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Address: 1 Kraljice Natalije Street, 11000 Belgrade, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

**Paper Accepted*** **ISSN Online 2406-0895**

**Original Article / Оригинални рад**

Gordana Sušić[1,†], Marija Atanasković [1], Roksanda Stojanović[1, 2], Goran Radunović[1,2]

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Густина кости код деце са јувенилним идиопатским артритисом после годину дана лечења етанерецептом

[1] Institute of Rheumatology Belgrade, Serbia
[2] School of Medicine, University of Belgrade, Serbia

**Received: August 11, 2017**
**Accepted: September 11, 2017**
**Online First: September 22, 2017**
**DOI: https://doi.org/10.2298/SARH170811175S**



† **Correspondence to:**
Gordana SUŠIĆ
Institute of Rheumatology,
Resavska 69, 11000 Belgrade, Serbia
Email: **susic.gordana@gmail.com**

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**SUMMARY**

**Introduction/Objective** Juvenile idiopathic arthritis (JIA) is the most frequent chronic inflammatory, rheumatic disease of childhood, associated with disturbance of bone mineral metabolism, which develops gradually and progressively if untreated eventually leads to osteoporosis in adulthood.
Aim of our study was to evaluate bone mineral density (BMD) in patients with JIA treated with etanercept ~~(ETN)~~ over one year .
**Methods** Prospective cohort study included 94 JIA patients (66 F, 28 M), median age 14.77 years. BMD was measured by dual-energy x-ray absorptiometry on the lumbar spine. Disease activity was assessed using ACR pedi 50 criteria.
**Results** After one year of treatment with etanercept we found a statistically significant increment in all osteodensitometry variables ($p<0.001$). Annual enhancement for whole group was: bone mineral content (BMC) 15.8%, BMD 7.2%, $BMD_{vol}$ 4.2%. Z score improved from -0.86 to -0.58 SD at the last visit, but decreased in RF positive polyarthritis patients. Patients with sJIA had the lowest Z-score. Z score correlated with functional disability level. BMD was lower in glucocorticoids treated group.
**Conclusion** Our results showed significant improvement of bone mineral density in children with JIA after one year of treatment with etanercept. RF positive and sJIA subtypes and treatment with glucocorticoids are the risk factors for impaired of bone mineral density.
**Key words**: juvenile idiopathic arthritis, bone mineral density, anti-TNF

**САЖЕТАК**

**Увод/Циљ** Јувенилни идиопатски артритис (ЈИА) је најчешће хронично, запаљенско реуматско обољење у детињству, удружено са поремећајем минералног костног метаболизма, који се развија постепено и прогресивно и доводи до остеопорозе у одраслом добу.
Циљ наше студије је био да се испита костни минерални статус код болесника са ЈИА након годину дана лечења етанерцептом ~~(ЕТН)~~.
**Метод** Проспективна кохортна студија је укључила 94 болесника са ЈИА (66ж, 28м) средњег узраста 14.77 година. Минерална густина кости (МГК) је мерена двоструком *X*- апсорпциометријом на лимбалној кичми. Степен активности болести је процењиван *ACR*50 критеријумима.
**Резултати** После годину дана лечења етанерцептом установили смо статистички значајно побољшање у свим остеодензитометријским показатељима ($p<0,001$). Годишње повећање за целу групу било је: укупно минерала у костима 5,8%, МГК 7,2%, МГК-вол 4,2%. З-скор се поправио са -0,86 до -0,58 СД на крају истраживања, али је у групи болесника са РФ позитивним полиартртисом дошло до смањења З-скора. Најнижи З-скор су имали болесници са сЈИА. З-скор је корелисао са степеном функцијске неспособности. Група лечена гликокортикоидима је имала значајно нижу минералну густину.
**Закључак** Значајно побољшање минералне густине кости код деце са ЈИА након годину дана лечења етанерцептом. Болесници са РФ позитивним полиартритисом и системским артртисом као и примена гликокортикоида имају већи ризик за поремећај костног метаболизма.
**Кључне речи**: јувенилни идиопатски артритис, минерална густина кости, анти-ТНФ

## INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most frequent, autoimmune, rheumatic disease in childhood. Inflammatory process affects primarily the synovial joints and cartilage, leading to excessive production of proinflammatory cytokines. Longstanding inflammation with beginning in the childhood, while the development of the skeletal system and growth are not yet completed, may cause many complications such as growth retardation, disturbance of bone metabolism leading to osteopenia and osteoporosis which become apparent when fracture occurred. [1, 2, 3].

Disturbance of bone metabolism in JIA develops gradually and progressively and it is the result interaction of many factors. The most important is disease activity and severity, genetic predisposition, duration of the disease, number of affected joints, poor nutrition, medications



especially glucocorticoids (GC), delayed puberty, reduced physical activity, lack of sun exposure and others [4].

There are evidences that JIA is associated with low bone mineral density (BMD), as result of impairment of bone mineral acquisition during adolescent growth spurt and inability of achievement of optimal peak bone mass. Forty-one percent of the adolescents with early-onset JIA had low bone mass >11 years after disease onset. The development of low total-body bone mineral content (BMC) correlated with duration of active disease, disease severity, measures of bone resorption, weight, and height [5]. It is reasonable approach in improving bone health and preventing fractures to suppress disease activity using more efficacy therapeutic options. Etanercept (ETN), as TNF blocker, has been shown its effectiveness inducing prompt and sustained suppression of disease activity [6,7]. Also there are growing evidences that ETN could have protective role and could prevent structural bone damage by increasing osteoblastic and decreasing osteoclastic activity [8].

There are several modalities of assessing paediatric skeleton, but DXA remains the preferred method because of its high precision, accuracy, reproducibility, speed and especially low radiation exposure and availability of reference data [9].

Aim of our study was to examine bone mineral status in patients with JIA after one year of treatment with ETN.

## METHODS

We undertook a prospective study that included 94 consecutive children with established diagnosis of JIA, referred to the Institute of Rheumatology, the main tertiary care referral hospital in the country, between January 2010 and December 2016. The main iclusion criterion was that those failed to achieve inactive disease according to Wallace et al. criteria [10] despite previously treatment with GC and/or methotrexate (MTX), or had intolerance to MTX have been started with ETN 0,4mg/kg of body weight twice weekly. The biologic was commenced to the local criteria for reimbursement covered by health system insurance.

According to ILAR classification [11] 10 (10.6%) pts. had systemic onset (sJIA), 28 (29.8%) patients. had polyarthritis rheumatoid factor (pJIA RF) negative, 15 (16.0%), polyarthritis RF positive, 20 (21.3%) pts. extended oligoarthritis, 19 (20.2%) had enthesitis and arthritis, and 2 patients (2.1%) had psoriatic arthritis, who were included in the polyarthicular seronegative group JIA for futher analysis, because their clinical presentation was arthritis of periferal joints.

The physical examination, laboratory investigations and functional ability assessment were done at the baseline and 12 months after initiation of ETN.

The impact of arthritis on physical ability was estimated using Serbian version of Childhood Health Assessment Questionnaire (CHAQ) [12]. This questionnaire, which contains 69 questions regarding usual daily living activities (DLA) was completed by a parent or a child if he/she was older than 12 years of age, and refers to physical ability during the week prior to the clinic visit. CHAQ

disability index (CHAQ DI) ranges from 0 (best) to 3 (worst). CHAQ DI represents the average sum of the entire eight areas covered by CHAQ and was divided into four categories: 0=no disability and 0.1-0.5=mild and 0.6-1.5=moderate, and >1.5=severe disability [13].

Disease activity was assessed according to the criteria by Giannini et al. [13] which include physician's global assessment of disease activity (PGA) on a 100-mm visual analogue scale (VAS), parent/patient's assessment of overall well-being on VAS (ranging 0 - the best to 100 mm- the worst), functional ability (CHAQ), number of joints with active arthritis and number of joints with limited range of motion (LOM) as a clinical variables, erythrocyte sedimentation rate (ESR) as laboratory sign of inflammation. Active joint was defined if joint swelling or any two of the following signs such as limited range of motion (LOM), joint pain/ tenderness or joint warmth were present. The patients were divided in two groups according to the American College of Rheumatology pediatric 50 definition of improvement [10]. If the patients demonstrated at least 50% improvement from the baseline in at least three of any six core set variables with no more than one indicator worsening by more than 30%, they were considered as responders.

The treatment was analysed, recording the number of patients receiving GC, MTX applied 10-15mg/m2 of body surface area per week.

Written inform consent form was taken from the parents or patients if they were above 18 years. The study was approved by the Ethic Committee of the Institute of Rheumatology of Belgrade, Serbia.

