Gout – asymptomatic hyperuricemia with/without asymptomatic monosodium urate crystal deposition: to be treated or not?

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SUMMARY
Elevation of serum uric acid level without clinically visible arthritis (known as asymptomatic hyperuricemia) is not traditionally considered to be gout disease, but only a possible cause of it, even though it may be accompanied by tissue uric acid crystal deposition. On the other hand, gout is traditionally recognized as recurrent, overt arthritis, visible only after a long period of time due to uric acid accumulation in joints. Advanced imaging techniques have substantially changed the perception of this problem, identifying gout as a low-grade chronic inflammatory disease from the very beginning, visible only by phases of acute arthritis attacks. According to ultrasonography, uric acid crystal hyperechoic aggregates (tophi) are seen not only in the symptomatic gout disease phase, but also in the preceding – asymptomatic (latent) – gout phase. New perception of the problem was approved by the recently described NETs (neutrophil extracellular traps) phenomenon. Also, hyperuricemia has recently been identified as a systemic disorder, responsible not only for the apparent gout arthritis, but also for the renal and cardiovascular disease occurrence and progression.

Positive effect of urate-lowering therapy (xanthine oxidase inhibitors and uricosurics) on hypertension and chronic kidney disease indicates a possibility of its utility in asymptomatic hyperuricemia and asymptomatic gout therapy, apart from the use in clinically manifested gout treatment and for certain conditions, such as tumor lysis syndrome.

Keywords: asymptomatic hyperuricemia; monosodium urate crystal deposition; gout; advanced imaging studies; ultrasonography; NETosis

INTRODUCTION
Gout is an inflammatory rheumatic disease, characterized by monosodium urate (MSU) crystal deposition in joints and connective tissues generally, localized periarticularly or subcutaneously. According to the current diagnostic algorithm (New York, Rome, and the American College of Rheumatology criteria), the acute gout arthritis attack is traditionally required for gout diagnosis [1]. The classical gout disease goes through four linear but discontinuous phases: 1. asymptomatic hyperuricemia phase (AHU); 2. recurrent acute arthritis phase; 3. intercritical phase (between two episodes of gout arthritis); and 4. chronic tophaceous gout phase [2]. Actual therapeutic paradigm does not treat the first phase (AHU) patients, and therapy candidates are only those with a visible gout arthritis attack (at least one) or patients with chronic, visible, tophaceous gout [3–6].

Recently discovered phenomenon of NETosis (NET – neutrophil extracellular traps) in gout has enabled a closer evaluation of AHU [7–10], together with advanced imaging techniques [11–15], in vivo and in vitro laboratory studies, retro and prospective cohort studies and randomized interventional trials. They have all shown that UA is not only a marker, but also a mediator of hypertension and renal dysfunction, thus offering arguments for the present diagnostic and therapeutic recommendations amendment proposal.

PATHOGENESIS OF GOUT NETOSIS
Hyperuricemia (HU) is the key risk factor for gout development. However, only 22% of people with extremely high level of serum uric acid (SUA) (more than 535 μmol/L, i.e. 8.9 mg/dL) will develop symptomatic gout in a period of five-year follow-up [4]. In contrast, 5% of gouty patients will never be presented with the SUA elevation.

Additional risk factor for gout development is monosodium urate crystal deposition in tissues, followed by the local tissue reaction presented in persons with high SUA level and even in those with normouricaemia. Crystal deposition depends on UA solubility, which is variable and decreased by high serum uric acid concentration, as well as by high acidity and low temperature.

Initiated by UA serum supersaturation, joint and connective tissue localized crystallization leads to the activation of cytokines and other inflammatory mediators. Interleukin 1β is the
principal and the most important proinflammatory cytokine, produced by resident cells of connective tissue, after the NALP3 inflammasome activation. