheral antineutrophil cytoplasmic antibody test) which came back normal. Esophagogastroduodenoscopy was performed and there were no macroscopic findings to indicate eosinophilic gastritis, as well as the existence of erosions, ulcerations nor neoformations. Computed tomography of the chest did not show the existence of any changes that would indicate granulomatous inflammation. The IgE immunoglobulin titer was in the reference range.

On the sixth day after admission, the patient had a fever for the first time, accompanied by an increase in leukocyte count and inflammatory parameters (leukocytes 77.1, C-reactive protein 236 mg/L). Blood cultures and other bacteriological analyzes, that were taken on several occasions, were sterile. Multislice computed tomography (MSCT) of the abdomen and small pelvis was performed and showed the existence of lobular, well vascularized lesion measuring around 7 × 5 × 8 cm, located supravesically along the anterior contour of the uterine corpus, in the convolutes of the small intestine, with hypodense zones in the center which differentially diagnostically corresponded to necrosis. She was examined by a gynecologist, and it was determined that the lesion did not belong to the internal genital organs.

Given the above, the patient was transferred to the Department of General Surgery with the intention of performing explorative laparotomy and further surgical procedure according to the intraoperative finding. Intraoperatively, a completely tumor-altered caecum was verified with partially necrotic walls and multiple abscesses within them (Figure 1). Further exploration did not reveal lesions suggestive of secondary deposits. Given the above, a resection was performed in a form right hemicolectomy (Figures 3, 4, and 5) along with local lymphadenectomy and reconstruction with ileo-transverso T-L anastomosis. Standard histopathological examination demonstrated a high grade epithelioid angiosarcoma with severe pleomorphism and solid growth pattern (Figure 2). R0-resection was verified and the presence of tumor tissue was confirmed in none of seven dissected lymph nodes. Patient was staged as $T_2N_0M_x$.

The postoperative period was marked by ventricular fibrillation on the fifth postoperative day. The patient was resuscitated and returned to sinus rhythm using direct current cardioversion shock. The rest of the hospitalization was uneventful and after seven days, the patient was discharged. No evidence of complications was noted during first two follow-ups. The control MSCT of the abdomen and small pelvis which was done 12 months after the operation did not show the existence of any pathological lesions.

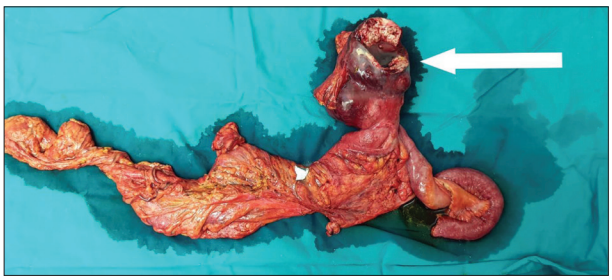


Figure 1. Photograph of the of intraoperative sample; a completely tumor-altered cecum is marked with the arrow

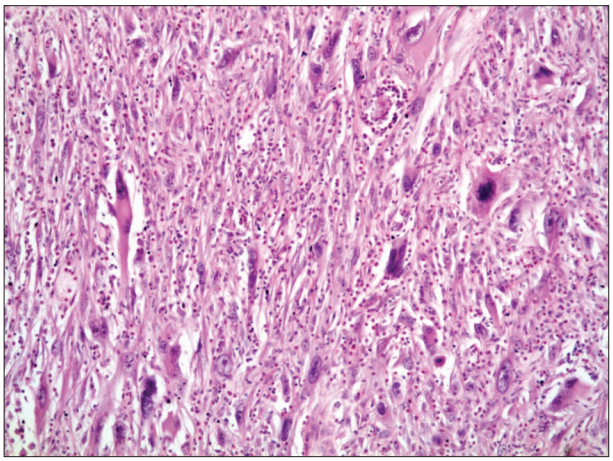


Figure 2. High grade epithelioid angiosarcoma with severe pleomorphism and solid growth pattern; round-polygonal epithelioid cells or spindle cells, with vesicular nuclei containing prominent nucleoli; a few cells were observed to have intracytoplasmic lumina containing erythrocytes or bizarre form (H&E; 10 ×)

We confirm that we have read the journal's position on issues involving ethical publication and affirm that this work is consistent with those guidelines. Written consent to publish all shown material was obtained from the patient.

DISCUSSION

Angiosarcoma is an aggressive tumor that arises from vascular endothelial cells. It accounts for 1% of all sarcomas and 0.001% of all colorectal malignancies [4]. It can be primary or secondary (metastatic). Roughly 60% primary occur in the skin and superficial soft tissue, but may also occur in the deep soft tissue and parenchymal organs such as the breast, heart, liver, spleen and bone.

Only a few angiosarcomas have been found in the digestive system, with most of them localized in the stomach and small intestine [2]. Colorectal angiosarcoma is a very rare finding. The first case was described in 1949 by Steiner and Palmer [5], and to our knowledge there were less than 40 described cases to this day, most of which were primary [1, 6, 7]. The prognosis is poor as the tumor metastasizes rapidly in more than 70% of cases [1]. The most common sites of metastatic disease are lymph nodes, liver, bone, and lungs, while other localizations are less represented [8].

The etiology of colorectal angiosarcoma is yet unclear. It may be related to long-term exposure to radiation, chemical agents such as polyvinylchloride, thorotrast, and arsenic, as well as a consequence of chronic lymphedema and amyloidosis [9, 10, 11]. Angiosarcoma has also been reported in association with implanted foreign material such as vascular (Dacron) grafts and orthopedic joint prostheses [12, 13, 14], breast implants [15, 16], or in patients with arteriovenous fistulas. [12, 13, 17] According to the findings of recent studies, protracted use of calcium channel blockers may lead to colorectal angiosarcoma [1]. The patient from our report was using calcium channel blockers.

In 2018, Wang et al. [1] summarized the results of 33 previously reported cases. The mean age of patients was 56 years (16–85 years) and the mean tumor size was 5 cm (1.5–12 cm) [1]. The majority of patients (61%) were female [18]. Most reported colorectal angiosarcomas have been localized to the sigmoid colon [1, 6, 7]. Wang et al. [1] reported that sigmoid colon was affected in 36% of cases, rectum in 33%, cecum in 21% of cases, ascending colon in 9%, and the transverse and descending colon in 3% of cases. Before him, Brown et al. [18] had similar results. The most common symptoms are gastrointestinal bleeding and abdominal or perianal pain [6, 7, 11]. Patients may also have symptoms of bowel obstruction and weight loss [6, 7]. Anemia was present in 42% of patients [6, 11]. Our patient had only moderate to severe microcytic anemia.

Patients can be easily misdiagnosed. On endoscopy, the mucosa may look normal or show hypervascularization. It may demonstrate an ulcerated or hemorrhagic, protuberant, near-circumferential mass lesion [8, 19, 20]. Due to the aggressive nature and non-specific symptoms, routine screening colonoscopies may be insufficient for timely assessment of these tumors, and the diagnosis is usually delayed in almost third of the cases [21]. On microscopy, in limited tissue biopsies, angiosarcomas may mimic poorly differentiated carcinomas, gastrointestinal stromal tumor, leiomyosarcomas, melanomas and sarcomas with epithelioid morphology [20, 22].

Due to its rarity, there are no specific guidelines for the diagnosis or the management, and its high aggressiveness prevents designing an optimal therapeutic approach [1]. Patients with angiosarcoma generally have a poor prognosis, but for now surgical treatment with R0 resection seems to be the only effective treatment modality. Wide margins are recommended because of the often-multifocal nature of angiosarcoma and its invasiveness [6, 21].

The long-term outcomes of adjuvant chemotherapy and radiotherapy remain unclear [1, 21, 23]. Komorowski et al. [24] reported a case involving a 19-year-old patient, who was operated on and later received adjuvant chemotherapy and radiotherapy. After 18 months, the patient had no signs of recurrence [24].

Tumor size and age at presentation have been suggested as prognostic factors that affect the course after treatment and overall survival. Better survival has been associated with tumors which are smaller than 5 cm, as the size has shown to be an independent prognostic factor [18].

Our patient had a tumor measuring nearly 8 cm and was without macroscopically visible secondary deposits. Also, the tumor was not found in any of dissected lymph nodes. The control MSCT of abdomen and small pelvis which was done 12 months after the operation did not show the existence of any pathological lesions.

In conclusion, we can say that both clinical and pathological diagnoses of colorectal angiosarcoma are challenging. Patients are presenting non-specific symptoms, which can lead to mismanagement and late diagnosis. A pathohistological diagnosis relies on immunohistochemical staining for endothelial markers. In limited tissue biopsies, it can be easily misdiagnosed. For now, surgical treatment with R0 resection seems to be the only effective treatment modality.

Conflict of interest: None declared.

REFERENCES

1. Wang Q, Zhao T, Mi BT, Zhang YL, Wei R, Tong HL, et al. Primary Colonic Angiosarcoma Seen in a Patient on Calcium Channel Blocker: A Case Report with Summary Analysis of 32 Other Cases from the Literature. Am J Case Rep. 2018;19:254–61. [DOI: 10.12659/ajcr.907287] [PMID: 29511155]
2. Chen YW, Dong J, Chen WY, Dai YN. Multifocal gastrointestinal epithelioid angiosarcomas diagnosed by endoscopic mucosal resection: A case report. World J Gastroenterol. 2020;26(29):4372–7. [DOI: 10.3748/wjg.v26.i29.4372] [PMID: 32848340]
3. Jehangir A, Le BH, Shogbesan O. Angiosarcoma of the Colon Presenting with Chronic Diarrhea, Rectal Bleeding, and Pelvic Discomfort. Cureus. 2017;9(3):e1117. [DOI: 10.7759/cureus.1117] [PMID: 28451476]
4. Al Beteddini OS, Brenez D, Firket C, Algaba R, Tabech A. Colonic angiosarcoma: A case report and review of literature. Int J Surg Case Rep. 2013;4(2):208–11. [DOI: 10.1016/j.ijscr.2012.11.021. [PMID: 23279809]
5. Steiner CA, Palmer LH. Angiosarcoma of the Colon : With Case Report. Ann Surg. 1949;129(4):538–42. [DOI: 10.1097/00000658-194904000-00015] [PMID: 17859337]
6. Radić S, Zovak M, Marić AG, Baturina S, Kirigin MS, Krušlin B. Multiple Primary Angiosarcomas of the Colon. Case Rep Pathol. 2021;2021:7237379. [DOI: 10.1155/2021/7237379] [PMID: 34545314]
7. Ottaiano A, Santorsola M, Perri F, Pace U, Marra B, Correra M, et al. Clinical and Molecular Characteristics of Rare Malignant Tumors of Colon and Rectum. Biology (Basel). 2022;11(2):267. [DOI: 10.3390/biology11020267] [PMID: 35205133]
8. Sherid M, Sifuentes H, Brasky J, Shah DA, Ehrenpreis ED. Clinical and endoscopic features of angiosarcoma of the colon: two case reports and a review of the literature. J Gastrointest Cancer. 2013;44(1):12–21. [DOI: 10.1007/s12029-012-9431-0] [PMID: 23397573]
9. Mundt KA, Dell LD, Crawford L, Gallagher AE. Quantitative estimated exposure to vinyl chloride and risk of angiosarcoma of the liver and hepatocellular cancer in the US industry-wide vinyl chloride cohort: mortality update through 2013. Occup Environ Med. 2017;74(10):709–16. [DOI: 10.1136/oemed-2016-104051] [PMID: 28490663]
10. Tripke V, Heinrich S, Huber T, Mittler J, Hoppe-Lotichius M, Straub BK, et al. Surgical therapy of primary hepatic angiosarcoma. BMC Surg. 2019;19(1):5. [DOI: 10.1186/s12893-018-0465-5] [PMID: 30630447]
11. Said S, Graham RP, Wu TT, Yasir S, Zhang L, Folpe AL. Colonic Angiosarcoma Arising in Association with Amyloid Deposits. Case Rep Gastrointest Med. 2020;2020:3780763. [DOI: 10.1155/2020/3780763] [PMID: 32509358]

12. Takamura K, Kobayashi H, Rubin BP, Kondo S, Asami F, Aoyagi R, et al. Aortic Angiosarcoma in Association with Endovascular Aneurysm Repair: Case Report and Review of the Literature. Am J Case Rep. 2021;22:e931740. [DOI: 10.12659/AJCR.931740] [PMID: 34118148]
13. Agaimy A, Ben-Izhak O, Lorey T, Scharpf M, Rubin BP. Angiosarcoma arising in association with vascular Dacron grafts and orthopedic joint prostheses: clinicopathologic, immunohistochemical, and molecular study. Ann Diagn Pathol. 2016;21:21–8. [DOI: 10.1016/j.anndiagpath.2016.01.002] [PMID: 27040926]
14. Lee JB, Jung JW, Kim WO, Ryoo YW, Lee KJ, Kim SA. Case of Rapidly Progressing Angiosarcoma after Total Hip Arthroplasty. Ann Dermatol. 2021;33(4):377–81. [DOI: 10.5021/ad.2021.33.4.377] [PMID: 34341642]
15. Rajan SS, Haider A, Burrell H, Whisker L, Tamimy M, McCulloch T, et al. Angiosarcoma arising in the capsule of a mammary silicone implant. Diagn Cytopathol. 2022;50(5):E119-E122. [DOI: 10.1002/dc.24919] [PMID: 34994526]
16. Russo D, Campanino MR, Cepurnaite R, Gencarelli A, De Rosa F, Corvino A, et al. Primary High-Grade Angiosarcoma of the Breast in a Young Woman With Breast Implants: A Rare Case and a Review of Literature. Int J Surg Pathol. 2020;28(8):906–12. [DOI: 10.1177/1066896920924087] [PMID: 32423273]
17. Kakisis JD, Antonopoulos C, Moulakakis K, Taliadoros A, Rontogianni D, Brountzos E, et al. Angiosarcoma of a Thrombosed Arteriovenous Fistula in a Renal Transplant Recipient. Ann Vasc Surg. 2019;56:357.e1-357.e4. [DOI: 10.1016/j.avsg.2018.10.014] [PMID: 30500642]
18. Brown CJ, Falck VG, MacLean A. Angiosarcoma of the colon and rectum: report of a case and review of the literature. Dis Colon Rectum. 2004;47(12):2202–7. [DOI: 10.1007/s10350-004-0698-5] [PMID: 15657674]
19. Allison KH, Yoder BJ, Bronner MP, Goldblum JR, Rubin BP. Angiosarcoma involving the gastrointestinal tract: a series of primary and metastatic cases. Am J Surg Pathol. 2004;28(3):298–307. [DOI: 10.1097/00000478-200403000-00002] [PMID: 15104292]
20. El Chaar M, McQuay N Jr. Sigmoid colon angiosarcoma with intraperitoneal bleeding and early metastasis. J Surg Educ. 2007;64(1):54–6. [DOI: 10.1016/j.cursur.2006.09.002] [PMID: 17320808]
21. Keyser D, Masoumy M, Ham PB, Biddinger P, Rahardja A, Legostaev A, et al. Angiosarcoma of the Colon. 2015;111(25):3068–9. [DOI: 10.1177/000313481508100412]
22. Ma J, Yan Y, He X, Yang Z. Case Report Multiple colonic epithelioid angiosarcoma: a case report and review of literature. Int J Clin Exp Med. 2018;11(9):10237–43.
23. Fukita Y, Yasuda I, Ishibashi H, Asaki T, Adachi S, Toyomizu M, et al. [Multifocal angiosarcoma of the gastrointestinal tract:a case report]. Nihon Shokakibyo Gakkai Zasshi. 2017;114(9):1665–74. Japanese. [DOI: 10.11405/nisshoshi.114.1665] [PMID: 28883296]
24. Komorowski AL, Darasz Z, Kołodziejski LS, Gruchała A. Primary angiosarcoma of the colon. Acta Chir Belg. 2004;104(4):465–7. [PMID: 15469166]

Ангиосарком цекума

Дејан Стевановић[1,2], Небојша Митровић[1,2], Дамир Јашаровић[1,2], Александар Лазић[1,2], Бранко Лукић[2]

[1]Универзитет у Београду, Медицински факултет, Београд, Србија;
[2]Клиничко-болнички центар „Земун", Служба опште хирургије, Београд, Србија

САЖЕТАК

Увод Примарни ангиосаркоми дигестивног система су ретки и чине 1% свих малигних саркома. Само је неколицина случајева описана у литератури. Захваћеност колоректума је изузетно ретка и знак је лоше прогнозе обично због већ постојећих удаљених промена. Дијагноза се често касно поставља због неспецифичних симптома и патолошких налаза који могу имитирати друге туморе.

Приказ болесника Жена старости 52 године јавила се на преглед због протраховане малаксалости, брзог умарања и повременог презнојавања. Мултислајсни скенер абдомена је показао постојање лобуларне, добро васкуларизоване лезије локализоване суправезикално уз предњи зид утеруса, унутар конволута танког црева. Болесница је оперисана, при чему је установљен потпуно туморски измењен цекум. Хистопатолошки налаз је потврдио да се ради о ангиосаркому високог градуса. Контролни мултислајсни скенер абдомена и мале карлице, спроведен после 12 месеци, није показао постојање патолошких лезија.

Закључак И клиничка и хистопатолошка дијагностика ангиосаркома колоректума су изазовне. Болесници имају неспецифичне симптоме, што може водити ка постављању погрешне дијагнозе. Хистопатолошка дијагностика се ослања на имунохистохемијско бојење на ендотелне маркере, због чега се у појединим условима налаз може погрешно протумачити као слабо диферентован аденокарцином или гастроинтестинални стромални тумор. Засад, хируршко лечење остаје једини ефикасан начин лечења.

Кључне речи: ангиосарком; цекум; гастроинтестинални ангиосарком; ангиосарком колона

DOI: https://doi.org/10.2298/SARH210402101K
UDC: 616.367-001.3-089

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Hepatolithiasis followed by recurrent cholangitis as a consequence of inadequate hepaticojejunostomy for common bile duct injury

Milana Kresoja Ignjatović[1,2], Dejan Lukić[1], Aleksandar Đermanović[1], Mladen Đurić[1,2], Mlađan Protić[1,2]

[1]Oncology Institute of Vojvodina, Department of Surgical Oncology, Sremska Kamenica, Serbia;
[2]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia

SUMMARY

Introduction Hepatolithiasis (HL) is defined as gallstones present in bile ducts above the common bile duct confluence, regardless of the coexistence of gallstones in other parts of the biliary tract. HL is common among patients with recurrent pyogenic cholangitis. Chronic infection can lead to the development of malignancy.

Case outline A 65-year-old woman presented with intermittent fever, jaundice, abdominal pain, and nausea. Eighteen years previously, the patient had an open cholecystectomy due to acute cholecystitis. During the early post-operative days, the patient developed icterus. Intrahepatic biliary ductal dilatation was confirmed by abdominal ultrasound. Due to suspicion of iatrogenic common bile duct injury, the patient underwent a second operation, during which the said injury was confirmed. "Non-Roux-en-Y" hepaticojejunostomy (HJ) was performed as a problem-resolving procedure. Despite the performed biliary bypass, the patient continued to have episodes of recurrent cholangitis over the 18 years. Given the patient's recurrent symptoms and results of MRI consistent with HL, surgical treatment was indicated. A left hepatectomy was performed, with Roux-en-Y HJ biliary reconstruction. The post-operative course was uneventful, after which the patient has been symptom-free.

Conclusion The main purpose of treating HL is to eliminate infection which leads to recurrent cholangitis and subsequent hepatic fibrosis. Adequate solution of HL decreases the need for repeated interventions and prevents progression of the disease to cholangiocarcinoma.

Keywords: hepatolithiasis; cholangitis; bile duct stones; hepatectomy; Roux-en-Y hepaticojejunostomy; bile duct injury

INTRODUCTION

Hepatolithiasis (HL) is defined as gallstones present in the bile ducts above the common bile duct confluence, regardless of the coexistence of gallstones in other parts of the biliary tract. HL occurs most often in East Asia, while it is rare in Western countries [1].

HL was the third most common cause of emergency abdominal surgery at the University Hospital in Hong Kong during the 1960s. A downward trend has been observed over the years, possibly due to improved standards of living and westernized diet. Increasing incidence of HL has been noted in Western countries with increasing immigration from East Asia to the West [2, 3, 4].

Recurrent pyogenic cholangitis is frequently followed by HL. Common presence of bacteria in bile and gallstones indicates the possibility of pattern connection between bacterial infection and the formation of brown pigment stones. *Escherichia coli*, *Clostridium* and *Bacteroides* show beta-glucuronidase activity and are most common bacterial species isolated from the bile of patients with HL. Clinically, HL may present as acute obstruction and recurrent bacterial cholangitis with all its possible complications, such as liver abscess and septicemic shock, or with chronic complications, which refers to cholangiocarcinoma [4–8].

The main purpose of treating HL is to eliminate infection, which leads to recurrent cholangitis and subsequent hepatic fibrosis. Adequate solution of HL decreases the need for repeated interventions and prevents progression of the disease to cholangiocarcinoma.

The surgical treatment of HL implies removal of the affected hepatic segment(s). Complete removal of the diseased hepatic segment or lobe is crucial to preventing disease recurrence and further chronic consequences [9–13]. Best surgical approach for treating HL is based on high-volume experience from a single center in China that proposed a system of classification known as "Dong's Classification" (Table 1) [9].

Herein we present a case of HL followed by recurrent cholangitis as a consequence of inadequate hepaticojejunostomy (HJ) for common bile duct injury.

CASE REPORT

A 65-year-old woman presented with intermittent fever, jaundice, abdominal pain, and

Received • Примљено: April 2, 2021
Revised • Ревизија: July 12, 2022
Accepted • Прихваћено: September 30, 2022
Online first: October 18, 2022

Correspondence to:
Milana KRESOJA IGNJATOVIĆ
Bulevar Oslobođenja 48
21000 Novi Sad, Serbia
milana.kresoja@mf.uns.ac.rs

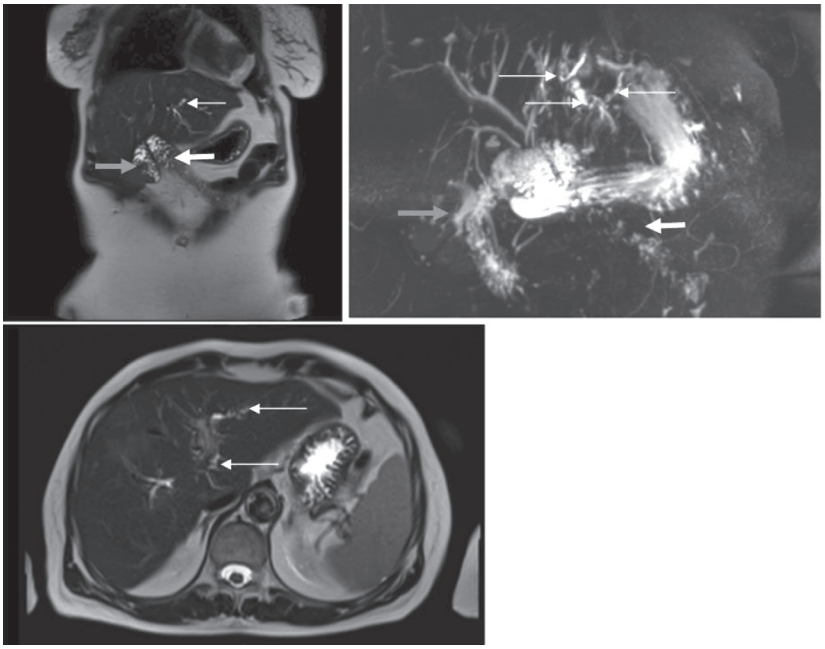


Figure 1. Abdominal magnetic resonance imaging and magnetic resonance cholangiopancreatography made before the problem-resolving operation: afferent jejunal limb of the non-Roux-en-Y hepaticojejunostomy (pointed out by a thick white arrow), efferent jejunal limb (pointed out by a gray arrow), and intrahepatic biliary calculi (pointed out by the thin white arrows)

nausea over a period of 18 years. During this period, the patient was admitted to hospital numerous times due to recurrent cholangitis.

Eighteen years previously, the patient underwent open cholecystectomy for acute cholecystitis. During the early post-operative days, the patient developed icterus. Intrahepatic biliary ductal dilatation was confirmed by the right upper quadrant abdominal ultrasound. Due to the suspicion of iatrogenic common bile duct injury, the patient underwent re-operation during which the said injury was confirmed. "Non-Roux-en-Y" HJ was performed as a problem-resolving procedure for the said injury. Despite performed biliary bypass, the patient continued to have episodes of recurrent cholangitis over a period of 18 years.

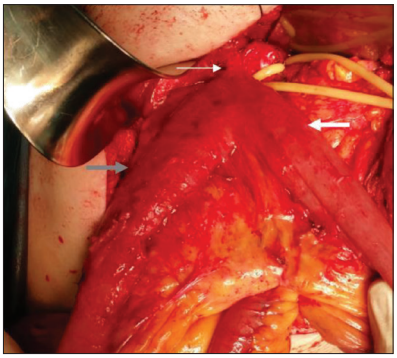


Figure 2. Cause of the disease: inadequate hepaticojejunostomy (non-Roux-en-Y) created at previous surgery (marked by a thin white arrow); efferent jejunal limb (marked by a gray arrow), and afferent jejunal limb (marked by a thick white arrow)

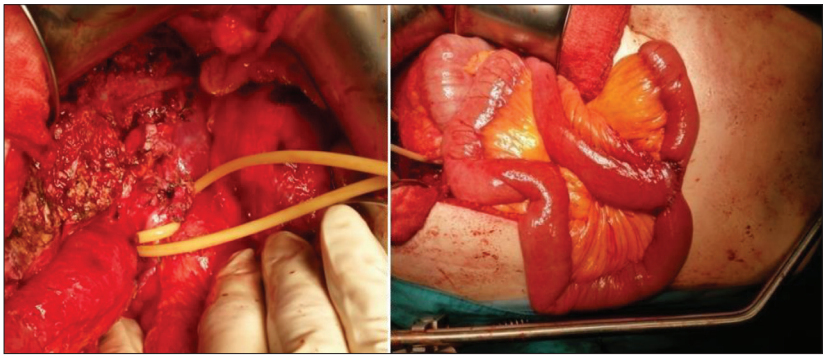


Figure 3. Treatment decision: left hepatectomy with Roux-en-Y hepaticojejunostomy reconstruction

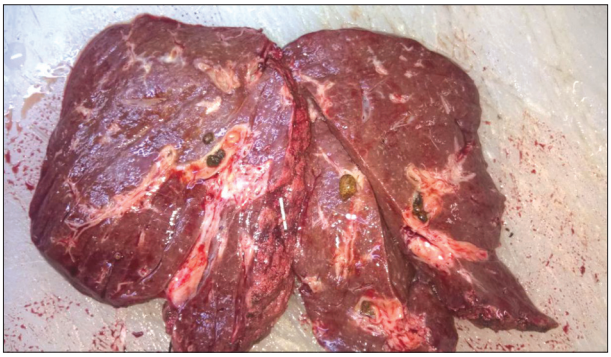


Figure 4. Specimen photography made by the pathologist: multiple intra-hepatic biliary stones

Table 1. Dong's classification of hepatolithiasis [9]

Type	Definition or content
Type I	localized stone disease: unilobar or bilobar
Type II IIa IIb IIc	diffuse stone disease; no atrophy of the hepatic parenchyma or stricture of the intrahepatic bile ducts; segment atrophy or/and stricture of the intrahepatic bile ducts; biliary cirrhosis and portal hypertension
Aditional Type E Ea Eb Ec	 extrahepatic stones; normal sphincter of Oddi; relaxation of the sphincter of Oddi; stricture of the Sphincter of Oddi

At the time of the last hospitalization, the following blood test results were performed: hemoglobin 130 g/l, erythrocytes 4.82×10^{12}/L, leukocytes 5.2×10^{9}/L, platelets 194×10^{9}/L, total bilirubin 9.4 μmol/L, aspartate aminotransverase 14 U/L, alanine aminotrasferase 14 U/L, gamma-glutamyl transferase 54 U/L, and alkaline phosphatase 132 U/L. Serology for Hepatitis B and C viruses

was negative. Signs of HL were present on the pre-operative abdominal magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) (Figure 1).

Surgical treatment was indicated considering the patient's complaints as well as the abdominal MRI findings that suggested HL.

The presence of intrahepatic biliary calculi within the left hepatic lobe were confirmed by the intra-operative ultrasound. Referring to Dong's Classification, the operation of choice was left hepatectomy with Roux-en-Y HJ biliary reconstruction (Figures 2 and 3). Tested intra-operative bile cultures came positive for *E. coli* and *Pseudomonas* sp.

Post-operative course was uneventful, and the patient has been symptom-free since. Histopathology showed findings consistent with chronic HL, chronic cholangitis, and secondary biliary cirrhosis (Figure 4).

This case report was approved by the institutional ethics committee, and written consent was obtained from the patient for the publication of the report and any accompanying images.

DISCUSSION

HL is defined as gallstones present in bile ducts above the common bile duct confluence, regardless of the coexistence of gallstones in other parts of the biliary tract. And regardless of whether the confluence is located intra- or extra-hepatically [1–4].

HL is most common in East Asia (Singapore 1.7%, Japan 2.2%, Hong Kong 3.1%, and Taiwan 50%). Once rare in Western countries, the rate of HL has been rising due to increased immigration from East to West (Western country prevalence < 1%). The highest incidence of HL occurs in the fifth to sixth decades of life and has been reported typically between the ages 30–70 years. The combination of intra- and extra-hepatic HL is more frequent in the older groups, while intrahepatic form of the disease occurs in the younger age groups [1–10].

HL and recurrent pyogenic cholangitis are in thin connection since most patients with HL experienced symptoms of pyogenic cholangitis at least once during the period of the disease. The high incidence of bacteria infested bile and gallstones indicate that there is a close association between bacterial infection and the formation of intrahepatic stones. There are several scenarios how bacteria find route into the biliary tract. One of them is ascending infection through the sphincter of Oddi, followed by bacteribilia via the portal venous system. Also, transient infection due to biliary stasis is possible. The most common bacterial species isolated from the bile of patients with HL are *E. coli*, *Clostridium* and *Bacteroides* spp. This literature data matches the bacteriology results of our case [6–9].

The main purpose of treating HL is to eliminate infection which leads to recurrent cholangitis and subsequent hepatic fibrosis. Adequate solution of HL decreases the need for repeated interventions and prevents progression of the disease to cholangiocarcinoma.

Choice of the treatment strategy for HL needs to be based on the following: 1) the structure of the calculi (cholesterol or calcium bilirubinate); 2) the location of the calculi in the bile duct and the most feasible approach to them; 3) well planned treatment that includes resolving of the bile duct stenosis; 4) evaluation of liver function, the extent of liver resection, and residual liver volume; and 5) investigation of the presence of intrahepatic bile duct malignancy. Therapeutic strategy must be planned by taking into consideration the history, nature, and extent of biliary tract surgery [11, 12, 13]. According to the Clinical Guidelines for Cholelithiasis written by the Japanese Society of Gastroenterology, treatment selection should be based on the presence or absence of prior biliary tract surgery [10].

Untreated HL can lead to serious consequences, such as biliary cirrhosis and even cholangiocarcinoma. Resection of the affected hepatic lobe that contains strictures, atrophy, and multi-segmental distribution of intrabiliary calculi has been effective in reducing the disease recurrence and progression of liver disease [11]. Uchiyama et al. [12] performed a retrospective study which compared invasive and non-invasive treatments and procedures in HL treatment to analyze the rate of residual stones and complications, as well as the long-term outcome. Out of 105,062 patients with cholelithiasis treated between 1989 and 1992, 2353 (2.24%) patients were diagnosed with HL. The authors concluded that the most effective therapy was surgery. According to a report by Japanese multi-center-based surveys, there has been a progressive increase in treatment of patients with HL who had previously undergone biliary surgery [14].

We present a patient with an 18-year long history of recurrent cholangitis after cholecystectomy during which a bile duct injury was made. The patient underwent early reoperation and non-Roux-en-Y HJ. As it shows in early postoperative days, this form of biliary reconstruction was inadequate, given the absence of dysfunctional jejunum loop (Roux-en-Y) [15].

Safar et al. [16] investigated 12 patients to compare CT, MRI, and MRCP findings of HL. Although cross-sectional imaging with CT scan is a useful technique for screening for intrahepatic stones with a sensitivity of 80–90%, CT is less useful than MRCP for precise topographic localization of stones proximal to the biliary confluence [17]. MR cholangiography is a non-invasive test providing high quality multi projection images. It not only detects the stones, but also provides detailed information of the biliary anatomy, which is useful for surgical planning [16, 17].

Pre-operative abdominal MRI in the case we present showed that the gallbladder was surgically removed, while the common bile duct was accidentally resected, with stenosis of the non-Roux-en-Y hepaticojejunal biliary reconstruction. The intrahepatic biliary ducts of both hepatic lobes were dilated, with moderate dilatation noted on the extrahepatic biliary ducts (diameter of the left and right hepatic duct up to 7 mm). Intra- and extra-hepatic biliary ducts showed intense contrast-enhanced signal, primarily due to inflammation.

The proposed system for the classification of HL, "Dong's Classification," is utilized to determine the best surgical approaches to resolve this disease (Table 1) [9]. Considering hepatectomy, the best candidates are patients with Type I and Type IIb HL. Patients with type II HL have a high risk of stone recurrence, thus the best solution is biliary stone extraction along with Roux-en-Y HJ or hepaticocutaneous jejunostomy. For the treatment of type IIb HL with segmental atrophy and/or strictures of the intrahepatic bile ducts hepatectomy is considered the optimal approach. Complete removal of the affected lobe or segment is mandatory for preventing the recurrence of bile stones and progressive liver diseases, including fibrosis and malignancy [18, 19].

Most often, the removal of the affected hepatic segment(s) is the best possible surgical approach. Stone extraction, resolving of strictures and consequent biliary stasis, which is responsible for stone formation, is achieved by liver resection [20]. The criteria for segmental/lobe liver resection in HL include the following: 1) HL limited to one lobe, particularly left-sided; 2) cholangitis followed by atrophy, fibrosis, and multiple abscesses; 3) suspected existence of associated cholangiocarcinoma, and 4) multiple intrahepatic stones with biliary strictures that cannot be treated percutaneously or endoscopically. Complete removal of the affected liver segment/lobe is mandatory to prevent recurrence and progressive disease [21, 22].

In the case we presented, inadequate biliary-enteric anastomosis (absence of dysfunctional jejunum loop) leads to a reflux of the digestive juice into the intrahepatic bile ducts, followed by intermittent bacterial infection and recurrent cholangitis. The chronic recurrent infection led to biliary strictures, formation of intrahepatic stones, and the increased risk for neoplasia in the form of cholangiocarcinoma. Therefore, we performed left hepatectomy followed by Roux-en-Y HJ.

ACKNOWLEDGMENT

This case report was presented at the 12th Biennial Congress of the European-African Hepato-Pancreato-Biliary Association (E-AHPBA), May 23–26, 2017, Mainz, Germany in the form of poster presentation. DOI: https://doi.org/10.1016/j.hpb.2019.10.035. Available at: https://www.hpbonline.org/article/S1365-182X(19)30775-0/fulltext.

Conflict of interest: None declared.

REFERENCES

1. Pu T, Chen JM, Li ZH, Jiang D, Guo Q, Li AQ, et al. Clinical online nomogram for predicting prognosis in recurrent hepatolithiasis after biliary surgery: A multicenter, retrospective study. World J Gastroenterol. 2022;28(7):715–31. [DOI: 10.3748/wjg.v28.i7.715] [PMID: 35317276]
2. Lorio E, Patel P, Rosenkranz L, Patel S, Sayana H. Management of Hepatolithiasis: Review of the Literature. Curr Gastroenterol Rep. 2020;22(6):30. [DOI: 10.1007/s11894-020-00765-3] [PMID: 32383039]
3. Xiao Z, Huang Z, Gao J, Wang J, Lei J, Zhou F, et al. The imbalance of biliary microflora in hepatolithiasis. Microb Pathog. 2021;157:104966. [DOI: 10.1016/j.micpath.2021.104966] [PMID: 34023439]
4. Liang L, Zhuang D, Feng X, Zhang K, Zhi X. The postoperative choledochoscopy in the management of the residual hepatolithiasis involving the caudate lobe: A retrospective study. Medicine (Baltimore). 2021;100(35):e26996. [DOI: 10.1097/MD.0000000000026996] [PMID: 34477129]
5. Kokoroskos N, Alifieris K, Agorgianitis L, Zouglos S, Delis S. Surgical management of hepatolithiasis: an institutional experience of a rare disease. Int Surg J. 2021;8(3):1016. [DOI: 10.18203/2349-2902.isj20210939]
6. Lu Q, Yang J, Wang P, Liu J, Fan Y, Fang C. Digital Surgical Diagnosis and Management of Hepatolithiasis. In: Fang C, Lau WY, editors. Biliary Tract Surgery. Singapore: Springer; 2021. p. 239–310. [DOI: 10.1007/978-981-33-6769-2_12]
7. Wang X, Chen A, Fu Q, Cai C. Comparison of the Safety and Efficacy of Laparoscopic Left Lateral Hepatectomy and Open Left Lateral Hepatectomy for Hepatolithiasis: A Meta-Analysis. Front Surg. 2021;8:749285. [DOI: 10.3389/fsurg.2021.749285] [PMID: 34869557]
8. Tsui WM, Chan YK, Wong CT, Lo YF, Yeung YW, Lee YW. Hepatolithiasis and the syndrome of recurrent pyogenic cholangitis: clinical, radiologic, and pathologic features. Semin Liver Dis. 2011;31(1):33–48. [DOI: 10.1055/s-0031-1272833] [PMID: 21344349]
9. Zhao H, Lu B. Prediction of Multiple Serum Tumor Markers in Hepatolithiasis Complicated with Intrahepatic Cholangiocarcinoma. Cancer Manag Res. 2022;14:249–55. [DOI: 10.2147/CMAR.S344711] [PMID: 35082529]
10. Tazuma S, Unno M, Igarashi Y, Inui K, Uchiyama K, Kai M, et al. Evidence-based clinical practice guidelines for cholelithiasis 2016. J Gastroenterol. 2017;52(3):276–300. [DOI: 10.1007/s00535-016-1289-7] [PMID: 27942871]
11. Suzuki Y, Mori T, Momose H, Matsuki R, Kogure M, Abe N, et al. Predictive factors for subsequent intrahepatic cholangiocarcinoma associated with hepatolithiasis: Japanese National Cohort Study for 18 years. J Gastroenterol. 2022;57(5):387–95. [DOI: 10.1007/s00535-022-01868-6] [PMID: 35357571]
12. Uchiyama K, Onishi H, Tani M, Kinoshita H, Ueno M, Yamaue H. Indication and procedure for treatment of hepatolithiasis. Arch Surg. 2002;137(2):149–53. [DOI: 10.1001/archsurg.137.2.149] [PMID: 11822950]
13. Zhang J, Xu Z, Wang L, Hou C, Wang G, Cui L, et al. Long-term outcomes of surgical approaches for bilateral hepatolithiasis: A real-world six-decade experience at a single center. J Hepatobiliary Pancreat Sci. 2022;29(9):994–1003. [DOI: 10.1002/jhbp.1204] [PMID: 35794790]
14. Wang Y, Huang C, Zhang H, Cai Y, Shen Z, Hu X, et al. Correlation Among Psychological Resilience, Social Support, and Coping Style in Patients With Complicated Hepatolithiasis. Front Behav Neurosci. 2022;16:939512. [DOI: 10.3389/fnbeh.2022.939512] [PMID: 35783232]
15. Tang Z, Huan Q, Chen J, Zheng H, Shao C, Yu D. Treatment of retained and regenerate hepaticolithiasis with hepatectomy: clinical analysis of 136 cases. [Online] Wprim.whocc.org.cn. Available at: http://wprim.whocc.org.cn/admin/article/articleDetail?WPRIMID=414718&articleId=41 4718 [Accessed March 1, 2021].
16. Safar F, Kamura T, Okamuto K, Sasai K, Gejyo F. Magnetic resonance T1 gradient-echo imaging in hepatolithiasis. Abdom Imaging. 2005;30(3):297–302. [DOI: 10.1007/s00261-004-0262-8] [PMID: 15965778]
17. Xue B, Wu S, Zhang M, Hong J, Liu B, Xu N, et al. A radiomic-based model of different contrast-enhanced CT phase for differentiate intrahepatic cholangiocarcinoma from inflammatory mass with hepatolithiasis. Abdom Radiol (NY). 2021;46(8):3835–44. [DOI: 10.1007/s00261-021-03027-6] [PMID: 33728532]
18. Garcia F, Acosta M, Lamberto A, Fernandez D, Grondona J, Bracco R. Surgical therapy for hepatolithiasis. HPB. 2019;21(Supplement 3):S536–S537. [DOI: 10.1016/j.hpb.2019.10.061]

19. Rabbi H, Rashid M, Hakim H, Ahmed A, Chowdhury A, Sarder M, et al. Recurrent pyogenic cholangitis with hepatolithiasis – 10 yrs surgical experience in Bangladesh. HPB. 2018;20(Supplement 2):S460. [DOI: 10.1016/j.hpb.2018.06.2881]
20. Mansilla-Vivar R, Alonso-Lázaro N, Argüello-Viudez L, Ponce-Romero M, Bustamante-Balen M, Pons-Beltrán V. New management of hepatolithiasis: Can surgery be avoided? Gastroenterol Hepatol. 2020;43(4):188–92. [DOI: 10.1016/j.gastrohep.2019.11.008] [PMID: 32122681]
21. Jia CK, Weng J, Chen YK, Yang QZ, Fu Y, Qin QF, et al. Hepatectomy with primary closure of common bile duct for hepatolithiasis combined with choledocholithiasis. World J Gastroenterol. 2015;21(12):3564–70. [DOI: 10.3748/wjg.v21.i12.3564] [PMID: 25834321]
22. Maharjan N, Joshi Lakhey P, Ghimire B, Kansakar PB, Bhandari RS. Multidisciplinary Management of Hepatolithiasis at a Tertiary Care Center in Nepal. JIOM Nepal. 2020;42(2):54–8. [DOI: 10.3126/jiom.v42i2.37538]

Хепатолитијаза праћена рекурентним холангитисима као последица неадекватне хепатикојејуностомије услед повреде заједничког жучног канала

Милана Кресоја Игњатовић[1,2], Дејан Лукић[1], Александар Ђермановић[1], Младен Ђурић[1,2], Млађан Протић[1,2]

[1]Институт за онкологију Војводине, Клиника за хируршку онкологију, Сремска Каменица, Србија;
[2]Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија

САЖЕТАК

Увод Хепатолитијаза се дефинише као присуство камена-ца у жучним водовима рачве заједничког жучног вода, без обзира на присуство каменаца у другим деловима жучног тракта. Често је присутна код болесника са рекурентним холангитисом. Присуство хроничне инфекције може довести до развоја малигнитета.

Приказ болесника Приказана је 65-годишња болесница са тегобама у виду повремене температуре, жутице, болова у трбуху и мучнине. Болесници је 18 година раније начињена отворена холецистектомија због акутног холецистиса. У раном постоперативном току болесница развија иктерус. Ултразвуком абдомена потврђена је дилатација интрахепатичних жучних водова. Индикована је поновна операција услед сумње на јатрогену повреду заједничког жучног вода, која је интраоперативно потврђена. У циљу решавања повреде начињена је хепатикојејуностомија по типу „не-*Roux-en-Y*" анастомозе. Упркос начињеном билијарном бајпасу, болесница је наредних 18 година имала епизоде рекурентних холангитиса. На основу тегоба болеснице и налаза магнетне резонанце који су указивали на хепатолитијазу индиковано је оперативно лечење. Начињена је лева хепатектомија са *Roux-en-Y* хепатикојејуностомијом. Постоперативни ток је протекао уредно и од тада је болесница без тегоба.

Закључак Примарни циљ лечења хепатолитијазе је ерадикација постојеће инфекције која доводи до рекурентног холангитиса и последичне хепатичне фиброзе. Адекватан третман хепатолитијазе доводи до смањења потребе за понављаним лечењем и спречава настанак холангиокарцинома.

Кључне речи: хепатолитијаза; холангитис; каменци жучних водова; *Roux-en-Y* хепатикојејуностомија; повреде жучних водова

DOI: https://doi.org/10.2298/SARH201023107R
UDC: 616.24-008-053.2

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Thyroglossal duct cyst as a cause of dyspnea in a two-year-old child

Katarzyna Resler[1], Monika Morawska-Kochman[1], Anna Czarnecka[2], Jessica Konopka[3], Tomasz Zatoński[1], Maciej Bagłaj[4]

[1]Wroclaw Medical University, Department of Otolaryngology, Head and Neck Surgery, Wroclaw, Poland;
[2]Wroclaw Medical University, Department of General Radiology, Interventional Radiology and Neuroradiology, Wroclaw, Poland;
[3]Ortopedicum Hospital, Krakow, Poland;
[4]Wroclaw Medical University, Department of Paediatric Surgery and Urology, Wroclaw, Poland

SUMMARY

Introduction Thyroglossal duct cysts are developmental, epithelial lesions localized in the neck's median line. They occur mainly in children and adolescents; however, they also occur in one-third of patients older than 20 years of age. The symptoms dependent on the size and location along the path of the thyroglossal duct.

Case outline This article presents a case, with diagnostic imaging and surgical treatment, of a two-year-old girl hospitalized due to dyspnea, caused by a large cyst localized at the base of the tongue during an upper respiratory tract infection. Before surgery, biochemical examinations, diagnostic imaging were performed to exclude ectopic thyroid tissue. Surgery was performed applying Sistrunk's procedure, which entailed excising the cyst's tissue at its origin.

Conclusion In patients presenting with thyroglossal duct cysts, upper respiratory tract infections increase the probability of discovering previously existing cysts. A cyst localized around the foramen cecum can cause inspiratory and expiratory dyspnea.

Keywords: thyroglossal duct cysts; dyspnea; children; Sistrunk's procedure

INTRODUCTION

Thyroglossal duct cysts (TDC), representing the most commonly occurring congenital lesions of the neck (around 70%), are epithelial lesions located in the mid-sagittal plane of the body [1, 2]. They occur primarily in children and adolescents (approximately 7% of the population) irrespective of sex [3]; however, only one in three of patients may be older than 20 years [4, 5].

At around the third week of embryonal development, in the *foramen cecum* region at the base of the tongue, the thyroid gland bud forms, which subsequently descends the neck, creating the thyroglossal duct. It achieves its final position at about six weeks and regresses in the eighth week. A cyst is a result of seromucous secretions through the persistent duct. Considering its embryological derivative, the cyst remains in communication with the body of the hyoid bone [6].

We present a case of a two-year-old child admitted to the hospital because of stridor, who was then diagnosed with lingual TDC. Clinical and radiographic features leading to a diagnosis are described and equated with those which are reported in the literature.

CASE REPORT

A two-year-old girl was presented to the Emergency Department with symptoms of acute laryngeal obstructive (inspiratory and expiratory) dyspnea noticed by the parents a few days before admission. Medical history revealed fever up to 39°C, as well as difficulty in swallowing solid foods. The parents became alarmed by the appearance of dyspnea and stridor. The girl was admitted to Pediatric Department. Laboratory studies on admission showed elevated inflammatory markers: C-reactive protein (CRP, norm: 0–5 mg/l) – 53.22 mg/l, leukocytosis (WBC, norm: 4–10 × 10^3/ul) – 23.23 × 10^3/ul. The remaining laboratory parameters were found to be within normal limits. On initial physical examination, a greyish-blue smooth mass was found at the base of the tongue, which blocked the laryngopharingeal view (Figure 1). Amoxicillin with clavulanic acid was administered intravenously (50 mg + 5 mg/kg every eight hours). A rapid improvement of the patient's condition was observed, along with a decrease in dyspnea. Inflammatory markers returned to normal. Due to sustained stridor, the child was referred for a diagnostic follow-up to the Laryngology Department. Magnetic resonance imaging (MRI) of the neck revealed a thin-walled homogenous lesion in the median plane, measuring 2 × 1, 1 × 2 cm, with

Received • Примљено: October 23, 2020
Revised • Ревизија: October 25, 2022
Accepted • Прихваћено: October 26, 2022
Online first: November 4, 2022

Correspondence to:
Katarzyna RESLER
Department of Otolaryngology, Head and Neck Surgery
Wroclaw Medical University
Borowska 213
Wroclaw 50-556, Poland
katarzyna.resler@umw.edu.pl

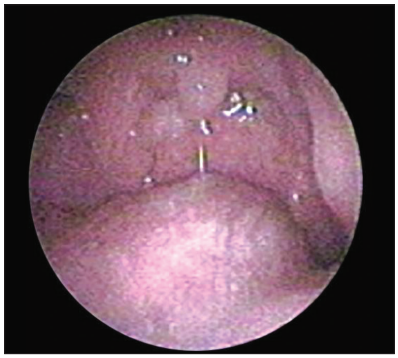


Figure 1. The endoscopic image of the thyroglossal duct cyst

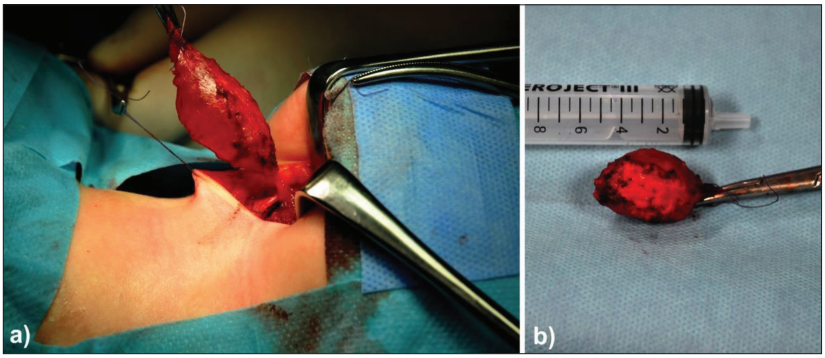


Figure 2. a) Thyroglossal duct cyst during surgical excision procedure; b) excised thyroglossal duct cyst

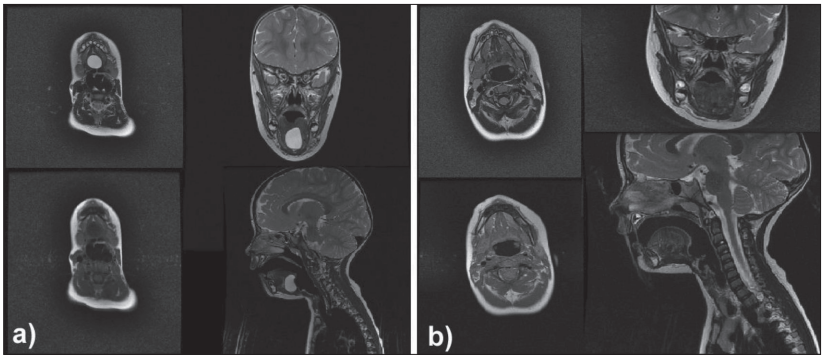


Figure 3. a) Magnetic resonance imaging (MRI) visualisation of the thyroglossal duct cyst; b) MRI of the surgical area after one year of follow-up

cyst-like characteristics in the laryngopharynx. Above, it communicated with the *foramen cecum* at the basis of the tongue and distally extended towards the hyoid bone, with a demarcated thyroglossal duct (Figure 2a). An ectopic thyroid tissue was excluded on diagnostic imaging (ultrasonography, MRI), and the presence of a properly developed thyroid gland in its anatomic position was confirmed. A provisional diagnosis of a lingual TDC was made, and the patient was referred for operative management. An anterosuperior cervical approach was applied. Intraoperative findings were consistent with a lingual TDC. The lesion was removed in its entirety from the level of the hyoid bone to the *foramen cecum* at the base of the tongue. The surgery included resection of the body of the hyoid bone (Figure 3). The postoperative course was uneventful, and the girl was discharged on the fourth postoperative day. Histological examination confirmed the diagnosis of a TDC. At follow-up review, the girl did not present any recurrence of the thyroglossal duct remnants (Figure 2b).

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

DISCUSSION

The lesion usually appears in the median line of the neck in its upper 1/3 part and rarely occurs at the base of the tongue (around 2.1%) [6, 7], the suprasternal notch (approximately 10%) [8], or within the thyroid gland parenchyma [9]. It presents as a smooth, painless, and soft growth occurring in the neck at the thyrohyoid membrane level, with proximity to the adjacent hyoid bone [10].

The cause of the development of this type of lesion is unknown. One theory proposes the lymphatic tissue's infectious hyperplasia, remaining with the thyroglossal duct, leading to its closure and forming a cyst [11]. It seems that the infectious factor present in the respiratory tract and teeth, especially in children, plays a key role. Other factors predisposing to the formation of this type of lesion in adults may include pregnancy and childbirth, as well as an autosomal dominant inherited genetic factor [12].

The symptoms depend on the location and size of the lesion and may include dyspnea, dysphagia, or speech difficulties [7]. The presence of a lesion on the base of the tongue can be hazardous due to potential obstruction of the laryngeal and pharyngeal airways. This mechanism is compared with the "ball valve effect" between the cyst and the laryngeal inlet. Secondary to the respiratory tract obstruction, the patient may present with stridor, raspy respiration, and the recruitment of auxiliary respiratory muscles. Large lesions in this location in newborns and infants may be lethal [13].

In differential diagnosis, it is imperative to have in mind a fact about an ectopically placed thyroid gland – more than 90% of ectopy cases present at the tongue's base [14]. In about 5% of cases, thyroid tissue can be found in the cyst wall [9]. The differential diagnostics should include dermoid cysts and steatocystomas. They are usually situated superficially, similarly to lipomas, and present with weakly demarcated borders. More medially localized lesions, which originate from the pharyngeal grooves, could indicate a fistula's presence instead of a TDC. The remaining lesions occurring at the midline position are thyroid nodules, hypertrophy of the pyramidal lobe of the thyroid, lymphadenopathy, parotid tumors, or lymphatic malformations.

Ultrasonography is the diagnostic imaging of choice and is characterized by a high sensitivity and specificity

(higher than 90%) [15]. This examination allows for the visualization of the cystic structure of the thyroid gland. However, it does not provide information on its relation with the surrounding tissues, especially the hyoid bone. Scintigraphy and computed tomography allow for proper identification of the thyroid gland [16, 17]. MRI confirms a diagnosis of the TDC and its close correlation with the hyoid bone. It also provides objective data for measuring the lesion and depicts the exact location [15, 18]. Fine-needle aspiration (FNA) biopsy is often used to confirm or exclude the presence of lesions with cystic characteristics. Still, it is challenging to administer the procedure without anesthesia in the pediatric population [19].

Most TDCs manifest following upper respiratory tract infections or secondary to their inflammation. Treatment should be commenced with broad-spectrum antibiotics targeting the oral cavity's flora and subsequently concluded with Sistrunk's operative procedure [20, 21]. Operating in an infectious episode is contraindicated due to the high risk of recurrence of the lesion [22, 23]. The incision and drainage of the lesion can be considered if an abscess is not reacting to pharmacologic treatment only. Operative management is markedly less challenging in the absence of fibrotic changes or cutaneous fistulas [24]. An alternative to operative treatment, described in the literature, is sclerotherapy with intralesional ethanol administration. This procedure can only be implemented in cases where the neoplastic lesions surrounding the duct had been excluded. However, the literature reports that this method's success is 1/3 of patients, with a high recurrence percentage [25].

Surgical resection of a cervical cyst is the method of choice. As one of the first pioneers, Schlange described how a resection of the lesions and the body of the hyoid bone is performed in one block. This method has decreased the recurrence of symptoms by about 20%. Subsequently, in 1920, Sistrunk modified the technique and expanded it, including the excision of the TDC, the middle part of hyoid bone, and the surrounding tissue along the path of the thyroglossal tract. It is worth noting the possibility of the occurrence of ramifications or doubling of the thyroglossal duct around the hyoid bone, which may impair the surgeon's ability to recognize it intraoperatively. Leaving a fragment of the duct may cause a recurrence of symptoms. For this reason, Horisawa et al. [26] recommend removing the root of the lesion in one block, with sparing of a small margin of the surrounding tissues. Recurrence of this disease is observed in around 5% of cases [8].

Concerning patients with undiagnosted TDCs, an upper respiratory tract infection may increase the probability of intense clinical manifestation of a highly localized TDC and hasten the diagnosis. Endoscopic examination may allow better diagnosis of difficult cases of dyspnea in children. In every pediatric patient presenting with an acute episode of dyspnea, TDC should be included in the differential diagnosis.

Conflict of interest: None declared.

REFERENCES

1. Abdel Razek AAK, Sherif FM. Differentiation of sublingual thyroglossal duct cyst from midline dermoid cyst with diffusion weighted imaging. Int J Pediatr Otorhinolaryngol. 2019;126:109623. [DOI: 10.1016/j.ijporl.2019.109623] [PMID: 31400658]
2. Mortaja S, Sebeih H, Alobida NW, Al-Qahtani K. Large Thyroglossal Duct Cyst: A Case Report. Am J Case Rep. 2020;21:e919745. [DOI: 10.12659/AJCR.919745] [PMID: 32358478]
3. Taha A, Enodien B, Frey DM, Taha-Mehlitz S. Thyroglossal Duct Cyst, a Case Report and Literature Review. Diseases. 2022;10(1):7. [DOI: 10.3390/DISEASES10010007] [PMID: 35225860]
4. Danau T, Verfaillie G, Gordts F, Rose T, Backer A De, Danau T, et al. Thyroglossal duct cysts in children : a 30-year survey with emphasis on clinical presentation , surgical treatment, and outcome. Acta Chir Belg. 2019;119(6):357–62. [DOI: 10.1080/00015458.2018.1529345] [PMID: 30388395]
5. Foti J, Grimaldo F. Infected Recurrent Thyroglossal Duct Cyst: A Case Report. Clin Pract Cases Emerg Med. 2020;4(3):411–3. [DOI: 10.5811/cpcem.2020.4.46863] [PMID: 32926699]
6. Ross J, Manteghi A, Rethy K, Ding J, Chennupati SK. Thyroglossal duct cyst surgery: A ten-year single institution experience. Int J Pediatr Otorhinolaryngol. 2017;101:132–6. [DOI: 10.1016/j.ijporl.2017.07.033] [PMID: 28964283]
7. Kohashi Y, Yamamoto T, Igarashi M, Nishimaki H. Unexpected difficult airway due to an undiagnosed congenital lingual thyroglossal duct cyst in a neonate without stridor: A case report. Clin Case Reports. 2022;10(2):e05475. [DOI: 10.1002/CCR3.5475] [PMID: 35228882]
8. Mukul S, Kumar A, Mokhtar E. Sublingual thyroglossal duct cyst (SLTGDC): An unusual location. J Pediatr Surg Case Reports. 2016;10:3–6. [DOI: 10.1016/j.epsc.2016.04.010]
9. Elechi HA. Hypothyroidism Following Sistrunk Procedure: Thyroglossal Duct Cyst or Ectopic Thyroid? African J Paediatr Surg AJPS. 2021;18(4):231–4. [DOI: 10.4103/AJPS.AJPS_147_20] [PMID: 34341309]
10. Anderson JL, Vu K, Haidar YM, Kuan EC, Tjoa T. Risks and complications of thyroglossal duct cyst removal. Laryngoscope. 2020;130(2):381–4. [DOI: 10.1002/lary.27918] [PMID: 30865298]
11. El-Ayman YA, Naguib SM, Abdalla WM. Huge thyroglossal duct cyst in elderly patient: Case report. Int J Surg Case Rep. 2018;51:415–8. [DOI: 10.1016/j.ijscr.2018.09.025] [PMID: 30360239]
12. Ramchandani R, Chumber S. Familial Occurrence of Thyroglossal Duct Cyst. Indian J Surg. 2017;79(6):566–8. [DOI: 10.1007/s12262-017-1648-5] [PMID: 29217911]
13. Hoque R, Bliwise DL. Large posterior lingual thyroglossal duct cyst pneumatically splinted with auto-continuous positive airway pressure at low pressures. Sleep Med. 2019;54:113–5. [DOI: 10.1016/j.sleep.2018.10.005] [PMID: 30544030]
14. Cheng TC, Lin YH. Lingual Thyroid. Ear, Nose Throat J. 2020;99(2):122–3. [DOI: 10.1177/0145561319885714] [PMID: 31852241]
15. Corvino A, Pignata S, Campanino MR, Corvino F, Giurazza F, Tafuri D, et al. Thyroglossal duct cysts and site-specific differential diagnoses: imaging findings with emphasis on ultrasound assessment. J Ultrasound. 2020;23(2):139–49. [DOI: 10.1007/s40477-020-00433-2] [PMID: 32052384]
16. Lukáš J, Drábek J, Lukáš D, Zemanová I, Rulseh A. Ectopic thyroid with benign and malignant findings: A case series. Int J Surg Case Rep. 2020;66:33–8. [DOI: 10.1016/j.ijscr.2019.11.011] [PMID: 31790949]
17. Patel S, Bhatt AA. Thyroglossal duct pathology and mimics. Insights Imaging. 2019;10(1):12. [DOI: 10.1186/s13244-019-0694-x] [PMID: 30725193]
18. Drusin MA, Pereira NM, Modi VK. Intralingual Thyroglossal Duct Cyst Excision. Laryngoscope. 2021;131(1):205–8. [DOI: 10.1002/lary.28610] [PMID: 32239767]
19. Korbi AE, Bouatay R, Houas J, Ameur KB, Harrathi K, Koubaa J. A rare location of thyroglossal duct cyst in a newborn. Pan Afr Med J. 2018;31:104. [DOI: 10.11604/pamj.2018.31.104.14777] [PMID: 31037165]

20. Thompson LDR. Thyroglossal Duct Cyst. Ear, Nose Throat J. 2017;96(2):54–5. [DOI: 10.1177/014556131709600204] [PMID: 28231361]
21. Isaacson G, Kaplon A, Tint D. Why Central Neck Dissection Works (and Fails) for Recurrent Thyroglossal Duct Remnants. Ann Otol Rhinol Laryngol. 2019;128(11):1041–7. [DOI: 10.1177/0003489419859033] [PMID: 31271039]
22. Cheng J, Lerebours R, Lee H. Current trends and 30-day surgical outcomes for thyroglossal duct cyst excision in children. Int J Pediatr Otorhinolaryngol. 2020;128:109725. [DOI: 10.1016/j.ijporl.2019.109725] [PMID: 31644997]
23. Mustafa AA, Favre NM, Kabalan MJ, Carr MM. Pediatric thyroglossal duct cyst excision: A NSQIP-P analysis of 30-day complications. Int J Pediatr Otorhinolaryngol. 2021;150:110937. [DOI: 10.1016/j.ijporl.2021.110937] [PMID: 34628171]
24. Batazzi A, Leng S, Ghionzoli M, Lo Piccolo R, Martin A, Facchini F, et al. Thyroglossal duct cyst: Factors affecting cosmetic outcome and recurrence. Pediatr Int. 2019;61(10):1020–4. [DOI: 10.1111/PED.13955] [PMID: 31282046]
25. Chung MS, Baek JH, Lee JH, Choi YJ, Yoon JH, Nam SY, et al. Treatment Efficacy and Safety of Ethanol Ablation for Thyroglossal Duct Cysts: A Comparison with Surgery. Eur Radiol. 2017;27(7):2708–16. [DOI: 10.1007/s00330-016-4659-x] [PMID: 27957639]
26. Horisawa M, Niinomi N, Ito T. What is the optimal depth for core-out toward the foramen cecum in a thyroglossal duct cyst operation? J Pediatr Surg. 1992;27(6):710–3. [DOI: 10.1016/s0022-3468(05)80097-1] [PMID: 1501029]

Циста тироглосалног канала као узрок диспнеје код двогодишњег детета

Катажина Реслер[1], Моника Моравска-Кохман[1], Ана Чарнецка[2], Јесика Конопка[3], Томаш Затонски[1], Мађеј Баглај[4]

[1]Медицински универзитет у Вроцлаву, Катедра за оториноларингологију и хирургију главе и врата, Вроцлав, Пољска;
[2]Медицински универзитет у Вроцлаву, Катедра за општу радиологију, интервентну радиологију и неурорадиологију, Вроцлав, Пољска;
[3]Болница *Ortopedicum*, Краков, Пољска;
[4]Медицински универзитет у Вроцлаву, Катедра за педијатријску хирургију и урологију, Вроцлав, Пољска

САЖЕТАК

Увод Цисте штитњаче су развојне, епителне лезије, локализоване у средњој линији врата. Јављају се углавном код деце и адолесцената, али и код трећине болесника старијих од 20 година. Симптоми зависе од величине и локације лезије.

Приказ болесника Овај чланак представља случај дијагностичког снимања и хируршког лечења двогодишње девојчице хоспитализоване због диспнеје, изазване великом цистом локализованом у дну језика, током инфекције горњих дисајних путева. Пре операције извршени су биохемијски прегледи, дијагностичка слика, како би се искључило ектопично ткиво штитњаче. Операција је изведена применом Систранкове методе, која је подразумевала изрезивање ткива цисте из локалитета порекла.

Закључак Код болесника са цистама тироглосалног канала, инфекције горњих дисајних путева повећавају вероватноћу откривања претходно постојећих циста. Циста око локалитета *foramen cecum* може изазвати диспнеју и током удисања и током издисања.

Кључне речи: цисте тироглосалног канала; диспнеја; деца; Систранков поступак

DOI: https://doi.org/10.2298/SARH220419082D
UDC: 616.348/.35-006.6-085

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Pathologic complete response in metastatic right-sided colon cancer treated with panitumumab and FOLFOX4 chemotherapy regimen

Miljana Džunić[1], Ana Cvetanović[1,2], Ivan Petković[1,2], Ivana Todorović-Stojanović[3]

[1]University Clinical Centre of Niš, Clinic of Oncology, Niš, Serbia;
[2]University of Niš, Faculty of Medicine, Niš, Serbia;
[3]Pirot General Hospital, Pirot, Serbia

SUMMARY

Introduction Recommended biological agents for the first-line treatment of left-sided metastatic colorectal cancer (mCRC) without mutations in *RAS/BRAF* genes are cetuximab or panitumumab, while for right-sided mCRC bevacizumab is advised instead. For transversal colon mCRC the data about biological treatment efficacy is lacking. We present a patient with right-sided mCRC originated from transversal colon where panitumumab and chemotherapy treatment resulted in an excellent outcome.

Case outline A 56-year-old woman was diagnosed with transversal colon adenocarcinoma, without *RAS* genes mutations, with multiple liver metastases disseminated in both lobes. After the operation of the primary tumor, the patient was treated with panitumumab and FOLFOX4 chemotherapy regimen. After two months of treatment, the dramatic response was evident – The diameter sum of the target lesions decreased by 70.5%. After two more months of therapy, further decrease by 22.5% was evident. Liver metastases were operated on. Histopathology revealed fibrotic and necrotic tissue in all suspicious lesions, except in one focus, where adenocarcinoma was found, but with 90% of surrounding necrosis. Twelve months after liver surgery the patient is without signs of the progressive disease.

Conclusion Detailed comprehensive studies of genetic features of mCRC hold a key to personalized treatment options and better outcomes for patients with mCRC.

Keywords: colorectal cancer; panitumumab; transversal colon; liver metastases

INTRODUCTION

Colorectal cancer (CRC) is among the most frequent and the most fatal malignancies [1]. Despite efforts towards primary prevention, screening colonoscopy and faecal tests, more than a half of patients will have metastatic colorectal cancer (mCRC), which has poor prognosis [2]. Addition of targeted biological treatment to chemotherapy and integration of surgery into the treatment paradigm of mCRC have contributed to survival improvement [3], being over 2.5 years, and still improving by tailoring treatment according to new predictive markers, such as primary tumor localization [4].

Monoclonal antibodies that block epidermal growth factor receptor (EGFR), cetuximab and panitumumab, are the standard of care in the first-line treatment of mCRC without *RAS* genes' mutations, with proven benefit in the left-sided primaries [5]. For right-sided mCRC, monoclonal antibody that neutralizes vascular endothelial growth factor (VEGF), bevacizumab is recommended instead [3]. However, there is not enough evidence about anti-EGFR efficacy in transversal colon, which is in the middle but formally belongs to the right side [6]. We present a patient with right-sided mCRC originated from transversal colon, where the treatment with panitumumab and 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) chemotherapy resulted in an excellent outcome.

CASE REPORT

A woman, age 56, was examined due to symptoms of frequent abdominal cramps and bloating. Colonoscopy revealed circumferential occlusive tumor in the transversal colon, and histopathology of biopsy specimen proved adenocarcinoma. The patient was on antihypertensive therapy due to mild hypertension. Her family history was negative for hereditary cancer.

Multislice computed tomography (MSCT) of the abdomen showed liver with multiple metastases, maximal diameter of 40 mm in the right hepatic lobe and 35 mm in the left lobe (Figure 1). MSCT of the thorax was without secondary deposits. Abnormal laboratory findings were elevated aspartate aminotransferase (65 U/L; reference range 10–37 U/L), alanine aminotransferase (74 U/L; reference range 10–42 U/L) and carcinoembryonic antigen (CEA) (104.8 ng/ml; reference range 0–5 ng/ml).

Due to subocclusive symptoms, right hemicolectomy was performed. Histopathology revealed adenocarcinoma, grade 2–3, pathologic TNM stage was pT3, N2a, with six of 15 lymph nodes positive for cancer, and prominent lymphatic and vascular invasion. Mutation test by

Received • Примљено: April 19, 2022
Revised • Ревизија: August 10, 2022
Accepted • Прихваћено: August 11, 2022
Online first: August 25, 2022

Correspondence to:
Miljana DŽUNIĆ
University Clinical Centre of Niš
Clinic of Oncology
48 Dr. Zoran Đinđić Boulevard
Niš 18000, Serbia
drmdzunic@gmail.com

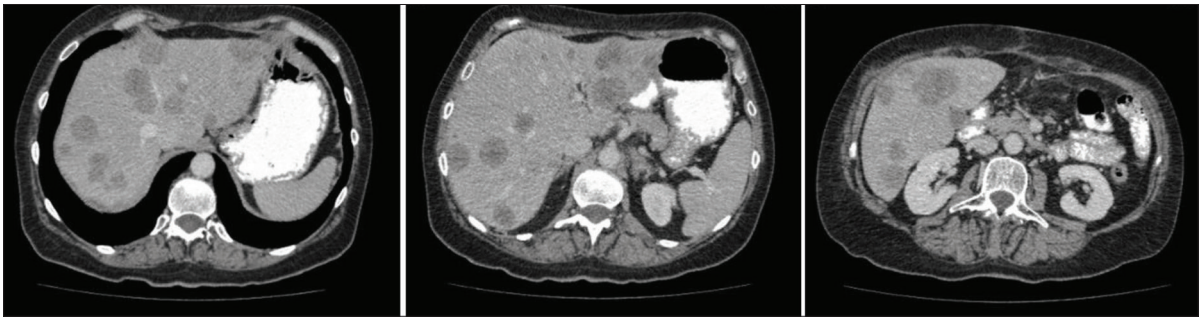


Figure 1. Multislice computed tomography before treatment, showing a liver with multiple metastases in both lobes, maximal diameter being 40 mm

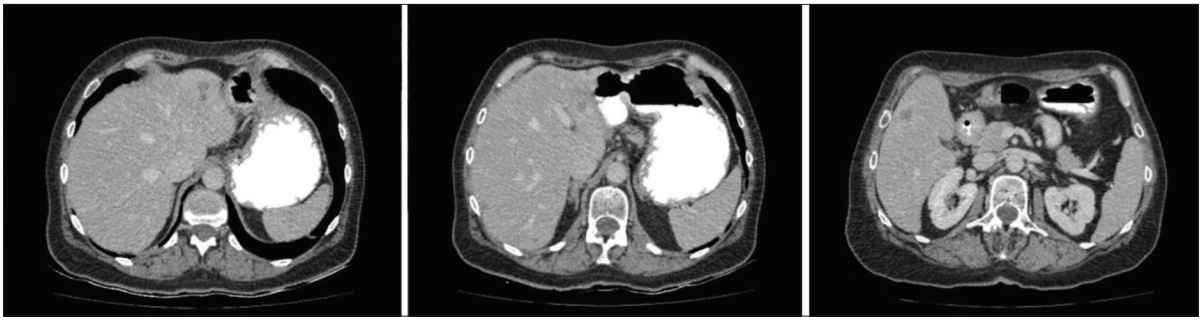


Figure 2. Multislice computed tomography after four cycles of panitumumab and FOLFOX4 therapy, showing the liver with several metastases, maximal diameter being 11 mm

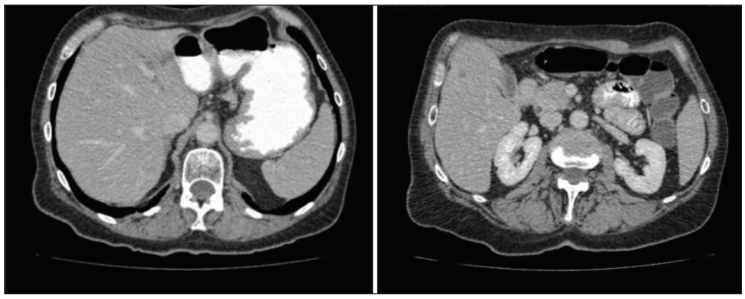


Figure 3. Multislice computed tomography after eight cycles of panitumumab and FOLFOX4 therapy, showing several liver lesions, maximal diameter being 10 mm

real-time polymerase chain reaction method did not detect mutations in exons 2, 3, and 4 of *KRAS* and *NRAS* genes in the tumor specimen.

The patient started treatment consisting of panitumumab (6 mg/kg, on the first day; biweekly) and FOLFOX4 (oxaliplatin 85 mg/m^2 on the first day; leucovorin 200 mg/m^2 on the first and second day; 5-fluorouracyl 400 mg/m^2 in bolus and 600 mg/m^2 in continuous infusion on the first and second day; biweekly). After four cycles of therapy (two months), MSCT of the abdomen showed liver with several metastases in both lobes, maximal diameter being 11 mm (Figure 2). The therapy response was estimated as partial response according to Response Evaluation in Solid Tumors (RECIST) criteria. Tumor marker CEA showed a sharp decline to 3.9 ng/ml. The patient developed rash on the face and the upper thorax, grade 2 according to Common Terminology Criteria of Adverse Events, well controlled with oral tetracycline and topical hydrocortisone treatment. After the same therapy for four more cycles, MSCT showed several liver lesions, maximal diameter being 10 mm (Figure 3); according to RECIST it was a stable disease. Tumor marker CEA was 2.2 ng/ml, and the levels of aspartate aminotransferase and alanine aminotransferase normalized.

The patient was operated on after receiving four more cycles of FOLFOX4 chemotherapy. The patient had liver operation, bisegmentectomy of S5 and S7 and metastasectomy of S3 and S4 liver segments. Four liver fragments with multiple whitish lesions, diameter ranging 2–7 mm, were microscopically analyzed. In one lesion metastatic adenocarcinoma focus was found, with 90% of surrounding necrosis. The other lesions consisted of fibrous and necrotic tissue, without vital tumor cells, proving pathological complete response (pCR).

After the surgery of liver metastases, regular follow-up was advised. At the last check up, 12 months after the surgery, the patient was without symptoms, MSCT scan was without signs of relapse, and tumor markers were in reference ranges.

The patient gave written informed consent to participate in the study, approved by the Ethics Committee of the Clinical Centre Niš and Faculty of Medicine, University of Niš. This case report has also been approved by the institutional ethics committee, and written consent was obtained from the patient for the publication of the case report.

DISCUSSION

The goal of systemic treatment in mCRC depends on the tumor burden and resectability of metastases [6]. In the case of unresectable oligometastatic disease, biological and chemotherapy should induce shrinkage of metastases to

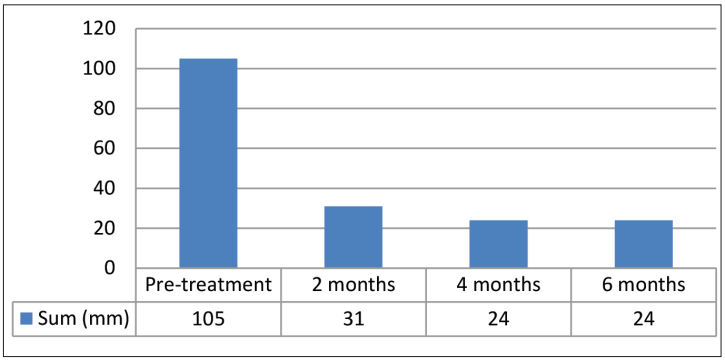


Figure 4. The sum of targeted lesions during treatment

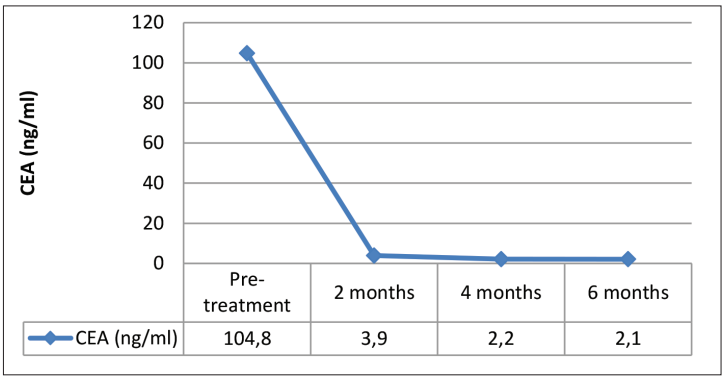


Figure 5. The level of carcinoembryonic antigen (CEA) during treatment

convert them to resectable, in order to be surgically removed. Numerous big cohort analyses have shown the benefit of surgery for liver or lung metastases, in terms of progression-free survival (PFS) and overall survival (OS) [7, 8]. A large rate of early liver recurrence after the resection of metastatic disease induced the search for prognostic and predictive factors, in order to select patients for which surgical procedure is most valuable. Reported good prognostic parameters for patients with operated colorectal liver metastases are older age, up to four metastases, metachronous disease, left-sided localization of primary tumor, and the absence of extrahepatic disease [9–12].

Conversion therapy should be the most potent one in terms of response rate and tumor shrinkage [13]. For patients whose tumors do not harbor mutations in *RAS* genes, *RAS* wild type (WT), anti-EGFR antibodies combined with chemotherapy induced better response rates and exhibited more frequent novel radiological parameters, such as early tumor shrinkage (ETS) and depth of response (DOR), compared to bevacizumab [14, 15]. The importance of ETS and DOR is even beyond conversion and resection rates, while it is proved that it correlates with survival outcomes [16, 17].

In recent years, tumor sidedness has become an important prognostic as well as predictive factor in mCRC treatment. Left colon extends from rectum to the splenic flexure, and right colon includes parts from transversal colon towards caecum. The two colon sides differ not only in embryological origin, vascular and nervous supply, main functions and microbiotic arrangement, but also in molecular mechanisms of tumorigenesis. The difference in driver mutations between the right- and left-sided CRC determines its pathologic behavior, prognosis, as well as anti-EGFR treatment efficacy [18]. A retrospective analysis of pivotal panitumumab trials showed that in patients with left-sided mCRC, panitumumab provided better outcomes, and patients with right-sided cancer did not have that benefit, in the *RAS* WT population, as well as in the *RAS*/*BRAF* WT subgroup [19, 20, 21]. A pooled analysis of six randomized trials revealed similar results, where the effect of the tumor side on the outcomes in patients treated with panitumumab or cetuximab was examined. Significant improvement in PFS and OS for patients treated with anti-EGFR antibodies was evident only for patients with left-sided mCRC, and for right-sided tumors such benefit was absent, except that the overall response rate was higher compared to bevacizumab treatment [22]. Conversely, most of the studies which examined the effect of tumor sidedness on bevacizumab treatment confirmed similar efficacy in both colon sides [23, 24]. Therefore, international guidelines for mCRC treatment suggest anti-EGFR treatment only for left-sided *RAS*/*BRAF* WT tumors, while right-sided mCRC (from caecum to hepatic flexure) should be treated with bevacizumab, irrespective of mutational status. However, the data regarding the effects of panitumumab/cetuximab in mCRC originating from transversal colon is lacking [3, 6].

We report an extraordinary effect of panitumumab and FOLFOX4 treatment in right-sided mCRC originated from transversal colon. The treatment with panitumumab and FOLFOX4 induced ETS by 70.5% (Figure 4), DOR to nearly 80% and rapid decline of CEA (Figure 5). Excellent response manifested as near total pCR, which is uncommon and very rare in mCRC treatment. The parameters such as ETS ≥ 20–30%, high DOR and pCR are linked with favorable prognosis in mCRC patients [16]. Surgery of liver metastases is also a contributing factor to better survival. Since the patient had all these positive prognostic factors, one could expect long PFS and OS.

A literature search found one similar case report of pCR in transversal colon cancer with retroperitoneal lymphadenopathy after cetuximab and FOLFOX6 treatment [25]. However, this clinical observation deserves further research in order to make definitive conclusions about transversal colon responsiveness to anti-EGFR therapy. Detailed comprehensive studies of genetic features of cancers originating from specific colon parts are needed, and hold a key to personalized treatment options and better outcomes for patients with mCRC.

ACKNOWLEDGEMENT

The paper is a part of Miljana Džunić's doctoral thesis.

The case was presented at the 58th National Cancer Symposium, in Belgrade, Serbia, on December 9, 2021.

Conflict of interest: None declared.

REFERENCES

1. Li N, Lu B, Luo C, Cai J, Lu M, Zhang Y, et al. Incidence, mortality, survival, risk factor and screening of colorectal cancer: A comparison among China, Europe, and northern America. Cancer Lett. 2021;522:255–68. [DOI: 10.1016/j.canlet.2021.09.034] [PMID: 34563640]
2. Cardoso R, Guo F, Heisser T, Hackl M, Ihle P, De Schutter H, et al. Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study. Lancet Oncol. 2021;22(7):1002–13. [DOI: 10.1016/S1470-2045(21)00199-6] [PMID: 34048685]
3. Yoshino T, Arnold D, Taniguchi H, Pentheroudakis G, Yamazaki K, Xu RH, et al. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann Oncol. 2018;29(1):44–70. [DOI: 10.1093/annonc/mdx738] [PMID: 29155929]
4. Piawah S, Venook AP. Targeted therapy for colorectal cancer metastases: A review of current methods of molecularly targeted therapy and the use of tumor biomarkers in the treatment of metastatic colorectal cancer. Cancer. 2019;125(23):4139–47. [DOI: 10.1002/cncr.32163] [PMID: 31433498]
5. Dzunic M, Petkovic I, Cvetanovic A, Vrbic S, Pejcic I. Current and future targets and therapies in metastatic colorectal cancer. J BUON. 2019;24(5):1785–92. [PMID: 31786838]
6. Benson AB, Venook AP, Al-Hawary MM, Arain MA, Chen J, Ciombor KK, et al. Colon Cancer, Version 2.2021. J Natl Compr Canc Netw. 2021;19(3):329–59. [DOI: 10.6004/jnccn.2021.0012] [PMID: 33724754]
7. Dzunic M, Andjelkovic-Apostolovic M, Vrbic S, Pejcic I, Petkovic I, Cvetanovic A, et al. Survival of patients with liver metastases from colorectal cancer treated with bevacizumab and FOLFOX4. J BUON. 2020;25(1):212–9. [PMID: 32277634]
8. Engstrand J, Nilsson H, Strömberg C, Jonas E, Freedman J. Colorectal cancer liver metastases - a population-based study on incidence, management and survival. BMC Cancer. 2018;18(1):78. [DOI: 10.1186/s12885-017-3925-x] [PMID: 29334918]
9. Wang Z, Wang X, Zhang Z, Wang X, Chen M, Lu L, et al. Association between Primary Tumor Location and Prognostic Survival in Synchronous Colorectal Liver Metastases after Surgical Treatment: A Retrospective Analysis of SEER Data. J Cancer. 2019;10(7):1593–600. [DOI: 10.7150/jca.29294] [PMID: 31205514]
10. Baldessari C, Spallanzani A, Gelsomino F, Bettelli S, Pugliese G, Salati M, et al. Outcome and prognostic factors after resection of liver metastases in patients with colorectal cancer. Ann Oncol. 2017;28(6):vi13–vi14. [DOI: 10.1093/annonc/mdx422.036]
11. de Haas RJ, Wicherts DA, Salloum C, Andreani P, Sotirov D, Adam R. Long term outcomes after hepatic resection for colorectal metastases in young patients. Cancer. 2010;116(3):647–58. [DOI: 10.1002/cncr.24721] [PMID: 19998351]
12. Džunić M, Petković I, Cvetanović A, Pejčić I, Vrbić S, Dinić S. Prognostic Parameters in Patients with Resected Liver Metastases from Colorectal Cancer after Biological and Chemotherapy. Acta Fac Med Naissensis. 2020;37(4):349–58. [DOI: 10.5937/afmnai2004349D]
13. Džunić M, Pejčić B, Anđelkovic-Apostolović M, Vrbić S, Pejčić I, Petković I. Predictors of therapy response and early recurrence in patients with potentially resectable colorectal liver metastases treated with bevacizumab and FOLFOX4 as a conversion therapy. Acta Med Medianae. 2019;58(3):72–9. [DOI:10.5633/amm.2019.0310]
14. Froelich MF, Petersen EL, Heinemann V, Nörenberg D, Hesse N, Gesenhues AB, et al. Impact of Size and Location of Metastases on Early Tumor Shrinkage and Depth of Response in Patients With Metastatic Colorectal Cancer: Subgroup Findings of the Randomized, Open-Label Phase 3 Trial FIRE-3/AIO KRK-0306. Clin Colorectal Cancer. 2020;19(4):291–300.e5. [DOI: 10.1016/j.clcc.2020.06.005] [PMID: 32917529]
15. Heinemann V, Stintzing S, Modest DP, Giessen-Jung C, Michl M, Mansmann UR. Early tumour shrinkage (ETS) and depth of response (DpR) in the treatment of patients with metastatic colorectal cancer (mCRC). Eur J Cancer. 2015;51(14):1927–36. [DOI: 10.1016/j.ejca.2015.06.116] [PMID: 26188850]
16. Sartore-Bianchi A, García-Alfonso P, Geissler M, Köhne CH, Peeters M, Price T, et al. Relationships Between Köhne Category/Baseline Tumor Load and Early Tumor Shrinkage, Depth of Response, and Outcomes in Metastatic Colorectal Cancer. Clin Colorectal Cancer. 2021;20(4):305–13. [DOI: 10.1016/j.clcc.2021.05.007] [PMID: 34172397]
17. Manca P, Corallo S, Randon G, Lonardi S, Cremolini C, Rimassa L, et al. Impact of early tumor shrinkage and depth of response on the outcomes of panitumumab-based maintenance in patients with RAS wild-type metastatic colorectal cancer. Eur J Cancer. 2021;144:31–40. [DOI: 10.1016/j.ejca.2020.11.017] [PMID: 33321462]
18. Mukund K, Syulyukina N, Ramamoorthy S, Subramaniam S. Right and left-sided colon cancers – specificity of molecular mechanisms in tumorigenesis and progression. BMC Cancer. 2020;20(1):317. [DOI: 10.1186/s12885-020-06784-7] [PMID: 32293332]
19. Rivera F, Karthaus M, Hecht JR, Sevilla I, Forget F, Fasola G, et al. Final analysis of the randomised PEAK trial: overall survival and tumour responses during first-line treatment with mFOLFOX6 plus either panitumumab or bevacizumab in patients with metastatic colorectal carcinoma. Int J Colorectal Dis. 2017;32(8):1179–90. [DOI: 10.1007/s00384-017-2800-1] [PMID: 28424871]
20. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol. 2014;25(7):1346–55. [DOI: 10.1093/annonc/mdu141] [PMID: 24718886]
21. Boeckx N, Koukakis R, Op de Beeck K, Rolfo C, Van Camp G, Siena S, et al. Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: results from two randomized first-line panitumumab studies. Ann Oncol. 2017;28(8):1862–8. [DOI: 10.1093/annonc/mdx119] [PMID: 28449055]
22. Arnold D, Lueza B, Douillard JY, Peeters M, Lenz HJ, Venook A, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol. 2017;28(8):1713–29. [DOI: 10.1093/annonc/mdx175] [PMID: 28407110]
23. He WZ, Liao FX, Jiang C, Kong PF, Yin CX, Yang Q, et al. Primary tumor location as a predictive factor for first-line bevacizumab effectiveness in metastatic colorectal cancer patients. J Cancer. 2017;8(3):388–94. [DOI: 10.7150/jca.16804] [PMID: 28261339]
24. Jordan F, Grundmann N, Schenkirsch G, Märkl B, Messmann H, Anthuber M, et al. Impact of primary tumor localization on the efficacy of bevacizumab in metastatic colorectal cancer. Anticancer Res. 2018;38(9):5539–46. [DOI: 10.21873/anticanres.12889] [PMID: 30194214]
25. Suetsugu T, Matsuhashi N, Takahashi T, Tanahashi T, Matsui S, Imai H, et al. Pathological complete response to mFOLFOX6 plus cetuximab therapy for unresectable colon cancer with multiple paraaortic lymph node metastases. Mol Clin Oncol. 2018;9(6):587–91. [DOI: 10.3892/mco.2018.1742] [PMID: 30546885]

Патолошки комплетан одговор код метастатског десностраног карцинома колона леченог панитумумабом и хемиотерапијским режимом *FOLFOX4*

Миљана Џунић[1], Ана Цветановић[1,2], Иван Петковић[1,2], Ивана Тодоровић-Стојановић[3]

[1]Универзитетски клинички центар Ниш, Клиника за онкологију, Ниш, Србија;
[2]Универзитет у Нишу, Медицински факултет, Ниш, Србија;
[3]Општа болница у Пироту, Пирот, Србија

САЖЕТАК

Увод Препоручени биолошки агенси за лечење левостраног метастатског колоректалног карцинома (мКРК) без мутација у генима *RAS*/*BRAF* јесу цетуксимаб или панитумумаб, док се за десностранi мКРК препоручује бевацизумаб. За мКРК трансверзалног колона нема података о ефикасности биолошке терапије. Приказујемо болесницу са десностраним мКРК порекла трансверзалног колона код које је третман са панитумумабом уз хемиотерапију резултовао одличним исходом.

Приказ болесника Код жене старости 56 година дијагностикован је аденокарцином трансверзалног колона, без мутација у *RAS* генима, са бројним метастазама у оба лобуса јетре. Након операције примарног тумора болесница је лечена применом панитумумаба и хемиотерапије *FOLFOX*4. После два месеца третмана евидентиран је драматичан одговор – сума дијаметара циљних лезија смањила се за 70,5%. После још два месеца терапије примећено је даље смањење за 22,5%. Накнадно су оперисане метастазе у јетри. Хистопатолошки налаз открио је фиброзно и некротично ткиво у свим сумњивим лезијама, изузев у једном фокусу, где је пронађен аденокарцином, али са околном некрозом од 90%. Дванаест месеци после хирургије јетре болесница је без прогресије болести.

Закључак Детаљно истраживање генетских карактеристика мКРК кључно је за примену персонализованих терапијских опција и бољи исход лечења болесника са мКРК.

Кључне речи: колоректални карцином; панитумумаб; трансверзални колон; метастазе у јетри

DOI: https://doi.org/10.2298/SARH220908099R
UDC: 616.155.194-053.2/.6

REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

The basis of prevention of iron deficiency anemia during childhood and adolescence

Nedeljko Radlović[1], Zoran Leković[2,3], Jelena Radlović[4], Marija Mladenović[5]

[1]Serbian Medical Society, Academy of Medical Sciences, Belgrade, Serbia;
[2]University Children's Hospital, Belgrade, Serbia;
[3]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[4]Railways of Serbia Institute for Health Care of Workers, Belgrade, Serbia;
[5]Singidunum University, Faculty of Health, Legal, and Business Studies, Valjevo, Serbia

SUMMARY
Anemia is a common and etiologically heterogeneous health problem both during the period of growth and development and in other phases of life. It is most often caused by a deficiency of iron, primarily due to inadequate nutrition, and less often as a consequence of various diseases. Particularly risk groups for the occurrence of anemia due to iron deficiency are children in the stages of rapid growth and development, i.e., in the first years after birth and during puberty. In accordance with the fact that it is better to prevent than to treat, in this article are given basic guidelines related to the prevention of this type of anemia in children and adolescents.
Keywords: iron deficiency anemia; children; adolescents; prevention

INTRODUCTION

Anemia is often and etiologically very heterogeneous pathological condition followed by hemoglobin (Hb) level in the blood below the lower reference value for the appropriate period of life (Table 1) [1]. It is most often caused by a deficiency of iron, primarily due to inadequate nutrition, and less often due to its malabsorption or loss through acute or chronic bleeding [2–10]. In addition, high iron loss from the body occurs in diseases accompanied by transferrin and ferritin exudation, such as extensive burns, exudative gastroenteropathy, nephrotic syndrome, and extensive exfoliative dermatitis [11, 12]. As the fetus creates significant iron reserves during the last trimester intended for adequate growth and development in the first 4–6 months after birth, it is clear that premature birth or intrauterine growth restriction (IUGR) will result in its deficiency [13, 14]. Also, an important etiological factors of iron deficiency and iron deficiency anemia during infancy are fetal–maternal hemorrhage, twin-to-twin transfusion and premature umbilical cord clamping during birth [10, 15, 16].

Table 1. Lower blood Hb reference value in children and adolescents [1]

Age	Hb (g/L)
0–30 days	15.0
1–23 months	10.5
2–9 years	11.5
Boys 10–17 years	12.5
Girls 10–17 years	12.0

It is estimated that 25–33% of the human population have anemia, 50% of which are due to iron deficiency [8]. According to the World Health Organization, the latest prevalence estimates of anemia in 2016 were 41.7% in children and 32.8% in women of reproductive age, being most prevalent in low- and middle-income countries [14].

In this paper are presented the key facts related to metabolism and physiological needs in iron, as well as basic guidelines for the prevention of its deficit during a period of growth and development.

IRON METABOLISM

Iron is a microelement essential for many processes in the human body. As a constituent of Hb and myoglobin it allows the transport of oxygen, and as part of cytochrome enzymes, catalase and peroxidase oxidative-reductive reactions. In addition, it is an indispensable factor in the synthesis of deoxyribonucleic acid, myelin, serotonin, noradrenaline, dopamine and other compounds [17]. Bearing in mind these facts, it is clear that iron is essential for all cells of the body, and that as a prooxidant, both inside and outside them, except at the time of transfer from one compound to another, is never free [17, 18].

Iron metabolism is a very complex process that involves its intake, intestinal absorption, blood flow, import into cells, incorporation into appropriate functional compounds and deposition [17]. Since iron excess has a toxic effect

Received • Примљено: September 8, 2022
Revised • Ревизија: October 9, 2022
Accepted • Прихваћено: October 10, 2022
Online first: October 14, 2022

Correspondence to:
Nedeljko RADLOVIĆ
Serbian Medical Society
Džordža Vašingtona 19
110000 Belgrade
Serbia
n.radlovic@beotel.net

and limited mechanisms of excretion from the body, the regulation of its homeostasis is primarily performed at the level of the mature intestinal epithelium of the small intestine, i.e., enterocytes [17]. The main role in this process is the hepatic polypeptide hormone hepcidin, which controls not only intestinal iron absorption but also its mobilization from the depot and transplacental transport [8, 17, 19, 20].

Iron absorption is performed in the proximal part of the small intestine, of which 85% in the duodenum [17]. Two main types of iron in foods, heme and non-heme, use different mechanisms of absorption [8, 17]. Heme iron, present in the meat, is transferred into the enterocyte via a specific membrane transport protein (heme carrier protein 1, HCP 1), after which it is released by proto-porphyrin IX under the action of hem-oxygenase-1 [17]. The degree of absorption of these mechanisms on iron in the state of high demands of the organism, and of the left disorders of digestion and absorption reaches 20–30%, and even up to 50% [8, 18]. The only food ingredient that compromises the absorption of heme iron is calcium [21]. Non-hem iron, present in other foods, has a significantly lower utilization rate, which in healthy, depending on the type of food and other factors, is only 1–10%, on average 4–5% [18]. Stimulating effects on intestinal absorption of non-hem iron are factors that favor its solubility (hydrochloric acid, gastric juice, citric, lactic and other organic acids) or reduction (enterocytic ferric reductase DcytB, vitamin C), and inhibitory compounds that make it insoluble (phosphates, phosphoproteins, phytates, oxalates, polyphenols, tannins, fibers, casein) or in competition with its absorption (copper, zinc, manganese, nickel, cobalt, lead, cadmium) [8, 18]. In addition, amino acids, extensive protein hydrolysates and beta-carotene have a beneficial effect on the absorption of non-hem iron, while calcium has an unfavorable effect [18]. Non-hem iron absorption is, after previous reduction, performed via a divalent metal transporter 1 (DMT1) located on the apical membrane of enterocytes [17, 19, 22]. Apart from iron, copper, zinc and other divalent metals are transmitted via DMT1, which explains the interdependence of their degree of absorption and content in the body. Iron present in ferritin of animal and vegetable foods is a separate form of absorption [23]. Also, breast milk lactoferrin-bound iron is absorbed through specific receptors on the apical membrane of enterocytes [24]. Upon passage into the enterocyte, the iron in conjunction with an as yet unidentified protein reaches its basolateral membrane where it is oxidized and via ferroportin 1 is exported and transferred to transferrin [17]. Oxidation of iron, which is a prerequisite for its exit from the cell and transfer to transferrin, is performed by hephaestin, enterocytic ferro-oxidase added to ferroportin 1 [25]. Through transferrin the iron reaches all cells of the body which via its transferrin receptors 1 uptake and transfer it to the cytoplasm via DMT1 [16, 17]. Excess of iron in enterocytes with apoferritin builds ferritin [19]. The import of iron into enterocytes and its binding to apoferritin are controlled by specific intracellular iron regulatory proteins (IRPs) [18, 19]. The same mechanism controls the homeostasis of iron in other cells of the body [26]. Consistent with its physiological role, its largest acceptors are the precursors of the red blood cell, as well as the cells that deposit it, i.e., hepatocytes and macrophages of spleen, liver and bone marrow. Given the limited transfer capacity, as well as short lifespan of enterocytes, which desquamate after 3–5 days, iron fraction which escapes the transport is lost, which represents a physiological barrier of its excess in the state of excessive oral intake [25].

As stated, the control of iron homeostasis is a very complex process whose main carriers are enterocytes and hepatocytes, or their regulatory proteins [8, 19, 27]. Intracellular IRPs play a key role in controlling the import of iron into enterocytes, and in its export hepcidin [20, 26]. The physiological inducer of IRPs is high iron content in enterocyte, and hepcidin in circulation and hepatocyte [27, 28]. By their effect IRPs interrupt the expression of DMT1 and ferri-reductase and stimulate ferritin synthesis, while hepcidin reacts with ferroportin 1 and leads to its internalization and degradation [27, 28]. By the same mechanism as in enterocyte, hepcidin regulates iron efflux from hepatocytes, macrophages and placental cells [27, 28]. The physiological significance of the activation of IRPs and hepcidin is contained in the protection of the body against excessive iron intake, while in the state of iron deficiency or hypoxia, the activity of these factors disappears [27, 28]. Sex hormones (testosterone, estrogens), growth hormone, and hypoxia-induced erythroblastic polypeptide erythroferrone have an important role in suppressing hepcidin expression [28, 29]. Being the reactant of the first stage of inflammation, hepcidin, by blocking the intestinal resorption of iron and its mobilization from the depot, is responsible for the occurrence of anemia in chronic infectious and other inflammatory diseases, as well as in some malignancies [8, 27, 30, 31, 32]. In addition, dysregulation of hepcidin is the pathogenetic basis of hereditary hemochromatosis, which in the first type is due to autosomal recessive defect in its expression, in the second as a result of insufficient stimulation of its secretion and in the third due to the absence of its effect caused by an autosomal dominant defect of ferroportin [27].

DIETARY REQUIREMENTS FOR IRON OF CHILDREN AND ADOLESCENTS

Dietary requirements for iron of children and adolescents are dependent on the rate of growth and the degree of physiological losses (Table 2) [33]. In girls with menstruation onset, the necessary dietary intake of iron is significantly higher compared to male peers. The needs in iron of infants born at term are low because within the first six months it is mainly provided from prenatally acquired stocks [33].

Table 3 shows the iron content of some of the basic foods [10, 34]. Within the standard diet, except in the first year after birth, the participation of heme and non-heme iron in meeting physiological needs is approximately equal [33]. Hem iron is present in meat, while non-hem iron is found in other foods. Due to its rich content and high

Table 2. Recommended dietary intake for iron in childhood and adolescence [33]

Age	Male	Females
0–6 months	0.27 mg*	0.27 mg*
7–12 months	11 mg	11 mg
1–3 years	7 mg	7 mg
4–8 years	10 mg	10 mg
9–13 years	8 mg	8 mg
14–18 years	11 mg	15 mg

Adequate intake*

Table 3. Iron content in certain types of food [10, 34]

Type of food	mg/100 g
Human milk	0.3–0.5
Cow's milk	0.3–0.6
Infant formula	4–12
Chicken meat	0.6–2
Turkey meat	0.8–2
Beef meat	3–3.1
Lamb meat	1.2–1.9
Pork meat	0.9–2.3
Sardines	2.2–3.6
Chicken liver	7.4
Chicken egg yolk	7.2
Beans and peas	2
Spinach	1.5–1.7
Cabbage	0.7
Potatoes	0.3
Whole-wheat flour	3.9
White wheat flour	2
Hazelnut	3
Walnut	2
Apple	0.1

utilization rate, meat is the best source of iron [35, 36]. Many other foods are abundant in iron, such as egg yolks, liver, various types of vegetables and nuts, but in a non-heme form, and are inferior to meat in this respect. Due to its low content, despite its extremely high absorption rate (about 50%), breast milk is not a rich source of iron [36]. Cow's, goat's and sheep's milk, cereals and fruits, due to their low concentration and/or scarce absorption, are a poor source of iron [10, 36].

Food grade iron is used to cover physiological losses and build up reserves, and during growth and development to incorporate into new body structures. About 65–75% of total body iron in an adult is found in erythrocytes, 10% in muscle, and rest in other tissues and depots [8]. On circulating iron accounts for only 0.1% of its total content in the body [37].

Iron from decayed and lysed erythrocytes and other cells is conserved and recycled [15, 33]. It is lost from the body in the desquamation of skin and mucous epithelium, and minimally through urine and sweat [33]. Hence, the degree of physiological iron loss is primarily proportional to body surface [33]. In addition, women in the generative period have an additional loss of iron by menstrual bleeding, and their needs are much greater than men [33]. This is also true for pregnant women, as a significant part of the iron ingested is directed towards increasing its erythrocyte mass, building the placenta and the needs of the fetus [33].

PREVENTION OF IRON DEFICIENCY IN CHILDREN AND ADOLESCENTS

Optimal nutrition is the basis of iron deficiency prevention. Exceptions are infants born preterm, with IUGR and as twins who also require iron supplementation. An important factor in the prevention of early infantile anemia is delayed cord clamping until 1–3 minutes after birth, which provides placental transfusion and iron-rich blood flow to the newborn [16, 36].

Optimal nutrition of the infant is based on breast milk and/or infant formula, as well as timely initiation and optimal intake of complementary foods. Although relatively poor in iron (0.3–0.5 mg / 100 ml), due to its high absorption rate breast milk to a term infant during the first 4–6 months covers the need for it [33, 36]. Adequate alternatives to breast milk deficiency are infant formulas [38]. Infant formulas contain 0.3–1.3 mg of elemental iron per 100 kcal [39]. The iron content in infant formulas is much higher compared to breast milk because its absorption rate is so much lower [36]. Because prenatally acquired trace element reserves are depleted during the first 4–6 months after birth, cows' milk formulas with a higher iron content (1.1–1.9 mg/100 kcal) are recommended for infants aged 6–12 months [40]. Due to the even lower utilization rate, the recommended iron content in formulas based on soy protein isolates intended for infants at that age is much higher (1.3–2.5 mg/100 kcal) [40]. According to current recommendations, complementary foods are introduced to a child aged 4–6 months [41, 42]. There are several reasons for this, and one of them is to cover the need for iron. Therefore, infants who only consume breast milk at 4–6 months of age are advised daily intake of appropriate iron preparation at a dose of 1 mg/kg [38]. The same is true for infants in the second half who are not eating enough meat and vegetables. However, children born pre-term or with IUGR, as their prenatally acquired iron reserves are extremely scarce, drug prophylaxis of sideropenic anemia begins at the end of the first month and continues until the end of the first year or until the optimum intake of non-milk food, especially meat [38]. The recommended daily dose of elemental iron to this infant on the breast milk diet, depending on the degree of prematurity and IUGR, is 2–3 mg / kg, and if fed with the appropriate cow's milk formula 1 mg/kg [36, 38, 43]. The iron content of standard cow's milk formulas intended to feed preterm infants by the age of 40 postconception varies from 1.5 to 2.5 mg/100 kcal [44]. At present, there is no clearly defined attitude regarding the introduction of complementary feeding in preterm infants. According to the experience of different groups of authors, its initiation to these children is generally delayed in proportion to the degree of prematurity, i.e., for as many as were born earlier [45, 46]. Ordinarily cow's milk and milk of other mammals, for a number of reasons, including poor iron content (about 0.5 mg/L) and low utilization rate

(5–10%), are not advised to the child in the first year [38]. In order to identify and correct sideropenic anemia in a timely manner, according to the American Academy of Pediatrics, routine blood counts should be performed for every 9–12-month-old child, and preterm, malnourished or otherwise suspected of iron deficiency and earlier [38].

Consistent with growth rate, stage of development and nutritional requirements, feeding the child after the first year is based on non-milk foods, including foods with rich and highly utilized iron content, such as meat, legumes and other types of vegetables [38]. However, in order to meet the need for calcium as well as other qualities, milk and dairy products remain a mandatory part of the child's menu. The daily amount of milk should be limited at the age of 1–3 years to 500 ml, from four to eight years to 600 ml and from nine to 18 years to 700 ml [36, 47]. This applies primarily to cows, goats and sheep's milk, which are poor sources of iron. Therefore, children aged 12–36 months instead of plain milk recommended follow-up formula, which, among other benefits, contains a significant amount of iron (1–3 mg/100 kcal) [48]. After the first year of life iron deficiency most commonly affects children aged 1–5 years and adolescents, especially girls starting menstruation [36, 49]. The iron deficiency of healthy children of these age groups is based on excessive intake of milk, dairy products and cereals at the expense of meat and vegetables [8, 38]. In line with the above facts, children and adolescents who do not eat at least two or three iron-rich foods every day do not provide adequate iron needs and require appropriate supplementation [50].

ACKNOWLEDGMET

The authors declare that the article was written according to the ethical standards of the Serbian Archives of Medicine as well as ethical standards of medical facilities for each author involved.

Conflict of interest: None declared.

REFERENCES

1. Lo SF. Laboratory testing in infants and children. In: Kligmena RM, Stanton BF, St Geme III JW, Schor NF, eds. Nelson Textbook of Pediatrics, 20th ed. Philaderlphia: Elsevier; 2016. p. 3460–72.
2. Cappellini MD, Musallam KM, Taher AT. Iron deficiency anaemia revisited. J Intern Med. 2020;287(2):153–70. [DOI: 10.1111/joim.13004] [PMID: 31665543]
3. Warner MJ, Kamran MT. Anemia, Iron Deficiency. [Updated 2018 Nov 14]. In: StatPearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2019 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448065/
4. Radlović N, Leković Z, Mladenović M, Radlović V, Vuletić B, Dučić S, et al. Frequency, severity and type of anemia in children with classical celiac disease. Srp Arh Celok Lek. 2019;147(3–4):189–92. [DOI: 10.2298/SARH181203021R]
5. Radlović N, Leković Z, Radlović V, Mandić J, Mladenović M, Radlović J, et al. Clinical features of non-classical celiac disease in children and adolescents. Srp Arh Celok Lek. 2021;149(1–2):48–52. [DOI: 10.2298/SARH200626070R]
6. Radlović N, Leković Z, Radlović V, Simić D, Ristić D, Vuletić B. Food allergy in children. Srp Arh Celok Lek. 2016;144(1–2):99–103. [DOI: 10.2298/sarh1602099r] [PMID: 27276868]
7. Leković Z, Radlović N, Brdar R, Vuletić B, Janić N, Ristić D, et al. Clinical characteristics of idiopathic ulcerative colitis in children. Srp Arh Celok Lek. 2011;139(3–4):170–3. [DOI: 10.2298/sarh1104170l] [PMID: 21618864]
8. Mantadakis E, Chatzimichael E, Zikidou P. Iron deficiency anemia in children residing in high and low-income countries: Risk factors, prevention, diagnosis and therapy. Mediterr J Hematol Infect Dis. 2020;12(1):e2020041. [DOI: 10.4084/MJHID.2020.041] [PMID: 32670519]
9. Gafter-Gvili A, Schechter A, Rozen-Zvi B. Iron deficiency anemia in chronic kidney disease. Acta Haematol. 2019;142(1):44–50. [DOI: 10.1159/000496492] [PMID: 30970355]
10. Chouraqui JP. Dietary approaches to iron deficiency prevention in childhood-A critical public health issue. Nutrients. 2022;14(8):1604. [DOI: 10.3390/nu14081604] [PMID: 35458166]
11. Radlovic N, Lekovic Z, Radlovic V, Simic D, Vuletic B, Ducic S, et al. Celiac crisis in children in Serbia. Ital J Pediatr. 2016;42:25. [DOI: 10.1186/s13052-016-0233-z] [PMID: 26931303]
12. Sreekanth S, Bhatia P, Meena J, Dawman L, Tiewsoh K. Iron deficiency in proteinuric children with nephrotic syndrome: A cross-sectional pilot study. Arch Pediatr. 2021;28(6):485–7. [DOI: 10.1016/j.arcped.2021.05.005] [PMID: 34226064]
13. Moreno-Fernandez J, Ochoa JJ, Latunde-Dada GO, Diaz-Castro J. Iron deficiency and iron homeostasis in low birth weight preterm infants: A systematic review. Nutrients. 2019;11(5):1090. [DOI: 10.3390/nu11051090] [PMID: 31100900]
14. World Health Organization; Geneva, Switzerland: 2017. [(accessed on 19 January 2020)]. Global Health Observatory Data Repository. Available online: apps.who.int/gho/data/node.main.
15. Qian Y, Ying X, Wang P, Lu Z, Hua Y. Early versus delayed umbilical cord clamping on maternal and neonatal outcomes. Arch Gynecol Obstet. 2019;300(3):531–43. [DOI: 10.1007/s00404-019-05215-8] [PMID: 31203386]
16. Sundararajan S, Rabe H. Prevention of iron deficiency anemia in infants and toddlers. Pediatr Res. 2021;89(1):63–73. [DOI: 10.1038/s41390-020-0907-5] [PMID: 32330927]
17. Ganz T. Systemic iron homeostasis. Physiol Rev. 2013;93(4):1721–41. [DOI: 10.1152/physrev.00008.2013] [PMID: 24137020]
18. Dasa F, Abera T. Factors affecting iron absorption and mitigation mechanisms: A review. Int J Agric Sc Food Technol. 2018;4(1):24–30. [DOI: 10.17352/2455-815X.000033]
19. Vogt AS, Arsiwala T, Mohsen M, Vogel M, Manolova V, Bachmann MF. On iron metabolism and its regulation. Int J Mol Sci. 2021;22(9):4591. [DOI: 10.3390/ijms22094591] [PMID: 33925597]
20. Ginzburg YZ. Hepcidin-ferroportin axis in health and disease. Vitam Horm. 2019;110:17–45. [DOI: 10.1016/bs.vh.2019.01.002] [PMID: 30798811]
21. Roughead ZK, Zito CA, Hunt JR. Inhibitory effects of dietary calcium on the initial uptake and subsequent retention of heme and nonheme iron in humans: comparisons using an intestinal lavage method. Am J Clin Nutr. 2005;82(3):589–97. [DOI: 10.1093/ajcn.82.3.589] [PMID: 16155272]
22. Shokrgozar N, Golafshan HA. Molecular perspective of iron uptake, related diseases, and treatments. Blood Res. 2019;54(1):10–6. [DOI: 10.5045/br.2019.54.1.10] [PMID: 30956958]
23. Theil EC, Chen H, Miranda C, Janser H, Elsenhans B, Nez MT, et al. Absorption of iron from ferritin is independent of heme iron and ferrous salts in women and rat intestinal segments. J Nutr. 2012;142(3):478–83. [DOI: 10.3945/jn.111.145854] [PMID: 22259191]
24. Lönnerdal B, Georgieff MK, Hernell O. Developmental physiology of iron absorption, homeostasis, and metabolism in the healthy term infant. J Pediatr. 2015;167(4 Suppl):S8–14. [DOI: 10.1016/j.jpeds.2015.07.014] [PMID: 26364027]
25. Knutson MD. Iron transport proteins: Gateways of cellular and systemic iron homeostasis. J Biol Chem. 2017;292(31):12735–43. [DOI: 10.1074/jbc.R117.786632] [PMID: 28615441]
26. Lane DJ, Merlot AM, Huang ML, Bae DH, Jansson PJ, Sahni S, et al. Cellular iron uptake, trafficking and metabolism: Key molecules and mechanisms and their roles in disease. Biochim Biophys Acta. 2015;1853(5):1130–44. [DOI: 10.1016/j.bbamcr.2015.01.021] [PMID: 25661197]

27. Arezes J, Nemeth E. Hepcidin and iron disorders: new biology and clinical approaches. Int J Lab Hematol. 2015;37 Suppl 1:92–8. [DOI: 10.1111/ijlh.12358] [PMID: 25976966]
28. Meynard D, Babitt JL, Lin HY. The liver: conductor of systemic iron balance. Blood. 2014;123(2):168–76. [DOI: 10.1182/blood-2013-06-427757] [PMID: 24200681]
29. Ganz T. Erythropoietic regulators of iron metabolism. Free Radic Biol Med. 2019;133:69–74. [DOI: 10.1016/j.freeradbiomed.2018.07.003] [PMID: 29981834]
30. Roth MP, Meynard D, Coppin H. Regulators of hepcidin expression. Vitam Horm. 2019;110:101–29. [DOI: 10.1016/bs.vh.2019.01.005] [PMID: 30798807]
31. Camaschella C, Nai A, Silvestri L. Iron metabolism and iron disorders revisited in the hepcidin era. Haematologica. 2020;105(2):260–72. [DOI: 10.3324/haematol.2019.232124] [PMID: 31949017]
32. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. Blood. 2019;133(1):40–50. [DOI: 10.1182/blood-2018-06-856500] [PMID: 30401705]
33. Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc: a Report of the Panel on Micronutrients. Washington, DC: National Academy Press; 2001.
34. Scherz H, Senser F. Food Composition and Nutrition Tables. Stuttgart: GmbH Sci Publ; 2000.
35. 2015–2020 Dietary Guidelines for Americans. 8th Edition. December 2015. U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2020-2025. 9th Edition. December 2020. Available at DietaryGuidelines.gov.
36. Domellöf M, Braegger C, Campoy C, Colomb V, Decsi T, Fewtrell M, et al; ESPGHAN Committee on Nutrition. Iron requirements of infants and toddlers. J Pediatr Gastroenterol Nutr. 2014;58(1):119–29. [DOI: 10.1097/MPG.0000000000000206] [PMID: 24135983]
37. Sarkar J, Potdar AA, Saidel GM. Whole-body iron transport and metabolism: Mechanistic, multi-scale model to improve treatment of anemia in chronic kidney disease. PLoS Comput Biol. 2018;14(4):e1006060. [DOI: 10.1371/journal.pcbi.1006060] [PMID: 29659573]
38. Baker RD, Greer FR; Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0–3 years of age). Pediatrics. 2010;126(5):1040–50. [DOI: 10.1542/peds.2010-2576] [PMID: 20923825]
39. Agostoni C, Domellöf M. Infant formulae: from ESPGAN recommendations towards ESPGHAN-coordinated global standards. J Pediatr Gastroenterol Nutr. 2005;41(5):580–3. [DOI: 10.1097/01.mpg.0000188741.46380.24] [PMID: 16254514]
40. Koletzko B, Bhutta ZA, Cai W, Cruchet S, El Guindi M, Fuchs GJ, et al. Compositional requirements of follow-up formula for use in infancy: recommendations of an international expert group coordinated by the Early Nutrition Academy. Ann Nutr Metab. 2013;62(1):44–54. [DOI: 10.1159/000345906] [PMID: 23258234]
41. Greer FR, Sicherer SH, Burks AW; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics. 2008;121(1):183–91. [DOI: 10.1542/peds.2007-3022] [PMID: 18166574]
42. Fewtrell M, Bronsky J, Campoy C, Domellöf M, Embleton N, Mis NF, et al. Complementary feeding: A position paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2017;64(1):119–32. [DOI: 10.1097/MPG.0000000000001454] [PMID: 28027215]
43. Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committeeon Nutrition. J Pediatr Gastroenterol Nutr. 2010;50(1):85–91. [DOI: 10.1097/MPG.0b013e3181adaee0] [PMID: 19881390]
44. ESPGHAN Committee o Nutrition, Aggett PJ, Agostoni C, Axelsson I, De Curtis M, Goulet O, Hernell O, et al. Feeding preterm infants after hospital discharge: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2006;42(5):596–603. [DOI: 10.1097/01.mpg.0000221915.73264.c7] [PMID: 16707992]
45. Barachetti R, Villa E, Barbarini M. Weaning and complementary feeding in preterm infants: management, timing and health outcome. Pediatr Med Chir. 2017;39(4):181. [DOI: 10.4081/pmc.2017.181] [PMID: 29502384]
46. Giannì ML, Bezze E, Colombo L, Rossetti C, Pesenti N, Roggero P, et al. Complementary feeding practices in a cohort of Italian late preterm infants. Nutrients. 2018;10(12):1861. [DOI: 10.3390/nu10121861] [PMID: 30513799]
47. United States Department of Agriculture. ChooseMyPlate.gov website. All about the dairy group. www.choosemyplate.gov/eathealthy/dairy. Updated: July 18, 2019. Accessed: September 17, 2019.
48. Hojsak I, Bronsky J, Campoy C, Domellöf M, Embleton N, Fidler Mis N, et al; ESPGHAN Committee on Nutrition. Young child formula: A position paper by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2018;66(1):177–85. [DOI: 10.1097/MPG.0000000000001821] [PMID: 29095351]
49. De Andrade Cairo RC, Rodrigues Silva L, Carneiro Bustani N, Ferreira Marques CD. Iron deficiency anemia in adolescents; a literature review. Nutr Hosp. 2014;29(6):1240–9. [DOI: 10.3305/nh.2014.29.6.7245] [PMID: 24972460]
50. National Institutes of Health, Office of Dietary Supplements. Dietary Supplement Fact Sheet: Iron. Available from: http://ods.od.nih.gov/factsheets/iron.asp [Accessed: March 3, 2017]

Основа превенције анемије узроковане недостатком гвожђа током детињства и адолесценције

Недељко Радловић[1], Зоран Лековић[2,3], Јелена Радловић[4], Марија Младеновић[5]

[1]Српско лекарско друштво, Академија медицинских наука, Београд, Србија;
[2]Универзитетска дечја клиника, Београд, Србија;
[3]Универзитет у Београду, Медицински факултет, Београд, Србија;
[4]Завод за здравствену заштиту радника „Железнице Србије", Београд, Србија;
[5]Универзитет „Сингидунум", Факултет здравствених, правних и пословних студија, Ваљево, Србија

САЖЕТАК

Анемија је чест и етиолошки хетероген здравствени проблем како у периоду раста и развоја, тако и у осталим фазама живота. Најчешће је узрокована недостатком гвожђа, пре свега због неадекватне исхране, а ређе као последица различитих болести. Посебно ризичне групе за појаву анемије услед недостатка гвожђа су деца у фазама брзог раста и развоја, тј. у првим годинама после рођења и током пубертета. У складу са чињеницом да је боље спречити него лечити, у овом чланку су дате основне смернице везане за превенцију ове врсте анемије код деце и адолесцената.

Кључне речи: анемија због недостатка гвожђа; деца; адолесценти; превенција

DOI: https://doi.org/10.2298/SARH220319103B
UDC: 618.177-089.888.11

REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Adjuvant therapy in assisted fertilization procedures

Jovan Bila, Svetlana Spremović-Rađenović

University Clinical Center of Serbia, Clinic of Obstetrics and Gynecology, Belgrade, Serbia;
University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY

Introduction Despite continuous advances in assisted reproductive technologies (ART), their outcomes are limited. Before introducing adjuvant therapy to improve the *in vitro* fertilization (IVF) outcome, it is important to identify appropriate groups of patients, and avoid equal approach for everyone.

The objective of this paper was to review the available literature on the most commonly used adjuvant therapy aiming to improve the outcome of IVF. The guidelines of the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine were used, and the available literature was analyzed by searching the Medline – PubMed and Cochrane databases using appropriate keywords for each entity.

Discussion A review of the literature found no consistent evidence for the standard use of metformin in patients with polycystic ovarian syndrome, nor for use of dehydroepiandrosterone, testosterone, and growth hormone in patients with premature ovarian failure or those with poor response to stimulation. The standard usage of prednisone and aspirin in the general population of patients in ART is also not recommended. Recently, the significance of the oxidative stress has been emphasized, which is why the use of antioxidants in the form of supplementation (melatonin, vitamins C, A, E, coenzyme Q) might be important in improving reproductive outcomes.

Conclusion The modern approach to the problem of infertility has become strictly individual. The application of adjuvant therapy in order to improve the outcome of ART procedures requires an analytical and critical approach in each individual case.

Keywords: *in vitro* fertilization; outcome; adjuvant therapy; supplementation

INTRODUCTION

Despite continuous advances in assisted reproductive technologies (ART), there are ongoing efforts to improve the outcomes of *in vitro* fertilization (IVF) procedures. The clinical pregnancies occur once in three to four IVF procedures, and one in five cycles ends with live birth [1].

Considering that the factors which affect procedure outcomes are presented long before the procedure actually begins, it is important to identify appropriate groups of patients, especially those who may develop ovarian hyperstimulation syndrome (OHSS) or may have inadequate response to stimulation, those with premature ovarian insufficiency, endometriosis, associated endocrine diseases, verified thrombophilia, etc. [2, 3]. Accordingly, a uniform approach for all patients should be avoided.

The aim of this paper was to review the available literature data on the most commonly used adjuvant therapy aimed at improving the IVF procedures' outcome.

We used European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine guidelines, and analyzed available literature by searching Medline – PubMed and Cochrane database using appropriate keywords for every entity.

METFORMIN

Prescribing metformin, especially in patients with polycystic ovary syndrome (PCOSy) is often based on the presumed existence of insulin resistance. It has not been shown that there is a significant improvement in the live birth rate (LBR) in PCOSy patients who used metformin before or during the IVF procedure, but the incidence of OHSS was lower [4]. Similar conclusions emerge from a recent meta-analysis that showed no association between metformin use in patients with PCOSy and clinical pregnancy rate (PR) and LBR in IVF [5]. However, the PR was significantly higher in those with a BMI greater than 26 kg/m^2, suggesting that insulin resistance might have been the part of total metabolic component, and the metformin usage was useful with consequent favorable outcomes of IVF [5, 6]. So, a complete endocrinological examination with the evaluation of metabolic status and insulin resistance should be recommended before the introduction of metformin as an adjuvant therapy in IVF patients.

Protocols with GnRH antagonists are recommended in patients with PCOSy, as they are safer [7]. However, a recent meta-analysis showed the lower LBR in PCOSy patients with metformin using the GnRH antagonist protocol [4]. ESHRE Guide to Ovarian Stimulation in IVF/ICSI procedures does not recommend the routine use of metformin in patients with PCOSy using GnRH

Received • Примљено: March 19, 2022
Revised • Ревизија: October 4, 2022
Accepted • Прихваћено: October 6, 2022
Online first: October 19, 2022

Correspondence to:
Jovan S. BILA
University of Belgrade
Faculty of Medicine
Clinic of Obstetrics and Gynecology
Dr Koste Todorovića 26
11000 Belgrade, Serbia
bilamsj@gmail.com

antagonist protocols to improve IVF outcomes [7]. The use of metformin as an adjuvant therapy in overweight/obese PCOSy patients undergoing IVF leads to decrease number of retrieved oocytes and does not influence the LBR [8]. The use of metformin as an adjuvant therapy in patients undergoing GnRH agonist protocols did not have a significant effect on the IVF outcomes either [8] (Table 1).

Table 1. Metformin and inositol as adjuvant therapy in *in vitro* fertilization

Therapy		Description
Metformin	Tso et al. [4]	There is no conclusive evidence that metformin treatment before or during ART cycles improved live birth rates in women with PCOSy; lower risk of OHSS
	Wu et al. [5]	Metformin treatment was associated with a decreased risk of OHSS but had no association with the overall clinical pregnancy rate or live birth rate among women with PCOSy undergoing IVF/ICSI-ET
	Abdalmageed et al. [8]	Usage of metformin could decrease the number of retrieved oocytes in overweight and obese PCOSy patient undergoing IVF
Inositol	Merviel et al. [10]	MI, at a dose of 4 g per day (2 g twice per day), three months prior to ovarian stimulation, is effective in normalizing ovarian function, improving oocyte and embryo quality in PCOSy
	Laganà et al. [11]	During IVF, MI is effective in both PCOSy and non-PCOSy women in saving gonadotropins, but reduces efficiently length of controlled ovarian hyperstimulation only in PCOSy women

PCOSy – polycystic ovarian syndrome; ART – assisted reproductive technologies; OHSS – ovarian hyperstimulation syndrome; IVF – *in vitro* fertilization; ICSI-ET – intracytoplasmic sperm injection – embryo transfer; MI – myo-inositol

INOSITOL

Inositols, classified as insulin sensitizers, are also recommended for the treatment of PCOSy [9]. The latest research has shown that myoinositol in a dose of 4 g daily (2 g twice a day), three months before ovarian stimulation is effective in normalizing ovarian function and obtaining quality oocytes and embryos in patients with PCOSy [10]. The meta-analysis confirmed the beneficial effect of inositol, even in relation to the gonadotropin doses [11]. Oral myoinositol supplementation can reduce the amount of gonadotropins used in both women with PCOSy and those without PCOSy, but it reduces the duration of stimulation only in the PCOSy patients [11] (Table 1).

SUBCLINICAL HYPOTHYROIDISM

Thyroid disorders in patients with infertility are primarily autoimmune thyroid disease (prevalence 5–10%) and subclinical hypothyroidism (prevalence 5–7%) [12]. Subclinical hypothyroidism leaves a wide field of doubts regarding the use of therapy in patients preparing for the IVF procedures. The most of data on subclinical hypothyroidism and IVF outcomes suggest that there is no association with lower LBR or higher miscarriage rates compared to patients with TSH < 2.5 mIU/L [13]. Patients with PCOSy have a higher prevalence of elevated TSH and autoimmune thyroiditis. In these patients, TSH levels > 3.5 mIU/L are associated with adverse ART outcomes, and levothyroxine treatment may improve the LBR in patients when TSH levels are > 4 mIU/L [13]. The routine TSH assessment is recommended as a part of infertility evaluation, but screening of anti-TPO antibodies only if TSH levels are > 2.5 mIU/L [13]. Systematic treatment of all euthyroid women with TSH > 2.5 mIU/L and elevated levels of anti-TPO antibodies is not recommended [13]. Treatment decision should be made taking into account infertility factors such as POF, poor ovarian response, older age (> 35 years), history of recurrent miscarriages, or the presence of high levels of other thyroid antibodies [13].

DEHYDROEPIANDROSTERONE (DHEA)

The use of DHEA before the procedure and further during stimulation is mainly reserved for patients who are marked as "poor responders." A literature review does not reveal a sufficient number of large and well-designed RCT that would support either improvement of the ovarian response or the IVF outcomes in these patients. A randomized trial of 140 patients with poor ovarian response who received DHEA at a dose of 75 mg daily for 12 weeks showed a significantly higher number of obtained oocytes, a higher fertilization rate, and a higher PR [14]. On the other hand, in the randomized study of 52 patients also receiving DHEA at a dose of 75 mg daily for 12 weeks there was no improvement in ovarian response or LBR [15]. A larger meta-analysis that included 17 RCTs provided inconsistent conclusions regarding the effectiveness of DHEA therapy before initiating IVF [16] (Table 2).

TESTOSTERONE

Testosterone is mostly reserved for the "poor responders," but there is inconsistent evidence regarding the improvement of ovarian response and overall outcomes. An earlier Cochrane meta-analysis did not prove that the use of testosterone in patients with poor response leads to a higher LBR [16]. A recent meta-analysis of seven RCTs and 573 patients showed a positive effect of transdermal testosterone administration on the LBR, PR, total oocyte, and embryo count [17]. Due to conflicting results, larger RCTs are needed to confirm the true clinical efficacy of testosterone (Table 2).

GROWTH HORMONE (GH)

The use of GH is not exclusively reserved for patients with a poor response to stimulation, it is also used in those with a normal response. Heterogeneity of applied doses,

Table 2. Dehydroepiandrosterone, testosterone and growth hormone as adjuvant therapy in *in vitro* fertilization

Therapy		Description
DHEA	Kotb et al. [14]	DHEA increases the number of oocytes, fertilization rate, fertilized oocytes, and clinical pregnancy rate and ongoing pregnancy rate in women with POR according to the Bologna criteria; DHEA was well tolerated by the patients and was associated with less COH days and gonadotropins doses
	Narkwichean et al. [15]	Pre-treatment DHEA supplementation, although statistical power in this study is low, did not improve the response to controlled ovarian hyperstimulation or oocyte quality or live birth rates during IVF treatment with long protocol in women predicted to have poor OR
	Nagels et al. [16]	In women identified as poor responders undergoing ART, pre-treatment with DHEA or testosterone may be associated with improved live birth rates; the overall quality of the evidence is moderate
T	Nagels et al. [16]	There was no evidence that the use of testosterone in patients with poor response leads to a higher LBR
	Noventa et al. [17]	Transdermal testosterone administration had positive effect on the LBR, PR, total oocyte and embryo count
GH	Zhu et al. [18]	GH treatment may not improve live birth rate in expected poor responders
	Li et al. [19]	GH addition can significantly improve the clinical pregnancy rate and live birth rate; furthermore, the GH addition time and collocation of medications may affect the pregnancy outcome

DHEA – dehydroepiandrosterone; T – testosterone; GH – growth hormone; IVF – *in vitro* fertilization; COH – controlled ovarian hyperstimulation; ART – assisted reproductive technologies; LBR – live birth rate; PR – pregnancy rate

as well as insufficient studies results are the limiting factor for recommending the standard use of GH in IVF [7]. A retrospective study (about 3000 patients) suggests that the use of GH, even in those with a poor response may be without the expected success [18]. However, there are indications that adjuvant GH therapy before and during stimulation improves the LBR in patients with expected poor response to stimulation [19] (Table 2).

PREDNISONE

Immune system plays a central role in providing endometrial receptivity, so it can be responsible for both embryo implantation and recurrent miscarriages [20]. The aim of corticosteroid therapy would be to reduce the aberrant populations of natural killer cells at the endometrium, to normalize cytokine expression, and/or to suppress endometrial inflammation [21]**.** A meta-analysis that included 16 RCTs with 2232 couples showed insufficient evidence that periimplantation glucocorticoid administration in IVF/ICSI cycles affects clinical outcomes [22]. A randomized study of 133 women who were positive for antinuclear antibodies (ANA) with a history of failed IVF implantation showed that combined treatment with prednisone 10 mg/day and aspirin 100 mg/day could improve the IVF outcome [23]. The current stand is that glucocorticoids are not indicated in women with recurrent miscarriages or repeated unsuccessful IVF procedures, unless autoimmune antibodies are evident. Their use in the absence of autoimmunity does not improve the implantation rate and may pose a potential risk to the outcome of a healthy pregnancy [21].

ASPIRIN

The use of aspirin as adjuvant therapy in IVF was also investigated a lot, but suggested doses and the therapy duration are quite different. They vary from 75, 80 to 100 mg per day, and can be applied until the final maturation of the follicles, up to 12 weeks of gestation or even until the advanced period of gestation [7]. A recent meta-analysis involved 13 RCTs and indicated that low doses of aspirin may improve PR in IVF/ICSI, with a recommended dose of 100 mg/day [24]. However, recent ESHRE recommendations point out that there is no clear evidence that adjuvant aspirin administration before or during ovarian stimulation improves the ovarian response in the context of oocytes count, as well as PR and LBR in the general population of patients and the patients with poor response in IVF/ICSI cycles [7].

ANTIOXIDANTS

A possible role of oxidative stress in IVF outcomes has recently been investigated [25]. The ART exposes both oocytes and embryos to high levels of free radicals during cell and embryonic culture [26]. High levels of oxidative stress in the follicular fluid are associated with poor oocyte maturation and embryo quality [26]. Mitochondrial dysfunction that is characterized by high levels of accumulated free radicals is the key cause of oxidative stress and oxidative stress-induced cell aging [27]. Antioxidants such as melatonin, coenzyme Q, vitamins A and E may be crucial for increasing the reproductive capacity by improving mitochondrial function. The recent meta-analysis which included five RCTs showed that oral supplementation of coenzyme Q increases PR in infertile women undergoing ART procedure, without influence on the on LBR or miscarriage rates [28]. The addition of micronutrients may have a significant effect on the redox status of the follicular microenvironment and, consequently, on the favorable outcome of IVF [29].

MELATONIN

Melatonin regulates various physiological processes, including circadian rhythms, apoptosis, and autophagy, and protects cells from oxidative stress [30]. Studies suggest that melatonin concentration in the follicular fluid is associated with oocytes maturation rate and embryo quality in women undergoing IVF [31]. Melatonin treatment with at least 3 mg/day can significantly increase its concentration in serum but also in the follicle fluid [32]. Recent

meta-analysis suggests that melatonin treatment significantly increases PR in ART, with an increase in total number of mature oocytes and quality embryos, but without a significant effect on LBR [33].

VITAMIN D

Vitamin D is important for oocyte development, production of Anti-Mullerian hormone (AMH), ovarian steroidogenesis, endometrial receptivity, etc. [34]. Chu et al. [35] reported that deficiency of vitamin D could be an important treating condition in women undergoing fertility treatment. A meta-analysis of nine cohort studies found that vitamin D deficiency was associated with decreased LBR in IVF/ICSI [34].

LUTEAL PHASE SUPPORT

There is a broad consensus that the use of progesterone (Pg) is recommended for the luteal phase support in IVF [7, 36, 37, 38]. Cochrane meta-analysis showed a higher LBR in patients receiving progesterone compared to those without it, with no differences in the applied doses or administration routes (vaginal, parenteral) [39]. Generally speaking, the recommended dose is 100 mg of micronized Pg 2–3/day, and dydrogesterone for oral administration [7]. The use of estrogen (E2) for the luteal phase support is quite widespread. The ESHRE guideline emphasize that E2 application is not necessary, as it does not improve IVF outcomes (PR, LBR) nor does it reduce the possibility of OHSS [7]. Meta-analysis of van der Linden et al. [39] supports this recommendation. On the other hand, RCT of Gizzo et al. [40] showed the advantage of higher doses of progesterone with mandatory addition of E2 in the short protocols with antagonist, or when E2 ≤ 5 nmol/l and endometrial thickness less than 10 mm. There were no clearly demonstrated benefits of E2 administration when the long protocol with agonists was used, particularly in patients older than 35 years [40]. The addition of human chorionic gonadotropin to support the luteal phase is similar in efficacy to Pg, but should be used with caution, especially when it is used for the final maturation of follicles due to the risk of OHSS [7, 39]. The analysis of a GnRH agonists' single application as an adjuvant to progesterone therapy six days after oocyte aspiration is also interesting, where studies have shown favorable cycle outcomes. However, there is still no evidence good enough for its safe use, considering the possible risk of OHSS [7, 39].

CONCLUSION

The modern approach to the problem of infertility has become strictly individual. In this context, the application of adjuvant therapy aimed at improving the IVF procedure outcomes requires an analytical and critical approach in each individual case. Although generalization is not recommended, a review of the literature shows that the use of inositol in the population of both PCOSy and non-PCOSy patients, and the use of antioxidants in all categories of patients with the problem of infertility can improve the IVF outcome. Additional evaluations of adjuvant DHEA, testosterone or growth hormone therapy in the group of patients with premature ovarian insufficiency and/or poor response to stimulation are needed. Endocrinological and/or immunological therapy should only be used when all diagnostic procedures were conducted with the proper patient evaluation.

NOTE

The authors declare that the article was written according to the ethical standards of the Serbian Archives of Medicine as well as ethical standards of medical facilities for each author involved.

Conflict of interests: None declared.

REFERENCES

1. Sunderam S, Kissin DM, Zhang Y, Jewett A, Boulet SL, Warner L, et al. Assisted Reproductive Technology Surveillance - United States, 2018. MMWR Surveill Summ. 2022;71(4):1–19. [DOI: 10.15585/mmwr.ss7104a1] [PMID: 35176012]
2. Spremović-Radjenović S, Bila J, Gudović A, Vidaković S, Dokić M, Radunović N. [Poor Ovarian Response to Stimulation for In Vitro Fertilization]. Srp Arh Celok Lek. 2015;143(5–6):354–61. In Serbian. [DOI: 10.2298/sarh1506354s] [PMID: 26259413]
3. Bila JS, Vidakovic S, Radjenovic SS, Dokic M, Surlan L, Sparic R. Predictors of IVF/ICSI success following treatment of endometriosis as the cause of primary infertility. Ginekol Pol. 2018;89(5):240–8. [DOI: 10.5603/GP.a2018.0042] [PMID: 30084475]
4. Tso LO, Costello MF, Albuquerque LET, Andriolo RB, Macedo CR. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2020;12(12):CD006105. [DOI: 10.1002/14651858.CD006105.pub4] [PMID: 33347618]
5. Wu Y, Tu M, Huang Y, Liu Y, Zhang D. Association of Metformin with Pregnancy Outcomes in Women with Polycystic Ovarian Syndrome Undergoing In Vitro Fertilization: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020;3(8):e2011995. [DOI: 10.1001/jamanetworkopen.2020.11995] [PMID: 32744629]
6. Trisovic M, Mladenovic O, Bila J, Lalic K, Kisic Tepavcevic D. The Predictive Value of Metabolic Syndrome in evaluation of pregnancy course and outcome. Clin Exp Obstet Gynecol. 2019;46(5):776–8. [DOI: 10.12891/ceog4804.2019]
7. ESHRE Reproductive Endocrinology Guideline Group. Ovarian stimulation for IVF/ICSI. Guideline of the European Society of Human Reproduction and Embryology. ESHRE, 2019.
8. Abdalmageed OS, Farghaly TA, Abdelaleem AA, Abdelmagied AE, Ali MK, Abbas AM. Impact of Metformin on IVF Outcomes in Overweight and Obese Women With Polycystic Ovary Syndrome: A Randomized Double-Blind Controlled Trial. Reprod Sci. 2019;26(10):1336–42. [DOI: 10.1177/1933719118765985] [PMID: 29576001]
9. Morley LC, Tang T, Yasmin E, Norman RJ, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev. 2017;11(11):CD003053. [DOI: 10.1002/14651858.CD003053.pub6] [PMID: 29183107]

10. Merviel P, James P, Bouée S, Le Guillou M, Rince C, Nachtergaele C, et al. Impact of myo-inositol treatment in women with polycystic ovary syndrome in assisted reproductive technologies. Reprod Health. 2021;18(1):13. [DOI: 10.1186/s12978-021-01073-3] [PMID: 33468143]
11. Laganà AS, Vitagliano A, Noventa M, Ambrosini G, D'Anna R. Myo-inositol supplementation reduces the amount of gonadotropins and length of ovarian stimulation in women undergoing IVF: a systematic review and meta-analysis of randomized controlled trials. Arch Gynecol Obstet. 2018;298(4):675–84. [DOI: 10.1007/s00404-018-4861-y] [PMID: 30078122]
12. Valdés S, Maldonado-Araque C, Lago-Sampedro A, Lillo JA, Garcia-Fuentes E, Perez-Valero V, et al. Population-Based National Prevalence of Thyroid Dysfunction in Spain and Associated Factors: Di@bet.es Study. Thyroid. 2017;27(2):156–66. [DOI: 10.1089/thy.2016.0353] [PMID: 27835928]
13. Poppe K, Bisschop P, Fugazzola L, Minziori G, Unuane D, Weghofer A. 2021 European Thyroid Association Guideline on Thyroid Disorders prior to and during Assisted Reproduction. Eur Thyroid J. 2021;9(6):281–95. [DOI: 10.1159/000512790] Erratum in: Eur Thyroid J. 2021;10(3):268. [PMID: 33718252]
14. Kotb MM, Hassan AM, AwadAllah AM. Does dehydroepiandrosterone improve pregnancy rate in women undergoing IVF/ICSI with expected poor ovarian response according to the Bologna criteria? A randomized controlled trial. Eur J Obstet Gynecol Reprod Biol. 2016;200:11–5. [DOI: 10.1016/j.ejogrb.2016.02.009] [PMID: 26963897]
15. Narkwichean A, Maalouf W, Baumgarten M, Polanski L, Raine-Fenning N, Campbell B, et al. Efficacy of Dehydroepiandrosterone (DHEA) to overcome the effect of ovarian ageing (DITTO): A proof of principle double blinded randomized placebo controlled trial. Eur J Obstet Gynecol Reprod Biol. 2017;218:39–48. [DOI: 10.1016/j.ejogrb.2017.09.006] [PMID: 28934714]
16. Nagels HE, Rishworth JR, Siristatidis CS, Kroon B. Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction. Cochrane Database Syst Rev. 2015;(11):CD009749. [DOI: 10.1002/14651858.CD009749.pub2] [PMID: 26608695]
17. Noventa M, Vitagliano A, Andrisani A, Blaganje M, Viganò P, Papaelo E, et al. Testosterone therapy for women with poor ovarian response undergoing IVF: a meta-analysis of randomized controlled trials. J Assist Reprod Genet. 2019;36(4):673–83. [DOI: 10.1007/s10815-018-1383-2] [PMID: 30610664]
18. Zhu J, Wang Y, Chen L, Liu P, Li R, Qiao J. Growth Hormone Supplementation May Not Improve Live Birth Rate in Poor Responders. Front Endocrinol (Lausanne). 2020;11:1. [DOI: 10.3389/fendo.2020.00001] [PMID: 32038495]
19. Li XL, Wang L, Lv F, Huang XM, Wang LP, Pan Y, et al. The influence of different growth hormone addition protocols to poor ovarian responders on clinical outcomes in controlled ovary stimulation cycles: A systematic review and meta-analysis. Medicine (Baltimore). 2017;96(12):e6443. [DOI: 10.1097/MD.0000000000006443] [PMID: 28328856]
20. Fox C, Morin S, Jeong JW, Scott RT Jr, Lessey BA. Local and systemic factors and implantation: what is the evidence? Fertil Steril. 2016;105(4):873–84. [DOI: 10.1016/j.fertnstert.2016.02.018] [PMID: 26945096]
21. Robertson SA, Jin M, Yu D, Moldenhauer LM, Davies MJ, Hull ML, et al. Corticosteroid therapy in assisted reproduction - immune suppression is a faulty premise. Hum Reprod. 2016;31(10):2164–73. [DOI: 10.1093/humrep/dew186] [PMID: 27591233]
22. Boomsma CM, Kamath MS, Keay SD, Macklon NS. Peri-implantation glucocorticoid administration for assisted reproductive technology cycles. Cochrane Database Syst Rev. 2022;6(6):CD005996. [DOI: 10.1002/14651858.CD005996.pub4] [PMID: 35771604]
23. Fan J, Zhong Y, Chen C. Combined treatment of prednisone and aspirin, starting before ovulation induction, may improve reproductive outcomes in ANA-positive patients. Am J Reprod Immunol. 2016;76(5):391–5. [DOI: 10.1111/aji.12559] [PMID: 27618792]
24. Wang L, Huang X, Li X, Lv F, He X, Pan Y, et al. Efficacy evaluation of low-dose aspirin in IVF/ICSI patients evidence from 13 RCTs: A systematic review and meta-analysis. Medicine (Baltimore). 2017;96(37):e7720. [DOI: 10.1097/MD.0000000000007720] [PMID: 28906358]
25. Thaker R, Mishra V, Gor M, Agarwal R, Sheth H, Kapadia P, et al. The role of stimulation protocol, number of oocytes retrieved with respect to follicular fluid oxidative stress and IVF outcome. Hum Fertil (Camb). 2020;23(1):23–31. [DOI: 10.1080/14647273.2018.1551630] [PMID: 30621481]
26. Tamura H, Takasaki A, Miwa I, Taniguchi K, Maekawa R, Asada H, et al. Oxidative stress impairs oocyte quality and melatonin protects oocytes from free radical damage and improves fertilization rate. J Pineal Res. 2008;44(3):280–7. [DOI: 10.1111/j.1600-079X.2007.00524.x] [PMID: 18339123]
27. Zhang Q, Ren J, Wang F, Pan M, Cui L, Li M, et al. Mitochondrial and glucose metabolic dysfunctions in granulosa cells induce impaired oocytes of polycystic ovary syndrome through Sirtuin 3. Free Radic Biol Med. 2022;187:1–16. [DOI: 10.1016/j.freeradbiomed.2022.05.010] [PMID: 35594990]
28. Florou P, Anagnostis P, Theocharis P, Chourdakis M, Goulis DG. Does coenzyme Q10 supplementation improve fertility outcomes in women undergoing assisted reproductive technology procedures? A systematic review and meta-analysis of randomized-controlled trials. J Assist Reprod Genet. 2020;37(10):2377–87. [DOI: 10.1007/s10815-020-01906-3] [PMID: 32767206]
29. Luddi A, Capaldo A, Focarelli R, Gori M, Morgante G, Piomboni P, et al. Antioxidants reduce oxidative stress in follicular fluid of aged women undergoing IVF. Reprod Biol Endocrinol. 2016;14(1):57. [DOI: 10.1186/s12958-016-0184-7] [PMID: 27604261]
30. Mehrzadi S, Pourhanifeh MH, Mirzaei A, Moradian F, Hosseinzadeh A. An updated review of mechanistic potentials of melatonin against cancer: pivotal roles in angiogenesis, apoptosis, autophagy, endoplasmic reticulum stress and oxidative stress. Cancer Cell Int. 2021;21(1):188. [DOI: 10.1186/s12935-021-01892-1] [PMID: 33789681]
31. Zheng M, Tong J, Li WP, Chen ZJ, Zhang C. Melatonin concentration in follicular fluid is correlated with antral follicle count (AFC) and in vitro fertilization (IVF) outcomes in women undergoing assisted reproductive technology (ART) procedures. Gynecol Endocrinol. 2018;34(5):446–50. [DOI: 10.1080/09513590.2017.1409713] [PMID: 29185361]
32. Fernando S, Wallace EM, Vollenhoven B, Lolatgis N, Hope N, Wong M, et al. Melatonin in Assisted Reproductive Technology: A Pilot Double-Blind Randomized Placebo-Controlled Clinical Trial. Front Endocrinol (Lausanne). 2018;9:545. [DOI: 10.3389/fendo.2018.00545] [PMID: 30283403]
33. Hu KL, Ye X, Wang S, Zhang D. Melatonin Application in Assisted Reproductive Technology: A Systematic Review and Meta-Analysis of Randomized Trials. Front Endocrinol (Lausanne). 2020;11:160. [DOI: 10.3389/fendo.2020.00160] Erratum in: Front Endocrinol (Lausanne). 2020;11:333. [PMID: 32292388]
34. Zhao J, Huang X, Xu B, Yan Y, Zhang Q, Li Y. Whether vitamin D was associated with clinical outcome after IVF/ICSI: a systematic review and meta-analysis. Reprod Biol Endocrinol. 2018;16(1):13. [DOI: 10.1186/s12958-018-0324-3] [PMID: 29426322]
35. Chu J, Gallos I, Tobias A, Robinson L, Kirkman-Brown J, Dhillon-Smith R, et al. Vitamin D and assisted reproductive treatment outcome: a prospective cohort study. Reprod Health. 2019;16(1):106. [DOI: 10.1186/s12978-019-0769-7] [PMID: 31307482]
36. Practice Committees of the American Society for Reproductive Medicine and the Society for Reproductive Endocrinology and Infertility. Diagnosis and treatment of luteal phase deficiency: a committee opinion. Fertil Steril. 2021;115(6):1416–23. [DOI: 10.1016/j.fertnstert.2021.02.010] [PMID: 33827766]
37. Tulic L, Tulic I, Bila J, Nikolic L, Dotlic J, Lazarevic-Suntov M, et al. Correlation of progesterone levels on the day of oocyte retrieval with basal hormonal status and the outcome of ART. Sci Rep. 2020;10(1):22291. [DOI: 10.1038/s41598-020-79347-2] [PMID: 33339878]
38. Spremović-Radjenović S, Bila J, Vidaković S, Radunović N. [Diagnosis and treatment of endometriosis – Recommendations for clinical practice]. Srp Arh Celok Lek. 2017;145(1–2):89–94. In Serbian. [DOI: 10.2298/SARH160404019S]
39. van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev. 2015;2015(7):CD009154. [DOI: 10.1002/14651858.CD009154.pub3] [PMID: 26148507]
40. Gizzo S, Andrisani A, Esposito F, Noventa M, Di Gangi S, Angioni S, et al. Which luteal phase support is better for each IVF stimulation protocol to achieve the highest pregnancy rate? A superiority randomized clinical trial. Gynecol Endocrinol. 2014;30(12):902–8. [DOI: 10.3109/09513590.2014.964638] [PMID: 25268567]

Адјувантна терапија у поступцима асистиране фертилизације

Јован Била, Светлана Спремовић-Рађеновић

Универзитетски клинички центар Србије, Клиника за гинекологију и акушерство, Београд, Србија;
Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Увод Без обзира на континуирани, вишедеценијски напредак у асистираним репродуктивним технологијама, ограничени су домети у погледу побољшања успешности њихових исхода. Пре укључивања адјувантне терапије са циљем унапређења исхода вантелесне оплодње важно је идентификовати одговарајуће групе пацијенткиња и избегавати једнак приступ за све.

Циљ овог рада је преглед доступне литературе о најчешће коришћеној адјувантној терапији у циљу побољшања исхода поступака вантелесне оплодње. У ту сврху коришћене су смернице Европског удружења за хуману репродукцију и ембриологију и Америчког удружења за репродуктивну медицину, а такође је анализирана доступна литература претраживањем база података *Medline – PubMed* и *Cochrane* уз коришћење одговарајућих кључних речи за сваки ентитет.

Дискусија Прегледом литературе нису нађени конзистентни докази за стандардну примену метформина код пацијенткиња са синдромом полицистичних јајника, као ни дехидроепиандростерона, тестостерона и хормона раста код пацијенткиња са превременом оваријалном инсуфицијенцијом или оних код којих се очекује лош одговор на стимулацију. Стандардна примена преднизона и аспирина у општој популацији пацијенткиња уведених у поступке вантелесне оплодње такође се не препоручује. У последње време истиче се значај оксидативног стреса у поступцима асистираних репродуктивних технологија, због чега примена антиоксиданата у виду суплементације (мелатонин, витамини *C*, *A*, *E*, коензим *Q*) може имати значаја у побољшању репродуктивних исхода.

Закључак Савремени приступ проблему инфертилитета је постао строго индивидуалан. У том контексту и примена адјувантне терапије са циљем побољшања исхода процедура асистираних репродуктивних технологија захтева аналитички и критички приступ у сваком индивидуалном случају.

Кључне речи: вантелесна оплодња; *IVF/ICSI*; исход; адјувантна терапија; суплементација

DOI: https://doi.org/10.2298/SARH220131085N
UDC: 615.849

CURRENT TOPIC / АКТУЕЛНА ТЕМА

Current aspects of radiobiology in modern radiotherapy – our clinical experience

Marina Nikitović[1,2], Tatjana P. Stanojković[3]

[1]Institute for Oncology and Radiology of Serbia, Department of Radiation Oncology, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]Institute for Oncology and Radiology of Serbia, Department of Experimental Oncology, Belgrade, Serbia

SUMMARY
Personalized radiation treatment is an important goal in radiation oncology. As a result, one of the main challenges in radiobiology today is predicting a patient's tissue radiosensitivity so that a personalized treatment can be tailored to that individual. For the first time since 2016, a group from the Institute of Oncology and Radiology of Serbia has begun performing translational research in the field of radiobiology. The aim of these studies is to identify molecular markers important for the prediction of radiosensitivity as well as the occurrence of toxic effects of radiotherapy.
In the past five years, significant international cooperation has been established with the Radiogenomic Consortium, as well as leading European and world experts in this field. In addition, during this period, several significant and promising results in this field were published, and a Laboratory for Radiobiology was established at the Institute of Oncology and Radiology of Serbia.
Keywords: radiosensitivity; radiotoxicity; Radiogenomics Consortium

INTRODUCTION

Radiotherapy (RT) is one of the most effective and important non-surgical modalities for the curative treatment of cancer. Unfortunately, RT is not specific only to cancer cells, and radiation-induced cytotoxic effects also occur in normal tissues. In fact, although RT is a local treatment, radiation toxicity can occur both in the RT field area as well as in the surrounding tissues and lead to acute and late complications. It is estimated that a total of 5–10% of patients will eventually develop severe long-term complications that negatively affect quality of life [1].

With improved cure rates, the quality-of-life issue has become increasingly significant, so strategies aimed at reducing toxicity are very important, and to that end, a new field of medicine, called radiobiology, was developed. Radiobiology is a branch of medical science that studies the relationship between the prescribed radiation dose and the consequent radiobiological effects on human cells [2]. Improvements in RT technologies have focused on enhancing precision and accuracy over the years, and as a result, advanced RT techniques such as intensity modulated RT and volumetric modulated arc therapy have been developed [3].

Despite these advances, normal tissue damage remains a limiting factor for RT efficacy, and RT is likely to become much more personalized in the future based on radiobiological factors. The results of researchers in radiobiology, such as the discovery of stem cells and the definition of radiation-activated signaling pathways, represent a fundamental discovery responsible for the further development of radiobiology as well as RT [4, 5].

The functional consequences of ionizing radiation on cells in the broadest sense include cell death, cell repair, effects on the cell cycle, altered gene expression, modification of signal transduction, mutagenesis, and genomic instability [6] (Figure 1).

Nowadays, there is a growing interest in identifying genetic variants associated with an increased risk of radiotoxicity. The reason for this is that it is considered that up to 80% of individual differences in the toxicity of normal tissue caused by RT are conditioned by numerous genetic and epigenetic factors. Many studies of gene expression profiles in peripheral blood lymphocytes of RT-treated patients have indicated an association between certain differentially expressed genes and acute and late radiotoxicity [7]. Therefore, determining the expression profile of a large number of genes by the method of miRNA markers' expression analysis or sequencing of new generation RNA is one of the most important research approaches in modern radiobiology, which allows the discovery of new potential biomarkers of RT effects [7, 8, 9].

Methodological approaches used in cellular radiosensitivity testing include assays to determine cell proliferation and survival, cytogenetic assays, methods to detect DNA damage, and apoptotic assays. Various *in vitro* assays for determining the radiosensitivity of patients' cells, such as lymphocytes or fibroblasts, are used to predict the possible occurrence of toxic effects

Received • Примљено: January 31, 2022
Revised • Ревизија: August 1, 2022
Accepted • Прихваћено: August 4, 2022
Online first: August 26, 2022

Correspondence to:
Marina NIKITOVIĆ
University of Belgrade
Faculty of Medicine
Institute for Oncology and Radiology of Serbia
Pasterova 14
11000 Belgrade
Serbia
marina.nikitovic@ncrc.ac.rs

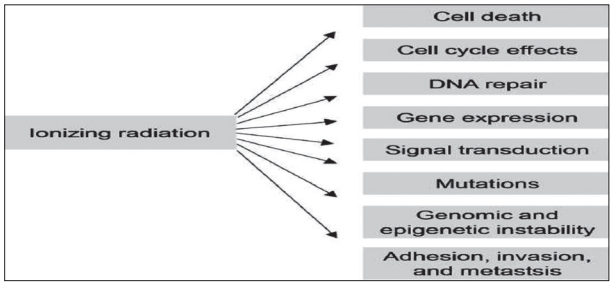


Figure 1. The effect of ionizing radiation on cells [5]

on normal tissue caused by RT. Numerous studies indicate that the level of apoptosis induced by *in vitro* radiation in the peripheral blood lymphocytes of patients before RT is associated with the occurrence of normal tissue radiotoxicity. The existence of a negative correlation between the levels of radiation-induced T lymphocyte apoptosis and the occurrence of toxicity after RT has been shown. Radiation-induced apoptosis of CD4+ T lymphocytes and CD8+ T lymphocytes could be used to identify radiosensitive patients before starting RT [1].

All of these studies should contribute to the identification of a group of patients at an increased risk for developing radiotoxicity. Based on that, an optimal therapeutic approach would be planned for each patient that would enable long-term preservation of the quality of life.

The manuscript was written in accordance with the ethical standards of the institution and the journal.

INITIATION OF RESEARCH AND ESTABLISHMENT OF THE LABORATORY FOR RADIOBIOLOGY

Modern RT uses various strategies and modalities to achieve the most effective clinical effect, and the introduction of individualized RT in clinical practice is imperative. Translational research in RT aims to identify and validate key predictive biomarkers for sensitivity to RT, as well as biomarkers for risk assessment for acute and late toxicity.

Figure 2. Prof. Marina Nikitović and Dr. Tatjana Stanojković at the Radiogenomic Consortium's 2017 annual meeting in Barcelona, Spain

In this way, it will be possible to identify patients prone to radiosensitive reactions before starting RT. This research can help radiation oncologists in the future and is the basis for designing the optimal treatment for the maximum benefit for each patient.

Following the novelty in research, the Institute for Oncology and Radiology of Serbia (IORS) is making constant efforts to strengthen the cooperation between clinicians and researchers, all with the aim of focusing on excellence and the application of research results in practice. In this sense, in 2015, Professor Marina Nikitović, radiation oncologist, and Tatjana Stanojković, Full Research Professor, molecular biologist, launched an initiative to form a team for radiobiology at IORS. Starting from previous studies of acute and late genitourinary toxicity, published in the doctoral thesis of Dr. Vesna Stanković, radiation oncologist, mentored by Professor Marina Nikitović, as well as published papers [10, 11], began the research within the study: "Predictive Significance of Inflammatory Mediators for Early Toxicity and Response to Radiotherapy in Patients with Prostate Cancer" This is the first time in Serbia that new translational research in the field of radiobiology and molecular radiation oncology has been launched at IORS. This investigation was a starting point for the further upgrade of the capacity in radiobiology in Serbia that has been under development for the past five years at IORS. Strengthening these topics, which are in the focus of the most influential European and world centers for cancer research and RT, will make a significant contribution to the advancement of cancer research at a national and international level.

Since 2016, the IORS team for radiobiology consists of researchers and radiation oncologists at the Department of Experimental Oncology, Laboratory for Biological Response Modifiers, as well as the Department of Radiotherapy of Solid Tumors. The team has experience in RT, radiobiology, and molecular RT; the application of enzyme-linked immunosorbent assay for determination of biomarkers; extraction of DNA and RNA from different starting materials; investigating microRNA in cancer; detection of polymorphic variants of various genes (single nucleotide polymorphisms); analysis of specific subpopulations of immune cells in patients by flow cytometry; data processing. Also, transcriptome profiling and radiosensitivity studies for radiotoxicity prediction in patients with prostate cancer have been initiated, as well as epigenetic studies in patients with glioblastoma. As a result of these activities, a Laboratory for Radiobiology was established at IORS.

INTERNATIONAL COOPERATION

From the start, Dr. Tatjana Stanojković and Professor Marina Nikitović, as team leaders, have developed a successful collaboration between the Serbian group and the Radiogenomics Consortium (Figure 2).

Figure 3. Workshop in Mannheim, Germany, within the joint German Research Foundation project (Institute for Oncology and Radiology of Serbia team associates Irina Besu Žižak, Marija Đorđić Crnogorac, Ivana Matić and Željko Žižak), 2017

Figure 4. Team from Serbia, Prof. Marina Nikitović, Dr. Tatjana Stanojković and Dr. Vesna Stanković, in the company of Prof. David Azria and French colleagues from the Radiogenomic Consortium, at the ESTRO meeting 2016 Montpellier France

Figure 5. Prof. Catharine West at the University of Belgrade, Faculty of Medicine, with the Institute for Oncology and Radiology of Serbia team for radiobiology (Prof. Marina Nikitović, Dr. Tatjana Stanojković, Dr. Ivana Matić, Dr. Marija Popović-Vuković, Dr. Dragana Stanić, and Dr. Nina Petrović), and colleagues from the Vinča Institute (Aleksandra Stanković and Ivan Jovanović), 2019

With this cooperation and the started translation research, the IORS is in the company of leading institutes in Europe and the United States in the field of RT and radiation biology (National Institutes of Health, National Cancer Institute, USA, University of Manchester, UK, University of Cambridge, UK, University of Rochester, USA, German Cancer Research Center (DKFZ), Germany). The team for radiobiology has a particularly successful cooperation with the Clinic for Radiation Oncology of the Medical Faculty of Mannheim, the University of Heidelberg, Germany, and the group of Prof. Karsten Herskind. From this cooperation, we especially emphasize the period 2017–2018, when they implemented the project titled "Individual Clinical Radiosensitivity-Toward Predicting and Modulation" under the auspices of the German Research Foundation (project manager on the German side was Prof. Carsten Herskind and on the Serbian side, Dr. Tatjana Stanojković) (Figure 3).

Within the Radiogenomics Consortium, cooperation was established with a research group from the Institute for Cancer Research in Montpellier (l'Institut de Recherche en Cancérologie de Montpellier (IRCM-U1194)) led by Prof. David Azria (Figure 4).

In addition, with Prof. Catharine West, Professor of Radiation Biology, at the University of Manchester, UK, who is also the leader of the European project REQUITE and the founder of the Radiogenomics Consortium, significant cooperation has been established. In 2019, Prof. West gave a notable lecture at the University of Belgrade, Faculty of Medicine, on the topic: "Validating Predictive Models and Biomarkers of Radiotherapy Toxicity to Reduce Side-Effects and Improve Quality of Life in Cancer Survivors – REQUITE project" (Figure 5).

Also, during 2019, within the research in this field, cooperation was initiated with the National Medical Research Center for Radiology of the Ministry of Health of the Russian Federation, Moscow, Russia. The research of the team for Radiobiology of the Institute of Oncology and Radiology of Serbia has also been recognized in Serbia. In 2017, a team of researchers received a grant for research within the "Start for Science" program of the Center for the Promotion of Science.

CONCLUSION

Scientific contribution of the team for radiobiology

Previously, four doctoral dissertations of young radiation oncologists (Dr. Katarina Kopčalić, Dr. Aleksandar Stepanović, Dr. Marija Popović-Vuković, and Dr. Jelena Stanić) were prepared as part of the initiated research, several papers were published in international journals, and several presentations were published at international and national conferences. Currently, a team of researchers has submitted a project proposal within the program

[HORIZON-WIDERA-2021-ACCESS-02-01] – [Twinning Western Balkans special]. The results of the competition are expected in 2022. Further application and participation in national and international scientific projects (Diaspora, Idea, People, Bilateral cooperation, COST actions, EU programs…) is planned (Table 1).

Table 1. Published results in the field of research for 2019–2021

Journal title	Institute for Oncology and Radiology of Serbia publications	Impact factor
Pathology Research and Practice 2019;215(4): 626–31.	Kopcalić K, Petrović N, Stanojković TP, Stanković V, Bukumirić Z, Roganović J, Malisić E, Nikitović M. Association between miR-21/146a/155 level changes and acute genitourinary radiotoxicity in prostate cancer patients: A pilot study.	1.794
Scientific Reports 2020;10(1):19002 Joint publication with University Healthcare Estates & Innovation	Stanojković TP, Matić IZ, Petrović N, Stanković V, Kopčalić K, Besu I, Đorđić Crnogorac M, Mališić E, Mirjačić-Martinović K, Vuletić A, Bukumirić Z, Žižak Ž, Veldwijk M, Herskind C, Nikitović M. Evaluation of cytokine expression and circulating immune cell subsets as potential parameters of acute radiation toxicity in prostate cancer patients.	4.379
Current Medicinal Chemistry, 2021 Aug 3	Petrović N, Stanojković TP, Nikitović M. MicroRNA in Prostate Cancer Radiobiology and Radiotherapy: Towards Prediction of Response to Radiation Treatment.	4.530

Notable published abstracts at international conferences concerning RT and radiosensitivity:

1. Janović Barbara S, Žižak Željko, Vujčić Miroslava T, Vujčić Zoran M, Stanković Vesna, Nikitović Marina, Stanojković Tatjana P. Comet assay as a tool for evaluation of DNA damage in prostate cancer patients after conventionally fractionated 3D conformal radiotherapy 46th EEMGS & 30th GUM Meeting March 18th-21st 2018, Potsdam, Germany.
2. Zizak Z, Janovic B, Besu Zizak I, Vujcic M, Vujcic Z, Stankovic V, Matic I, Nikitovic M, Stanojkovic T. In vitro radiosensitivity and repair kinetics of pbmcs from prostate cancer patients and healthy donors evaluated by comet assay. ESMO Open 2018;3(Suppl 2):A276/PO-129. 25th Biennial Congress of the European Association for Cancer Research, Amsterdam, The Netherlands, 30 June - 3 July 2018. doi: https://doi.org/10.1136/esmoopen-2018-EACR25.653
3. Mališić E, Petrović N, Nikitović M, Stanojković T. Association between TGFB1 C-509T polymorphism and acute toxicity after radiotherapy for prostate cancer. 5th Congress of the "Serbian Association for Cancer Research - SDIR" with international participation „Translational potential of cancer research in Serbia", December 3, 2021 Abstract book p.60. P33.
4. Mališić E, Petrović N, Nikitović M. Impact of TGFB1 Leu10Pro polymorphism on acute radiotherapy-induced toxicity in prostate cancer patients. 5th Congress of the "Serbian Association for Cancer Research - SDIR" with international participation "Translational potential of cancer research in Serbia", December 3, 2021 Abstract book p. 61. P34.
5. Mališić E, Petrović N, Nikitović M. XRCC3 Thr241Met gene polymorphism and acute radiotherapy induced toxicity for prostate cancer. ESTRO 2022. 06-10 May 2022, Copenhagen, Denmark.

Conflict of interests: None declared.

REFERENCES

1. Azria D, Lapierre A, Gourgou S, De Ruysscher D, Colinge J, Lambin P, et al. Data-Based Radiation Oncology: Design of Clinical Trials in the Toxicity Biomarkers Era. Front Oncol. 2017;7:83. [DOI: 10.3389/fonc.2017.00083] [PMID: 28497027]
2. Joiner MC, van der Kogel AJ, editors. Basic clinical radiobiology. CRC press; 2018 Aug 28.
3. Lapierre A, Bourillon L, Larroque M, Gouveia T, Bourgier C, Ozsahin M, et al. Improving Patients' Life Quality after Radiotherapy Treatment by Predicting Late Toxicities. Cancers (Basel). 2022;14(9):2097. [DOI: 10.3390/cancers14092097] [PMID: 35565227]
4. Kirsch DG, Diehn M, Kesarwala AH, Maity A, Morgan MA, Schwarz JK, et al. The Future of Radiobiology. J Natl Cancer Inst. 2018;110(4):329–40. [DOI: 10.1093/jnci/djx231] [PMID: 29126306]
5. Fukunaga H, Butterworth KT, McMahon SJ, Prise KM. A Brief Overview of the Preclinical and Clinical Radiobiology of Microbeam Radiotherapy. Clin Oncol (R Coll Radiol). 2021;33(11):705–12. [DOI: 10.1016/j.clon.2021.08.011] [PMID: 34454806]
6. Halperin EC, Wazer DE, Perez CA, Brady LW, Perez & Brady's Principles and Practice of Radiation Oncology. 7th ed. Philadelphia (PA), USA: LWW/Wolters Kluwer; 2018. p. 47.
7. Benitez CM, Knox SJ. Harnessing genome-wide association studies to minimize adverse radiation-induced side effects. Radiat Oncol J. 2020;38(4):226–35. [DOI: 10.3857/roj.2020.00556] [PMID: 33233031]
8. Moreno-Villanueva M, Zhang Y, Feiveson A, Mistretta B, Pan Y, Chatterjee S, et al. Single-Cell RNA-Sequencing Identifies Activation of TP53 and STAT1 Pathways in Human T Lymphocyte Subpopulations in Response to Ex Vivo Radiation Exposure. Int J Mol Sci. 2019;20(9):2316. [DOI: 10.3390/ijms20092316] [PMID: 31083348]
9. Stepanović A, Nikitović M, Stanojković TP, Grujičić D, Bukumirić Z, Srbljak I, et al. Association between microRNAs 10b/21/34a and acute toxicity in glioblastoma patients treated with radiotherapy and temozolomide. Sci Rep. 2022;12(1):7505. [DOI: 10.1038/s41598-022-11445-9] [PMID: 35525840]
10. Stankovic V, Džamic Z, Pekmezovic T, Tepavcevic DK, Dozic M, Saric M, et al. Acute and Late Genitourinary Toxicity after 72 Gy of Conventionally Fractionated Conformal Radiotherapy for Localised Prostate Cancer: Impact of Individual and Clinical Parameters. Clin Oncol (R Coll Radiol). 2016;28(9):577–86. [DOI: 10.1016/j.clon.2016.04.041] [PMID: 27184943]
11. Stankovic V, Nikitovic M, Pekmezovic T, Kisic Tepavcevic D, Saranovic Dj, Djuric-Stefanovic A, Saric M. Toxicity of the lower gastrointestinal tract and its predictive factors after 72Gy conventionaly fractionated 3D conformal radiotherapy of localised prostate cancer. J BUON. 2016;21(5):1224–32. [PMID: 27837627]

Актуелни аспекти радиобиологије у савременој радиотерапији – наше клиничко искуство

Марина Никитовић[1,2], Татјана П. Станојковић[3]

[1]Институт за онкологију и радиологију Србије, Одељење за радијациону онкологију, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Институт за онкологију и радиологију Србије, Одељење за експерименталну онкологију, Београд, Србија

САЖЕТАК

Персонализована радиотерапија је важан циљ у радијационој онкологији. Стога је један од главних изазова у радиобиологији данас предвиђање радиосензитивности нормалног ткива болесника како би се радиотерапијски третман прилагодио сваком болеснику понаособ. Група са Института за онкологију и радиологију Србије први пут је од 2016. године почела да развија транслациона истраживања из области радиобиологије.

Циљ ових студија је идентификовање молекуларних маркера важних за предвиђање радиосензитивности, као и појаву нежељених токсичних ефеката радиотерапије.

У протеклих пет година основана је значајна међународна сарадња са Конзорцијумом за радиогеномику, као и водећим европским и светским стручњацима из области радиогеномике. Такође, у овом периоду објављено је неколико значајних и обећавајућих резултата и основана је Лабораторија за радиобиологију на Институту за онкологију и радиологију Србије.

Кључне речи: радиосензитивност; радиотоксичност; Конзорцијум за радиогеномику

IN MEMORIAM

Зоран В. Кривокапић (1955–2022)

У Београду је 9. септембра 2022. године у 68. години преминуо академик Зоран В. Кривокапић, наш најистакнутији стручњак за колоректалну хирургију и проктологију, творац наше савремене колопроктолошке школе.

Зоран Кривокапић је рођен 27. августа 1955. године у Косовској Митровици, у којој је завршио основну и средњу школу као вуковац. На Медицинском факултету Универзитета у Београду дипломирао је 1980. године, а следеће је примљен на Другу хируршку клинику Медицинског факултета, на којој је и започела његова хируршка каријера. Након четири године, 1985. он је магистрирао, а већ наредне је положио и специјалистички испит из Опште хирургије.

Своја истраживања у оквиру магистарског рада и докторске дисертације саопштио је у својој првој монографији („Мере превенције попуштања анастомозе на дебелом цреву"), објављеној 1990. године.

По преласку на Прву хируршку клинику 1993. године, бива постављен за начелника 3. одељења, које је већ било усмерено ка колоректалној хирургији и проктологији.

Своју академску каријеру Зоран је започео 1989. године, када је изабран за асистента на Катедри хирургије Медицинског факултета; исте године је одбранио и докторску дисертацију. За редовног професора је изабран 2007. године.

У свом академском напредовању Зоран се непрестано, скоро континуирано стручно усавршавао у најпознатијим светским хируршким центрима (Лондон, Њујорк, Токио, Холандија, Шведска и др.). Одлазак у Болницу Светог Марка (*St. Mark's Hospital*) у Лондону 1988. године, у којој је неколико месеци био и хонорарни асистент, представља прекретницу и полазиште његове међународне каријере. Међутим, кључну улогу у њој је имао Бил Хилд (Ричард Џон Хилд) из Безинстока крај Лондона, творац радикалне промене хируршког приступа карциному

ректума увођењем оригиналне методе мезоректалне ампутације ректума. Зоран је врло брзо постао његов блиски сарадник и пријатељ. Он је његову операцију, данас општеприхваћену као „златни стандард", популарисао и увео у праксу и код нас.

Међународна репутација и углед Зорана Кривокапића јасно се огледају у почасном чланству у хируршким удружењима значајног броја европских земаља, као знак препознавања његових вредности (Италија, Румунија, Мађарска, Бугарска, Русија, Израел). За члана престижног енглеског Краљевског колеџа хирурга (*FRCS*) изабран је 1998. године. Такође, био је члан Америчког друштва колоректалних хирурга (*FASCRS*), а 2019. године је био изабран за почасног члана Европског удружења колопроктолога; био је и почасни члан Румунске академије медицинских наука, као и почасни доктор наука Универзитета у Јашију и Крајови у Румунији.

Зоран Кривокапић је учествовао у шест међународних хируршких радионица (*live surgery*) у Турској, Енглеској, Израелу, Естонији, Румунији, Египту.

Received • Примљено: December 13, 2022
Accepted • Прихваћено: December 15, 2022
Online first: December 16, 2022

Correspondence to:
Dragoslav M. STEVOVIĆ
University of Belgrade
Faculty of Medicine
Department of Surgery
Belgrade, Serbia
(retired)
dragor936@gmail.com

Богата и плодна стручна и научна каријера Зорана Кривокапића била је крунисана његовим избором за редовног члана САНУ 2018. године.

Он је био руководилац и главни истраживач у нашој земљи у неколико међународних пројеката (*Quasar*, Велика Британија; *Prosper*, Норвешка; *Meccland*, Грчка; *Mutographs of Cancer*, Француска), као и пројекта у оквиру Академије („Молекуларна основа одговора на хемиорадиотерапију у карциному ректума“). Зоран је био један од главних твораца националног програма за рано откривање рака дебелог црева и водича добре клиничке праксе за лечење те болести.

Као међународно признат и цењен стручњак, Зоран је био предавач у Енглеској школи за радиотерапију и лечење карцинома ректума (*Estro*) у Лондону, а као гостујући предавач на Универзитету Јужне Каролине и *Keck School of Medicine* Универзитета Јужне Калифорније. Такође, био је чест предавач на медицинским факултетима бивших нам република (Скопље, Подгорица, Бањалука, Фоча).

Зоран је био члан уређивачких одбора 14 часописа (осам иностраних). У његовој библиографији записано је 580 радова, пет ауторских монографија и 49 поглавља у другим публикацијама (монографије, књиге, уџбеници) у осам међународних издања.

У нашем СЛД-у Зоран Кривокапић је био председник Хируршке секције (2003–2008), чији је рад значајно унапредио довођењем страних предавача и организовањем заједничких састанака са хирурзима суседних земаља. За нас је од посебног значаја било развијање тесне сарадње са хирурзима из Републике Српске, у којој је он био чест и радо виђен гост и предавач.

Зоран Кривокапић је 1997. године био покретач и оснивач Друштва колопроктолога Југославије, мултидисциплинарног удружења, које је квалитетом своје активности убрзо стекло међународни углед. Током 22 године рада Друштво је организовало 10 бијеналних међународних симпозијума, са преко 350 иностраних предавача из преко 50 земаља.

У сарадњи са тимом својих сарадника, Зоран је извео преко 7000 операција колоректалног карцинома, као и преко 200 репарација и реконструкција повређених аналних сфинктера; то је једна од највећих личних серија у Европи.

За свој стручни, научни и друштвени вредан рад Зоран је добио бројне награде, међу којима се издвајају награде СЛД-а за научноистраживачки рад (2006. г.) и за животно дело (2017. г.), Светогорски орден председника Републике и награда за научни допринос и животно дело Медицинског факултета Универзитета у Београду (2021. г.).

У животу Зорана Кривокапића постојале су две велике „љубави“: пре свега хирургија, а затим кошарка, коју је играо од ране младости све до својих зрелих година. Спорт је у њему васпитао и развио упорност, победнички дух и жељу да се увек буде први и на врху, али усадио и сазнање да се до врхова долази само и једино дуготрајним и мукотрпним радом. Кошарка му је била много више од рекреације; била је растерећење од стреса који хирургија неизбежно носи са собом.

Изузетан ученик и следбеник Била Хилда, који је већ постао легенда савремене колоректалне хирургије, Зоран је, захваљујући свом неспорном таленту, самопоуздању и непресушној енергији, своју мануелну вештину довео до савршенства, строго поштујући путеве сложене и деликатне топографије колона и ректума. Тиме је себе уздигао до самих врхова ове хирургије, не само код нас. У свој „стваралачки опус“ он је уградио преко 50 дијагнозних и оперативних поступака, које је успешно преносио и на своје сараднике и ширио оперишући у преко педесет градова у Србији и околним некадашњим републикама заједничке нам домовине.

Овако богату професионалну каријеру могла је успешно да изнесе само личност изузетних особина, а Зоран Кривокапић је то био. Његова упорност и амбиција да се увек буде међу најбољима, што је он и постигао, била је заснована и подржана самопрегорним и непрекидним радом на личном усавршавању и напредовању. Његовим сарадницима је било напорно да га прате, али су они заузврат имали изванредног учитеља и пре свега искреног пријатеља, који је увек био ту да помогне, подржи, заштити, ако треба и укори, али и богато награди.

Зоран Кривокапић је заорао дубок траг, који ће трајно остати у колективном памћењу генерација које долазе. Нама ће то бити залог и утеха за бол услед његовог превременог одласка.

Проф. др Драгослав М. Стевовић
редовни професор на Катедри хирургије
Медицинског факултета
Универзитета у Београду,
у пензији

Пре подношења рукописа Уредништву часописа „Српски архив за целокупно лекарство“ (СА) сви аутори треба да прочитају Упутство за ауторе (*Instructions for Authors*), где ће пронаћи све потребне информације о писању и припреми рада у складу са стандардима часописа. Веома је важно да аутори припреме рад према датим пропозицијама, јер уколико рукопис не буде усклађен с овим захтевима, Уредништво ће одложити или одбити његово публиковање. Радови објављени у СА се не хонорарашу. За чланке који ће се објавити у СА, самом понудом рада Српском архиву сви аутори рада преносе своја ауторска права на издавача часописа – Српско лекарско друштво.

ОПШТА УПУТСТВА. СА објављује радове који до сада нису нигде објављени, у целости или делом, нити прихваћени за објављивање. СА објављује радове на енглеском и српском језику. Због боље доступности и веће цитираности препоручује се ауторима да радове свих облика предају на енглеском језику. У СА се објављују следеће категорије радова: уводници, оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови, актуелне теме, радови за праксу, радови из историје медицине и језика медицине, медицинске етике, регулаторних стандарда у медицини, извештаји са конгреса и научних скупова, лични ставови**,** наручени коментари, писма уреднику, прикази књига, стручне вести, *In memoriam* и други прилози. Оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови и актуелне теме, публикују се искључиво на енглеском језику, а остале врсте радова се могу публиковати и на српском језику само по одлуци Уредништва. Радови се увек достављају са сажетком на енглеском и српском језику (у склопу самог рукописа). Текст рада куцати у програму за обраду текста *Word*, фонтом *Times New Roman* и величином слова 12 тачака (12 *pt*). Све четири маргине подесити на 25 *mm*, величину странице на формат А4, а текст куцати с двоструким проредом, левим поравнањем и увлачењем сваког пасуса за 10 *mm*, без дељења речи (хифенације). Не користити табулаторе и узастопне празне карактере (спејсове) ради поравнања текста, већ алатке за контролу поравнања на лењиру и *Toolbars*. За прелазак на нову страну документа не користити низ „ентера“, већ искључиво опцију *Page Break*. После сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*. Подаци о коришћеној литератури у тексту означавају се арапским бројевима у угластим заградама – нпр. [1, 2], и то редоследом којим се појављују у тексту. Странице нумерисати редом у доњем десном углу, почев од насловне стране.

При писању текста на енглеском језику треба се придржавати језичког стандарда *American English* и користити кратке и јасне реченице. За називе лекова користити искључиво генеричка имена. Уређаји (апарати) се означавају фабричким називима, а име и место произвођача треба навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или супскрипту (нпр. ^{99}Tc, *IL*-6, O_2, $Б_{12}$, *CD*8). Уколико се нешто уобичајено пише курзивом (*italic*), тако се и наводи, нпр. гени (*BRCA1*).

Уколико је рад део магистарске тезе, односно докторске дисертације, или је урађен у оквиру научног пројекта, то треба посебно назначити у Напомени на крају текста. Такође, уколико је рад претходно саопштен на неком стручном састанку, навести званичан назив скупа, место и време одржавања, да ли је рад и како публикован (нпр. исти или другачији наслов или сажетак).

КЛИНИЧКА ИСТРАЖИВАЊА. Клиничка истраживања се дефинишу као истраживања утицаја једног или више средстава или мера на исход здравља. Регистарски број истраживања се наводи у последњем реду сажетка.

ЕТИЧКА САГЛАСНОСТ. Рукописи о истраживањима на људима треба да садрже изјаву у виду писаног пристанка испитиваних особа у складу с Хелсиншком декларацијом и одобрење надлежног етичког одбора да се истраживање може извести и да је оно у складу с правним стандардима. Експериментална истраживања на хуманом материјалу и испитивања вршена на животињама треба да садрже изјаву етичког одбора установе и треба да су у сагласности с правним стандардима.

ИЗЈАВА О СУКОБУ ИНТЕРЕСА. Уз рукопис се прилаже потписана изјава у оквиру обрасца *Submission Letter* којом се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. За додатне информације о различитим врстама сукоба интереса посетити интернет-страницу Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME; http://www.wame.org*) под називом „Политика изјаве о сукобу интереса“.

АУТОРСТВО. Све особе које су наведене као аутори рада треба да се квалификују за ауторство. Сваки аутор треба да је учествовао довољно у раду на рукопису како би могао да преузме одговорност за целокупан текст и резултате изнесене у раду. Ауторство се заснива само на: битном доприносу концепцији рада, добијању резултата или анализи и тумачењу резултата; планирању рукописа или његовој критичкој ревизији од знатног интелектуалног значаја; завршном дотеривању верзије рукописа који се припрема за штампање.

Аутори треба да приложе опис доприноса појединачно за сваког коаутора у оквиру обрасца *Submission Letter*. Финансирање, сакупљање података или генерално надгледање истраживачке групе сами по себи не могу

оправдати ауторство. Сви други који су допринели изради рада, а који нису аутори рукописа, требало би да буду наведени у Захвалници с описом њиховог доприноса раду, наравно, уз писани пристанак.

ПЛАГИЈАРИЗАМ. Од 1. јануара 2019. године сви рукописи подвргавају се провери на плагијаризам/аутоплагијаризам преко *SCIndeks Assistant* – Cross Check (iThenticate). Радови код којих се докаже плагијаризам/аутоплагијаризам биће одбијени, а аутори санкционисани.

НАСЛОВНА СТРАНА. На првој страници рукописа треба навести следеће: наслов рада без скраћеница; предлог кратког наслова рада, пуна имена и презимена аутора (без титула) индексирана бројевима; званичан назив установа у којима аутори раде, место и државу (редоследом који одговара индексираним бројевима аутора); на дну странице навести име и презиме, адресу за контакт, број телефона, факса и имејл адресу аутора задуженог за кореспонденцију.

САЖЕТАК. Уз оригинални рад, претходно и кратко саопштење, преглед литературе, приказ случаја (болесника), рад из историје медицине, актуелну тему, рад за рубрику језик медицине и рад за праксу, на другој по реду страници документа треба приложити сажетак рада обима 100–250 речи. За оригиналне радове, претходно и кратко саопштење сажетак треба да има следећу структуру: Увод/Циљ рада, Методе рада, Резултати, Закључак; сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) статистичке анализе и ниво значајности. Закључак не сме бити уопштен, већ мора бити директно повезан са резултатима рада. За приказе болесника сажетак треба да има следеће делове: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак; сегменте такође писати као посебан пасус који почиње болдованом речи. За остале типове радова сажетак нема посебну структуру.

КЉУЧНЕ РЕЧИ. Испод Сажетка навести од три до шест кључних речи или израза. Не треба да се понављају речи из наслова, а кључне речи треба да буду релевантне или описне. У избору кључних речи користити *Medical Subject Headings – MeSH (http://www.nlm.nih.gov/mesh)*.

ПРЕВОД НА СРПСКИ ЈЕЗИК. На трећој по реду страници документа приложити наслов рада на српском језику, пуна имена и презимена аутора (без титула) индексирана бројевима, званичан назив установа у којима аутори раде, место и државу. На следећој – четвртој по реду – страници документа приложити сажетак (100–250 речи) с кључним речима (3–6), и то за радове у којима је обавезан сажетак на енглеском језику. Превод појмова из стране литературе треба да буде у духу српског језика. Све стране речи или синтагме за које постоји одговарајуће име у нашем језику заменити тим називом. Уколико је рад у целости на српском језику, потребно је превести називе прилога (табела, графикона, слика, схема) уколико их има, целокупни текст у њима и легенду на енглески језик.

СТРУКТУРА РАДА. Сви поднаслови се пишу великим масним словима (болд). Оригинални рад и претходно и кратко саопштење обавезно треба да имају следеће поднаслове: Увод (Циљ рада навести као последњи пасус Увода), Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе и актуелну тему чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор прегледног рада мора да наведе бар пет аутоцитата (као аутор или коаутор) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ случаја или болесника чине: Увод (Циљ рада навести као последњи пасус Увода), Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од пет аутора.

Прилоге (табеле, графиконе, слике итд.) поставити на крај рукописа, а у самом телу текста јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публиковање.

СКРАЋЕНИЦЕ. Користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (стандардне скраћенице, као нпр. ДНК, сида, ХИВ, АТП). За сваку скраћеницу пун термин треба навести при првом навођењу у тексту, сем ако није стандардна јединица мере. Не користити скраћенице у наслову. Избегавати коришћење скраћеница у сажетку, али ако су неопходне, сваку скраћеницу објаснити при првом навођењу у тексту.

ДЕЦИМАЛНИ БРОЈЕВИ. У тексту рада на енглеском језику, у табелама, на графиконима и другим прилозима децималне бројеве писати са тачком (нпр. 12.5 ± 3.8), а у тексту на српском језику са зарезом (нпр. 12,5 ± 3,8). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм (грам) – *kg* (*g*), литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса (°*C*), количину супстанце у молима (*mol*), а притисак крви у милиметрима живиног стуба (*mm Hg*). Све резултате хематолошких, клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (*SI*).

ОБИМ РАДОВА. Целокупни рукопис рада који чине – насловна страна, сажетак, текст рада, списак литературе, сви прилози, односно потписи за њих и легенда (табеле, слике, графикони, схеме, цртежи), насловна страна и сажетак на српском језику – мора износити за оригинални рад, рад из историје медицине и преглед литературе до 5000 речи, а за претходно и кратко саопштење, приказ болесника, актуелну тему, рад за праксу, едукативни чланак и рад за рубрику „Језик медицине“ до 3000 речи; радови за остале рубрике могу имати највише 1500 речи.
Видео-радови могу трајати 5–7 минута и бити у формату *avi, mp4*(*flv*). У првом кадру филма мора се навести: у наднаслову Српски архив за целокупно лекарство, наслов рада, презимена и иницијали имена и средњег слова свих аутора рада (не филма), година израде. У другом кадру мора бити уснимљен текст рада у виду апстракта до 350 речи. У последњем кадру филма могу се навести имена техничког особља (режија, сниматељ, светло, тон, фотографија и сл.). Уз видео-радове доставити: посебно текст у виду апстракта (до 350 речи), једну фотографију као илустрацију приказа, изјаву потписану од свег техничког особља да се одричу ауторских права у корист аутора рада.

ПРИЛОЗИ РАДУ су табеле, слике (фотографије, цртежи, схеме, графикони) и видео-прилози.

Свака табела треба да буде сама по себи лако разумљива. Наслов треба откуцати изнад табеле, а објашњења испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле цртати искључиво у програму *Word*, кроз мени *Table–Insert–Table*, уз дефинисање тачног броја колона и редова који ће чинити мрежу табеле. Десним кликом на мишу – помоћу опција *Merge Cells* и *Split Cells* – спајати, односно делити ћелије. Куцати фонтом *Times New Roman*, величином слова 12 *pt*, с једноструким проредом и без увлачења текста. Коришћене скраћенице у табели треба објаснити у легенди испод табеле. Уколико је рукопис на српском језику, приложити називе табела и легенду на оба језика. Такође, у једну табелу, у оквиру исте ћелије, унети и текст на српском и текст на енглеском језику (никако не правити две табеле са два језика!).

Слике су сви облици графичких прилога и као „слике“ у CA се објављују фотографије, цртежи, схеме и графикони. Слике означавају се арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолуције најмање 300 *dpi* и формата записа *tiff* или *jpg* (мале, мутне и слике лошег квалитета неће се прихватати за штампање!). Уколико аутори не поседују или нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 *dpi* и у оригиналној величини. Уколико је рад неопходно илустровати са више слика, у раду ће их бити објављено неколико, а остале ће бити у е-верзији чланка као *PowerPoint* презентација (свака слика мора бити нумерисана и имати легенду).
Видео-прилози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi, mp4*(*flv*). Уз видео доставити посебно слику која би била илустрација видеоприказа у *e*-издању и објављена у штампаном издању. Уколико је рукопис на српском језику, приложити називе слика и легенду на оба језика.

Слике се у свесци могу штампати у боји, али додатне трошкове штампе сносе аутори.

Графикони треба да буду урађени и достављени у програму *Excel*, да би се виделе пратеће вредности распоређене по ћелијама. Исте графиконе прекопирати и у *Word*-ов документ, где се графикони означавају арапским бројевима према редоследу навођења у тексту. Сви подаци на графикону куцају се у фонту *Times New Roman*. Коришћене скраћенице на графикону треба објаснити у легенди испод графикона. У штампаној верзији чланка вероватније је да графикон неће бити штампан у боји, те је боље избегавати коришћење боја у графиконима, или их користити различитог интензитета. Уколико је рукопис на српском језику, приложити називе графикона и легенду на оба језика.

Цртежи и схеме се достављају у *jpg* или *tiff* формату. Схеме се могу цртати и у програму *CorelDraw* или *Adobe Illustrator* (програми за рад са векторима, кривама). Сви подаци на схеми куцају се у фонту *Times New Roman*, величина слова 10 *pt*. Коришћене скраћенице на схеми треба објаснити у легенди испод схеме. Уколико је рукопис на српском језику, приложити називе схема и легенду на оба језика.

ЗАХВАЛНИЦА. Навести све сараднике који су допринели стварању рада а не испуњавају мерила за ауторство, као што су особе које обезбеђују техничку помоћ, помоћ у писању рада или руководе одељењем које обезбеђује општу подршку. Финансијска и материјална помоћ, у облику спонзорства, стипендија, поклона, опреме, лекова и друго, треба такође да буде наведена.

ЛИТЕРАТУРА. Списак референци је одговорност аутора, а цитирани чланци треба да буду лако приступачни читаоцима часописа. Стога уз сваку референцу обавезно треба навести *DOI* број чланка (јединствену ниску карактера која му је додељена) и *PMID* број уколико је чланак индексиран у бази *PubMed/MEDLINE*.

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту. Број референци не би требало да буде већи од 30, осим у прегледу литературе, у којем је дозвољено да их буде до 50, и у метаанализи, где их је дозвољено до 100. Број цитираних оригиналних радова мора бити најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Уколико се домаће монографске публи-

кације и чланци могу уврстити у референце, аутори су дужни да их цитирају. Већина цитираних научних чланака не би требало да буде старија од пет година. Није дозвољено цитирање апстраката. Уколико је битно коментарисати резултате који су публиковани само у виду апстракта, неопходно је то навести у самом тексту рада. Референце чланака који су прихваћени за штампу, али још нису објављени, треба означити са *in press* и приложити доказ о прихватању рада за објављивање.

Референце се цитирају према Ванкуверском стилу (униформисаним захтевима за рукописе који се предају биомедицинским часописима), који је успоставио Међународни комитет уредника медицинских часописа (*http://www.icmje.org*), чији формат користе *U.S. National Library of Medicine* и базе научних публикација. Примере навођења публикација (чланака, књига и других монографија, електронског, необјављеног и другог објављеног материјала) могу се пронаћи на интернет-страници *http://www.nlm.nih.gov/bsd/uniform_requirements.html*. Приликом навођења литературе веома је важно придржавати се поменутог стандарда, јер је то један од најбитнијих фактора за индексирање приликом класификације научних часописа.

ПРОПРАТНО ПИСМО (*SUBMISSION LETTER*). Уз рукопис обавезно приложити образац који су потписали сви аутори, а који садржи: 1) изјаву да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, 2) изјаву да су рукопис прочитали и одобрили сви аутори који испуњавају мерила ауторства, и 3) контакт податке свих аутора у раду (адресе, имејл адресе, телефоне итд.). Бланко образац треба преузети са интернет-странице часописа (*http://www.srpskiarhiv.rs*).

Такође је потребно доставити копије свих дозвола за: репродуковање претходно објављеног материјала, употребу илустрација и објављивање информација о познатим људима или именовање људи који су допринели изради рада.

ЧЛАНАРИНА, ПРЕТПЛАТА И НАКНАДА ЗА ОБРАДУ ЧЛАНКА. Да би рад био објављен у часопису *Српски архив за целокупно лекарство*, сви аутори који су лекари или стоматолози из Србије морају бити чланови Српског лекарског друштва (у складу са чланом 6. Статута Друштва) и измирити накнаду за обраду чланака (*Article Processing Charge*) у износу од 3000 динара. Аутори и коаутори из иностранства су у обавези да плате накнаду за обраду чланака (*Article Processing Charge*) у износу од 35 евра. Уплата у једној календарској години обухвата и све наредне, евентуалне чланке, послате на разматрање у тој години. Сви аутори који плате ову накнаду могу, уколико то желе, да примају штампано издање часописа. Треба напоменути да ова уплата није гаранција да ће рад бити прихваћен и објављен у *Српском архиву за целокупно лекарство*. Обавеза плаћања накнаде за обраду чланка не односи се на студенте основних студија и на претплатнике на часопис.

Установе (правна лица) не могу преко своје претплате да испуне овај услов аутора (физичког лица). Уз рукопис рада треба доставити копије уплатница за чланарину и претплату / накнаду за обраду чланка, као доказ о уплатама, уколико издавач нема евиденцију о томе. Часопис прихвата донације од спонзора који сносе део трошкова или трошкове у целини оних аутора који нису у могућности да измире накнаду за обраду чланка (у таквим случајевима потребно је часопису ставити на увид оправданост таквог спонзорства).

СЛАЊЕ РУКОПИСА. Рукопис рада и сви прилози уз рад достављају се искључиво електронски преко система за пријављивање на интернет-страници часописа: *http://www.srpskiarhiv.rs*

НАПОМЕНА. Рад који не испуњава услове овог упутства не може бити упућен на рецензију и биће враћен ауторима да га допуне и исправе. Придржавањем упутства за припрему рада знатно ће се скратити време целокупног процеса до објављивања рада у часопису, што ће позитивно утицати на квалитет чланака и редовност излажења часописа.

За све додатне информације, молимо да се обратите на доле наведене адресе и број телефона.

АДРЕСА:
Српско лекарско друштво
Уредништво часописа „Српски архив за целокупно лекарство“
Ул. краљице Наталије 1
11000 Београд
Србија

Телефони: (+381 11) 409-2776, 409-4479
E-mail: *office@srpskiarhiv.rs*
Интернет адреса: *http://www.srpskiarhiv.rs*

ISSN 0370-8179
ISSN Online 2406-0895
OPEN ACCESS

Before submitting their paper to the Editorial Office of the Serbian Archives of Medicine, authors should read the Instructions for Authors, where they will find all the necessary information on writing their manuscript in accordance with the journal's standards. It is essential that authors prepare their manuscript according to established specifications, as failure to do so will result in paper being delayed or rejected. Serbian Archives of Medicine provides no fee for published articles. By submitting a paper for publishing consideration, authors of a paper accepted for publication in the Serbian Archives of Medicine grant and assign all copyrights to the publisher – the Serbian Medical Society.

GENERAL INSTRUCTIONS. *Serbian Archives of Medicine* publishes papers that have not been, either in their entirety or partially, previously published, and that have not been accepted for publication elsewhere. *Serbian Archives of Medicine* publishes papers in English and Serbian. For better availability and citation, authors are encouraged to submit articles of all types in English. The journal publishes the following article types: editorials, original papers, preliminary and short communications, case reports, video-articles, images in clinical medicine, review articles, current topics, articles for practitioners, history of medicine articles, language of medicine articles, medical ethics (clinical ethics, publication ethics) and regulatory standards in medicine, congress and scientific meeting reports, personal view articles, invited commentaries, letters to the editor, book reviews, professional news, In memoriam and other articles. Original papers, case reports, preliminary and short communications, review articles, current topics, video-articles and images in clinical medicine are published in English only, while other article types may be published in Serbian if the Editorial Office reaches such decision.

The papers are always submitted with Summary in both English and Serbian, included in the manuscript file. The text of the manuscript should be typed in *MS Word* using the *Times New Roman* typeface, and font size 12 pt. The text should be prepared with margins set to 25 mm and onto A4 paper size, with double line spacing, aligned left and the initial lines of all paragraphs indented 10 mm, without hyphenation. Tabs and successive blank spaces are not to be used for text alignment; instead, ruler alignment control tool and *Toolbars* are suggested. In order to start a new page within the document, *Page Break* option should be used instead of consecutive enters. Only one space follows after any punctuation mark. If special signs (symbols) are used in the text, use the *Symbol* font. References cited in the text are numbered with Arabic numerals within parenthesis (for example: [1, 2]), in order of appearance in the text. Pages are numbered consecutively in the right bottom corner, beginning from the title page.

When writing text in English, linguistic standard American English should be observed. Write short and clear sentences. Generic names should be exclusively used for the names of drugs. Devices (apparatuses, instruments) are termed by trade names, while their name and place of production should be indicated in the brackets. If a letter-number combination is used, the number should be precisely designated in superscript or subscript (i.e., 99Tc, IL-6, O2, B12, CD8). If something is commonly written in italics, such as genes (e.g. BRCA1), it should be written in this manner in the paper as well.

If a paper is a part of a master's or doctoral thesis, or a research project, that should be designated in a separate note at the end of the text. Also, if the article was previously presented at any scientific meeting, the name, venue and time of the meeting should be stated, as well as the manner in which the paper had been published (e.g. changed title or abstract).

CLINICAL TRIALS. Clinical trial is defined as any research related to one or more health related interventions in order to evaluate the effects on health outcomes. The trial registration number should be included as the last line of the Summary.

ETHICAL APPROVAL. Manuscripts with human medical research should contain a statement that the subjects' written consent was obtained, according to the Declaration of Helsinki, the study has been approved by competent ethics committee, and conforms to the legal standards. Experimental studies with human material and animal studies should contain statement of the institutional ethics committee and meet legal standards.

CONFLICT OF INTEREST STATEMENT. The manuscript must be accompanied by a disclosure statement from all authors (contained within the Submission Letter) declaring any potential interest or stating that the authors have no conflict of interest. For additional information on different types of conflict of interest, please see World Association of Medical Editors (WAME, *www.wame.org*) policy statement on conflict of interest.

AUTHORSHIP. All individuals listed as authors should be qualified for authorship. Every author should have participated sufficiently in writing the article in order to take responsibility for the whole article and results presented in the text. Authorship is based only on: crucial contribution to the article conception, obtaining of results or analysis and interpretation of results; design of manuscript or its critical review of significant intellectual value; final revision of the manuscript being prepared for publication.

The authors should enclose the description of contribution to the article of every co-author individually (within the Submission Letter). Funding, collection of data or general supervision of the research group alone cannot justify authorship. All other individuals having contributed to the preparation of the article should be mentioned in the *Acknowledgment* section, with description of their contribution to the paper, with their written consent.

PLAGIARISM. Since January 1, 2019 all manuscripts have been submitted via SCIndeks Assistant to Cross Check (software iThenticate) for plagiarism and auto-plagiarism control. The manuscripts with approved plagiarism/auto-plagiarism will be rejected and authors will not be welcome to publish in Serbian Achieves of Medicine.

TITLE PAGE. The first page of the manuscript (cover sheet) should include the following: title of the paper without any abbreviations; suggested running title; each author's full names and family names (no titles), indexed by numbers; official name, place and country of the institution in which authors work (in order corresponding to the indexed numbers of the authors); at the bottom of the page: name and family name, address, phone and fax number, and e-mail address of a corresponding author.

SUMMARY. Along with the original article, preliminary and short communication, review article, case report, article on history of medicine, current topic article, article for language of medicine and article for practitioners, the summary not exceeding 100–250 words should be typed on the second page of the manuscript. In original articles, the summary should have the following structure: Introduction/Objective, Methods, Results, Conclusion. Each segment should be typed in a separate paragraph using boldface. The most significant results (numerical values), statistical analysis and level of significance are to be included. The conclusion must not be generalized, it needs to point directly to the results of the study. In case reports, the summary should consist of the following: Introduction (final sentence is to state the objective), Case Outline (Outline of Cases), Conclusion. Each segment should be typed in a separate paragraph using boldface. In other types of papers, the summary has no special outline.

KEYWORDS. Below the summary, 3 to 6 keywords or phrases should be typed. The keywords need not repeat words in the title and should be relevant or descriptive. *Medical Subject Headings – MeSH* (*http://www.nlm.nih.gov/mesh*) are to be used for selection of the keywords.

TRANSLATION INTO SERBIAN. The third page of the manuscript should include: title of the paper in the Serbian language; each author's full name and family name (no titles), indexed by numbers; official name, place and country of the institution in which authors work. On the fourth page of the manuscript the summary (100–250 words) and keywords (3–6) should be typed, but this refers only to papers in which a summary and keywords are compulsory. The terms taken from foreign literature should be translated into comprehensible Serbian. All foreign words or syntagms that have a corresponding term in Serbian should be replaced by that term.

If an article is entirely in Serbian (e.g. article on history of medicine, article for "Language of medicine," etc.), captions and legends of all enclosures (tables, graphs, photographs, schemes) – if any – should be translated into English as well.

STRUCTURE OF THE MANUSCRIPT. All section headings should be in capital letters using boldface. Original articles and preliminary and short communications should have the following section headings: Introduction (objective is to be stated in the final paragraph of the Introduction), Methods, Results, Discussion, Conclusion, References. A review article and current topic include: Introduction, corresponding section headings, Conclusion, References. The firstly named author of a review article should cite at least five auto-citations (as the author or co-author of the paper) of papers published in peer-reviewed journals. Co-authors, if any, should cite at least one auto-citation of papers also published in peer-reviewed journals. A case report should consist of: Introduction (objective is to be stated in the final paragraph of the Introduction), Case Report, Discussion, References. No names of patients, initials or numbers of medical records, particularly in illustrations, should be mentioned. Case reports cannot have more than five authors. Letters to the editor need to refer to papers published in the *Serbian Archives of Medicine* within previous six months; their form is to be comment, critique, or stating own experiences. Publication of articles unrelated to previously published papers will be permitted only when the journal's Editorial Office finds it beneficial.

All enclosures (tables, graphs, photographs, etc.) should be placed at the end of the manuscript, while in the body of the text a particular enclosure should only be mentioned and its preferred place indicated. The final arrangement (position) of the enclosures will depend on page layout.

ABBREVIATIONS. To be used only if appropriate, for very long names of chemical compounds, or as well-known abbreviations (standard abbreviations such as DNA, AIDS, HIV, ATP, etc.). Full meaning of each abbreviation should be indicated when it is first mentioned in the text unless it is a standard unit of measure. No abbreviations are allowed in the title. Abbreviations in the summary should be avoided, but if they have to be used, each of them should be explained when first mentioned in the text of the paper.

DECIMAL NUMBERS. In papers written in English, including text of the manuscript and all enclosures, a decimal point should be used in decimal numbers (e.g. 12.5 ± 3.8), while in Serbian papers a decimal comma should be used (e.g. 12,5 ± 3,8). Wherever applicable, a number should be rounded up to one decimal place.

UNITS OF MEASURE. Length, height, weight and volume should be expressed in metric units (meter – m, kilogram – kg, gram – g, liter – l) or subunits. Temperature should be in Celsius degrees (°C), quantity of substance in moles (mol), and blood pressure in millimeters of mercury column (mm Hg). All results of hematological, clinical and biochemical measurements should be expressed in the metric system according to the International System of Units (SI units).

LENGTH OF PAPER. The entire text of the manuscript – title page, summary, the whole text, list of references, all

enclosures including captions and legends (tables, photographs, graphs, schemes, sketches), title page and summary in Serbian – must not exceed 5,000 words for original articles, review articles and articles on history of medicine, and 3,000 words for case reports, preliminary and short communications, current topics, articles for practitioners, educational articles and articles for "Language of medicine", congress and scientific meeting reports; for any other section maximum is 1,500 words.

Video-articles are to last 5–7 minutes and need to be submitted in the flv video format. The first shot of the video must contain the following: title of the journal in the heading (*Serbian Archives of Medicine*), title of the work, last names and initials of first and middle names of the paper's authors (not those of the creators of the video), year of creation. The second shot must show summary of the paper, up to 350 words long. The final shot of the video may list technical staff (director, cameraman, lighting, sound, photography, etc.). Video-articles need to be submitted along with a separate summary (up to 350 words), a single still/photograph as an illustration of the video, and a statement signed by the technical staff renouncing copyrights in favor of the paper's authors. To check the required number of words in the manuscript, please use the menu *Tools-Word Count*, or *File-Properties-Statistics*.

ARTICLE ENCLOSURES are tables, figures (photographs, schemes, sketches, graphs) and video-enclosures.

TABLES. Each table, with its legend, should be self-explanatory. The title should be typed above the table and any explanatory information under the table. Tables should be numbered in Arabic numerals in order of citation in the text. Use *MS Word*, the menu *Table-Insert-Table*, inserting the adequate number of rows and columns. By the right click of the mouse, use the options *Merge Cells* and *Split Cells*. Use *Times New Roman*, font size 12 pt, with single line spacing and no indent to draw tables. Abbreviations used in tables should be explained in the legend below each respective table.

If the manuscript is entirely in the Serbian language, tables and corresponding legend should be both in Serbian and English. Also, the table cells should contain text in both languages (do not create two separate tables with a single language!).

FIGURES. Figures are all types of visual enclosures, and photographs, schemes, sketches and graphs are published as 'figures' in the *Serbian Archives of Medicine.* Figures should be numbered in Arabic numerals in order of citation in the text. Only original digital photographs (black-and-white or color), of minimum 300 dpi, and *jpg* or *tiff* format, are acceptable (small, blurry and photographs of poor quality will not be accepted for publishing!). If authors do not possess or are not able to provide digital photographs, then the original photos should be scanned in 300 dpi, and saved in original size. If a paper needs to be illustrated with a considerable number of figures, several figures will be published within the paper, and the rest will be available in the electronic version of the paper as a PowerPoint presentation (every figure needs to be numbered and be accompanied by legend). Video-enclosures (illustrations of a paper) can last 1–3 minutes and are submitted in the *flv* format. Along with the video, a still/photograph representative of the video is also needed, as it will be used as a placeholder in the electronic version of the paper, and as an illustration in the printed version.

If the manuscript is entirely in the Serbian language, photographs and corresponding legend should be both in Serbian and English.

Photographs may be printed and published in color, but possible additional expenses are to be covered by the authors.

GRAPHS. Graphs should be plotted in *Excel* in order to see the respective values distributed in the cells. The same graphs should be copied and pasted to the *Word* document, numbered in Arabic numerals by order of citation in the text. The text in the graphs should be typed in *Times New Roman*. Abbreviations used in graphs should be explained in the legend below the respective graph. In the printed versions of papers, graphs are generally published in black-and-white; therefore, it is suggested to avoid the use of colors in graphs, or to utilize colors of significant difference in brightness.

If the manuscript is entirely in the Serbian language, graphs and corresponding legend should be both in Serbian and English.

SCHEMES (SKETCHES). Schemes and sketches are to be submitted in *jpg* or *tiff* format. Schemes should be drawn in *CorelDraw* or *Adobe Illustrator* (programs for drawing vectors, curves, etc.). The text in the schemes should be typed in *Times New Roman*, font size 10 pt. Abbreviations used in schemes should be explained in the legend below the respective scheme. If the manuscript is entirely in the Serbian language, schemes and corresponding legend should be both in Serbian and English.

ACKNOWLEDGMENT. List all those individuals having contributed to preparation of the article but having not met the criteria of authorship, such as individuals providing technical assistance, assistance in writing the paper or running the department securing general support. Financial aid and all other support in the form of sponsorship, grants, donations of equipment and medications, etc., should be mentioned too.

REFERENCES. The reference list is the responsibility of the authors. Cited articles should be readily accessible to the journals readership. Therefore, following each reference, its DOI number and PMID number (if the article is indexed for MEDLINE/PubMed) should be typed. References should be numbered in Arabic numerals in order of citation in the text. The overall number of references should not exceed 30, except in review articles, where maximum of 50 is acceptable, and in meta-analysis, where up to 100

references are allowed. The number of citations of original articles must be at least 80% of the total number of references, and the number of citations of books, chapters and literature reviews less than 20%. If monographs and articles written by Serbian authors could be included in the reference list, the authors are obliged to cite them. The majority of the cited articles should not be older than five years. Use of abstracts as references is not allowed. If it is important to comment on results published solely in the form of an abstract, it is necessary to do so within the text of the article. The references of articles accepted for publication should be designated as *in press* with the enclosed proof of approval for publication.

The references are cited according to the Vancouver style (*Uniformed Requirements for Manuscripts Submitted to Biomedical Journals*), rules and formats established by the International Committee of Medical Journal Editors (*http://www.icmje.org*), used by *the U.S. National Library of Medicine* and scientific publications databases. Examples of citing publications (journal articles, books and other monographs, electronic, unpublished and other published material) can be found on the web site *http://www.nlm.nih.gov/bsd/uniform_requirements.html*. In citation of references, the defined standards should be strictly followed, because it is one of the essential factors of indexing for classification of scientific journals.

SUBMISSION LETTER. The manuscript must be accompanied by the Submission Letter, which is signed by all authors and includes the following: 1) statement that the paper has never been published and concurrently submitted for publication to any other journal; 2) statement that the manuscript has been read and approved by all authors who have met the criteria of authorship; and 3) contact information of all authors of the article (address, email, telephone number, etc.). Blank Submission Letter form can be downloaded from the journal's web site (*http://srpskiarhiv.rs/global/pdf/SubmissionletterformFINAL.pdf*).

Additionally, the authors should submit the following copies of all permits for: reproduction of formerly published material, use of illustrations and publication of information on known people or disclosure of the names of people having contributed to the work.

MEMBERSHIP FEE AND SUBSCRIPTION RATES. In order to publish their article in the *Serbian Archives of Medicine*, all authors and co-authors, medical doctors and doctors of dental medicine, must be members of the Serbian Medical Society (according to the Article #6 of the Statute of the SMS) for the year in which the manuscript is being submitted. All authors pay an "Article Processing Charge" for the coverage of all editing and publishing expenses. Domestic authors pay 3,000 RSD, and those from abroad €35. The editing and publishing fee is required for substantive editing, fact and reference validations, copy editing, and publishing online and in print. An author who had already paid the fee can have more articles submitted for publishing consideration in the year the fee was paid. All authors who pay this fee may, if they desire so, receive the printed version of the journal in the year when the fee is paid. Please note that the payment of this charge does not guarantee acceptance of the manuscript for publication and does not influence the outcome of the review procedure, in accordance with good publishing practice. The journal accepts donations from sponsors to create a sum for payment reductions or waivers for authors unable to cover the Article Processing Charge (a justification of the inability to pay should be provided in such cases).

The requirement for paying the Article Processing Charge does not apply to students or to journal subscribers. Institutions (legal entities) cannot by their subscription cover this condition on behalf of the authors (natural persons). Copies of deposit slips for membership and Article Processing Charge should be enclosed with the manuscript. Foreign authors are under no obligation to be members of the Serbian Medical Society. All the relevant information can be obtained via email address of the Editorial Office (*office@srpskiarhiv.rs*) and on the journal's web site (*http://srpskiarhiv.rs/en/subscription/*).

SUBMISSION. Our online submission system will guide you through the process of entering your article details and uploading your files. All correspondence, including notification of Editorial Office, requests for revision and Editor's decision will be sent by e-mail.

Please submit your manuscript and all enclosures via: ***http://www.srpskiarhiv.rs***.

NOTE. The papers not complying with these instructions will not be reviewed and will be returned to the authors for revision. Observing the instructions for preparation of papers for the *Serbian Archives of Medicine* will shorten the time of the entire process of publication and will have a positive effect on the quality and timely release of the journal's issues.

For further information, please contact us via the following address:

ADDRESS:
Serbian Archives of Medicine
Editorial Office
Kraljice Natalije 1
11000 Belgrade
Serbia
Phones: (+381 11) 409-2776, 409-4479
E-mail: *office@srpskiarhiv.rs*
Website: *www.srpskiarhiv.rs*

ISSN 0370-8179
ISSN Online 2406-0895
OPEN ACCESS

CIP – Каталогизација у публикацији
Народна библиотека Србије, Београд

61(497.11)

СРПСКИ архив за целокупно лекарство : званичан часопис Српског лекарског друштва = Serbian Archives of Medicine : official journal of the Serbian Medical Society / главни и одговорни уредник Гордана Теофиловски-Парапид. - Књ. 1 (1874)-књ. 2 (1875) ; књ. 3 (1879)- књ. 8 (1881) ; књ. 9 (1887)-књ. 10 (1888) ; књ. 11 (1894)-књ. 12 (1895) ; год. 1, бр. 1/2 (1895)- . - Београд : Српско лекарско друштво, 1874-1875; 1879-1881; 1887-1888; 1894-1895; 1895-(Београд : Службени гласник). - 29 cm

Двомесечно. - Текст на енгл. језику. - Има суплемент или прилог: Српски архив за целокупно лекарство. Суплемент = ISSN 0354-2793. - Друго издање на другом медијуму: Српски архив за целокупно лекарство (Online) = ISSN 2406-0895
ISSN 0370-8179 = Српски архив за целокупно лекарство
COBISS.SR-ID 3378434

The Journal Serbian Archives of Medicine is indexed in: Science Citation Index Expanded, Journal Reports/Science Edition, Web of Science, Scopus, EBSCO, Directory of Open Access Journal, DOI Serbia

CONTENTS