Osteodensitometry examination was performed using dual-energy x-ray absorptiometry (DXA) device LUNAR DPX-L paediatric software. Measurement of BMD was performed on the lumbar spine (anterior-posterior scan), and for analysis was taken value from L2-L4 segment, at the beginning of treatment with ETN and 12 months later. Patients during examination were in the supine position with flexed hips and knees at 90 degrees, in order to correct the physiological lordosis lumbar spine.

For analysis was taken area BMD expressed in g/cm2, bone mineral content (BMC) in g/cm and Z-score expressed in standard deviation (SD). Z-score means patient's BMD mean- BMD from an age and gender-matched reference group divided by SD for reference group and the manufacture's database of Italian population of children was used. According to the Z-score patients were divided in two gruops: group I with Z-score < -1SD and group II with Z-score ≥ -1SD.

In order to eliminate the effect of the length of the bone to BMD, we used the formula $BMD_{vol}$ = BMD x [4 / π x width L2-L4 region in cm], representing volumetric bone mineral density [$BMD_{vol}$] expressed in $g/cm^3$ [14].

Data were evaluated by descriptive statistics and analytical models with the SPSS software package for Windows, version 16. To describe groups descriptive statistics methods were used: the grouping and graphical representation; calculating measures of central tendency (arithmetic mean X,

the median Med); calculating measures of variability (standard deviation - SD, standard score variations - SSD) and calculating the relative numbers.

From analytical statistical methods used tests to test differences between groups of respondents for parametric data Student's t-test and analysis of variance, and nonparametric data Mann Whitney U test and chi 2 test. To test the normality of distribution of data was used Kolmogorov-Smirnov test. To assess correlation data were applied to a single linear correlation and Spearman's rank correlation.

## RESULTS

The median age at the baseline of 94 patients with JIA was 14.77 years (range 5 - 20 years) the median disease duration was 4.42 years (0.72-19.84). Almost three quarter of patients was female. Demographic and clinical characteristics of patients are shown in the table 1.

**Table 1. Baseline demographic and clinical features of patients.**

| Characteristics | Value (n=94) |
|---|---|
| Female/male ratio | 66/28 (70.2/29.8) |
| Age , median (min-max), yrs | 14.77 (5.0–20.0) |
| Age at the onset of the beginning of the disease (median min-max), yrs | 9.0 (1.08–16.0) |
| Disease duration, median (min-max) yrs | 4.42 (0.72–19) |
| **JIA subtypes** | |
| Systemic (soJIA) | 10 (10.6) |
| Polyarticular, RF negative (pJIA RF-) | 28 (29.8) |
| Polyarticular, RF positive (pJIA RF+) | 15 (16.0) |
| Oligoarticular, extended (eoJIA) | 20 (21.3) |
| Enthesitis related arthritis (ERA) | 19 (20.2) |
| Psoriatic arthritis | 2 (2.1) |
| No patients on methotrexate | 79 (84.0) |
| No patients with glicocorticoids | 22 (23.4) |

At the entry of study 12 patients (12.8%) were preschool age, 20 (21.3%) were 7-12 years old, and 62 (66%) were teenage. The patients were 9 years old (median) at the time of first symptoms of JIA, and 33 (35.1%) were preschool age. More than half patients (57.4%) had disease duration shorter than 2 years and 11 patients (11.7%) suffered from arthritis more than 10 years.

All patients had polyarthritis, nonresponding or had adverse events to previous methotrexate treatment. It was the first condition for prescribing biologic therapy covered by health insurance system in our country. The most frequent was polyarticular seronegative arthritis group, belonged one third of patients.

At the baseline 79 patients (84.0%) were treated with MTX and 22 patients (23.4%) received oral glucocorticoids.

**Table 2. Disease activity core set variables at the baseline and 12 months after.**

| Variables | Baseline | 12 mo | % of improvement | *p* |
|---|---|---|---|---|
| PGA (mm) | 46.4 | 9.2 | 81.8 | <0.001 |
| Parent/patient's assessment of well-being (mm) | 37.5 | 12.4 | 47.9 | <0.01 |
| Number of joints with LOM | 10.1 | 4.7 | 69.9 | <0.001 |
| Number of active joints | 9.7 | 0.2 | 81.1 | <0.001 |
| CHAQ | 0.7 | 0 | 66.8 | <0.001 |
| ESR (mm/h) | 34 | 17 | 39.8 | <0.001 |

All value are median. LOM- limited range of motion; PGA-physician global assessment; CHAQ- childhood health assessment questionnaire; ESR- erythrocyte sedimentation rate.

Disease activity core set criteria according to Giannini et al. [13] at the baseline and at the last visit after 12 months were present at the table 2.



We found significant improvement in all six core set variables representing disease activity, a year after introducing of ETN (p<0.001); the most pronounced improvement was observed in PGA and clinical manifestations of disease (81%). At the baseline 56 (59.5%) of patients had moderate and severe functional disability (DI 0.5-1.5 and above 1.5), but on the end of follow up period 77 (81.9%) of patients had no or mild limitation in performing everyday activities (p<0.001).

At the last visit 82 patients (87.2%) met the ACR pedi 50 criteria, assigned as responders, while 12 patients (12.8%) didn't show satisfied therapeutic effect, assigned them in group nonresponders. Among nonresponders group there were 3 patients with sJIA, 5 with pJIA RF negative and 3 patients with RF positive polyarthritis. Nonresponders were slightly older, all except one female, they were younger at the beginning of the disease, but it was not statistical important except related to GC treatment disease and disease duration which was longer in nonresponders. In nonresponder group at the baseline 50%, at the last visit 33.3% of patients were continued GC treatment. In responder group only 2 pts. at the end used GC.

**Table 3. Ostedensitometry evaluation of the patients at baseline and 12 months after.**

| Variables | Baseline (mean ± SD) | 12 mo (mean±SD) | *p* |
|---|---|---|---|
| BMD | 0.90± 0.25 | 0.95±0.240 | <0.001 |
| BMC | 32.75±16.65 | 36.19±16.18 | <0.001 |
| Z-score | -0.86±1.23 | -0.58±1.21 | <0.001 |
| $BMD_{vol}$ | 0.31±0.05 | 0.32±0.55 | <0.001 |

BMD- bone mineral density; BMC - bone mineral content; $BMD_{vol}$ - bone mineral density volumetric.

At the baseline these two groups did not differ with regard to osteodensitometry variables: BMD, BMC, Z-score and $BMD_{vol}$. Bone mineral status of patients at the baseline and at the last evaluation is presented on the table 3.

After one year of treatment with ETN it was shown statistical significant increment in all ostedensitometry variables (p<0.001). Mean annual enhancement for BMC was 15.8%, 7.2% for BMD and 4.2% for $BMD_{vol}$ for whole group. The Z-score also improved from -0.86 to -0.58 SD after one year of treatment.

According to the type of arthritis there was intergroup diffrence in Z-score at the baseline was border (p=0.052) and after one year (p=0.033). The lowest Z-score had the patients with sJIA (-2.14, respectively -1.87 SD), all of them were on GC.

Analysing separately groups according to the arthritis subtype, after 12 months of treatment all osteodensitometry values significantly improved in seronegative polyarticular onset (p<0.001), and ERA patients (for BMD and $BMD_{vol}$, p<0.001, for Z-score and BMC p<0.01). Contrary, in pJIA RF positive patients Z-score decrised from -0.63 to -0.69 SD. In this group only statistical significant improvement was found only in BMC (p=0.041).

**Table 4. Z-score according to the arthritis subtype.**

| Arthritis subtype | Baseline* | 12 mo** | *p*\| |
|---|---|---|---|
| Systemic | -2.14 | -1.87 | p=0.085 |
| Polyarticular, RF negative | -0.66 | -0.36 | **p=0.005** |
| Polyarticular, RF positive | -0.63 | -0.69 | p=0.377 |
| Oligoarticular, extended | -0.85 | -0.66 | **p=0.041** |
| Enthesitis related arthritis | -0.76 | -0.31 | **p=0.010** |

Intergroup (Kruskal Wallis).
*p=0.052; ** p=0.033

Results are presented on the table 4.

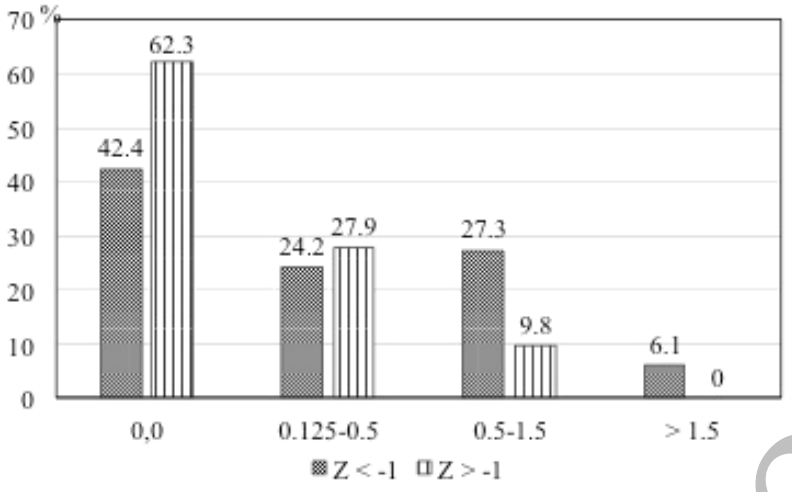
At the first osteodensitometry measurement 44 patients (46.8%) had Z-score



below -1SD, one year after 11/44 patients improved their Z-score ($p<0.01$ ). During the study period we observed significant height and weight increasing in of the patients (data not shown).

Disability index calculated from CHAQ negatively correlated with Z-score at the baseline, as well a year after ($p=0.017$ vs. $p=0.002$). One third of patients with moderate and severe functional limitation had Z score below -1SD from reference value. Seventy percent of patients with very low BMD (<-2SD) had moderate or severe disability on baseline, and 50% on the last examination. Values are presented on the figure 1.




*p*=0.021

**Figure 1. Correlation Z score with disability level on the last evaluation.**

BMD, BMC and $BMD_{vol}$ were lower in the GC group ($p<0.01$). At the end of study GC were stopped in 12/22 patients (54.4%), in 6/22 patients (27.3%) dosage of GC was decreased and in 4 patients (18.3%) the dosage of GC was not changed, all of them were nonresponders.

## DISCUSSION

Last 15 years outcome of children with JIA dramatically improved with introducing of biologics as regular therapeutic option. Etanercept has been the first anti TNF-blocker licensed for use in JIA. Remarkable, rapid and sustained efficacy of ETN in controlling inflammation, inhibiting progression of joint destruction and acceptable safety profile was confirmed [6,7].

We performed prospective study to investigate bone mineral status in patients with JIA treated one year with ETN. Our results confirmed excellent ETN efficacy in suppression disease activity, which reflected in PGA (improvement was high 82%), also in parent/patient's assessment, from clinical point of view (number of joints with active arthritis decreased from 9,7 to 0,2), as well laboratory signs of inflammation (ESR). Rapid decrement of C reactive protein and thrombocytes, and enhancement of hemoglobin also recorded, but data not shown.

There are many risk factors contribute to bone fragility: high level disease activity, poor nutrition, reduced physical activity, growth impairment, puberty delay and inability to reach adequate peak bone mineral accretion, treatment especially with GC and others According to Markula-Patjas et al. compressive fracture, mainly thoracic, were associated with high level of disease activity, high body mass index (BMI) and exposing to high dose of GC, but not with disease duration nor BMD [15].



Assessment of paediatric skeleton can be perform by many methods: x-ray, quantitative computed tomography, quantitative ultrasonography, magnetic resonance imaging, but DXA remains preferred method for clinical measurement of bone mineral density in children because of many advantages previously mentioned. Paediatric Position Development Conference of the International Society of Clinical Densitometry put JIA on the list of secondary diseases that may affect the skeleton and gave recommendations for interpretation of DXA results in paediatric population. The terms ″osteopenia″ and ″osteoporosis″ should be avoid in paediatric age. BMC and BMD Z-score 2 and more SD below expected should be labelled ″low for age″. Diagnosis of osteoporosis in children can be made when both low bone mass and bone fracture history are present [16].

In our previous study we confirmed decreased BMD in JIA patients, comparing with healthy peers (Z-score -1.02 vs. -0.09 SD, $p<0.001$). Systemic onset, polyarthritis, longer treatment and higher cumulative GC dosage, higher damage (functional status and radiologic stage) were risk factors for low BMD. Some of these patients were participated in this study but then were not treated with biologics [17]. This study didn't include control group, but patients were prospectively followed during one year and results on baseline served for further statistical analysis.

Lien et al. explored predictors of bone mass in children with early arthritis (mean disease duration 19.3 months) comparing with healthy children. Low BMD and BMC was defined as a value between -1 and -2 SD, and very low below -2 SD of reference values in a healthy population. During two-year follow-up period it was found that 24% of patients and 12% of controls had low and very low total BMC. Bone formation and resorption, as physical exercise against gravity were reduced in the patient group. The results of this study point out that bone metabolism disturbance begins in the early stages of the disease. Patients with polyarthritis had significantly lower BMC compared to the children with oligoarthritis [18].

In our study 28,7% had low, and very low BMD 18,1% at the baseline. This group belonged 17 patients, median disease duration 6,3 years, mean active joints 12, with moderate functional disability (CHAQ –DI 0,88). After one year of treatment number of patients with low BMD decreased to 19,2% and 15,9% of patients had Z-score below -2SD. Only one girl with sJIA had compressive vertebral fracure. Her Z-score on baseline was -3,9, decreased to the end of study to -4,4 SD, nonresponder , GC tretment duration 7 yrs.

French et al. [5] found that 40% of patients with JIA average age 35years, disease duration of 27 yrs. had osteopenia at the spine and femoral neck. Risk factors for developing OP were: second and more functional class during adolescence, inadequate participation in organized sports and other forms of physical activity during adolescence, smoking, insufficient dietary calcium intake during adolescence. According to the results majority of adult patients reached normal peak of bone mass, but it was significantly lower compared to the healthy population.



Unquestionable role on bone remodelling addressed to proinflammatory cytokines such as a tumor necrosis factor (TNF), interleukin (IL) 1, IL-6, IL- 17, as well matrix metalloproteinases (MMPs) produced in synovial membrane, which lead to destruction of joint bone and cartilage. Their presence in affected joints can cause excessive osteoclastogenesis , bone resorption and suppression of osteobastogenesis [19]

The first study addressed to bone mineral status on JIA patients treated with ETN published by Simonini et al. [20], included 20 pts. The patiens were younger and dises,e duration was shorter, and functional disabilty was higher than in our study. Bone status was determinated by broaband ultrasound attenuation (BUA) at the calcaneus, however he agreed that DXA remains gold standard for measuring BMD. After one year of ETN tretament responders showed higher BUA and Z score than nonresponders.

We found in the responder group important improvement in all densitometry variables compared to the baseline; in nonresponder group statistical significant improvement was only for BMC, which could be explain by increasing linear growth, which was observed, but data not present.

Patients with sJIA on both evaluations had the lowest Z-score and there was no increasing during treatment with anti TNF blocker. Similar results presented Stagi et al. [21] in large cohort group of 245 patients, wider range of age (9-28 yrs.) than our. Patients with sJIA had significant reduction in cortical and trabecular BMD as well compared to control group. In our group Z-score decreased in RF pJIA patients during one year. There were all female, 6/15 were treated with GK, CHAQ 0,725 corresponded to moderate functional disability. In sJIA patients Z score didn't significantly increase, confirmed that both JIA suptypes have unfavorable oucome resulting in joint destructuion and higher disability in adulthood.

It is well know deleterious effect of GC on inhibition of bone formation caused by a decrease in the number of osteoblasts which eventually leads to decrease in bone remodeling and increases the tendency towards fractures. Patients treated with GC had lower BMD compared to non GC treated in our group. On the last observation $BMD_{vol}$ and Z-score didn’t improved significantly. We didn’t analyse in more details GC group (duration, cumulative dosage etc). Thorton et al. [22] examined bone health in adults with history of JIA, oral GC was associated with lower BMD at both spine and hip. Similar results revealed in study Tang et al. [23], main predictors of low spine BMD were subtype JIA, disease activity, BMD, GC exposure.

It is undoubtly that reduced bone mass and density in JIA develope as results not olny impairment of bone turnover, but also lower muscle strenght, poorer physical health and hight level of funcional disability.

We are aware of some limitation of our study. We had no control group healthy children and did not include biochemical markers of bone turnover. One year of follow up period is too short for understanding all aspects of anti TNF blockers on bone mineral metabolism.



## CONCLUSION

Our results confirmed significant improvement in BMD during one year of treatment with ETN, as well its efficacy on disease activities. Longitudinal studies and larger cohort could give better understanding long-term outcome and safety of anti TNF blockers

In meantime our task as physicians is carefully monitor our patients, apply the best therapeutic options for better control disease activity and advice they to make some life changes as avoidance of smoking and alcohol excess, participation in weight-bearing exercise and sports activities, consuption of dietary calcium intake and vitamin D supplementation in order to prevent long-term consequences on growing skeleton.

## ACKNOWLEDGEMENT

We wish to thank Dr Dejan Stevanovic for helpful comments on the manuscript.

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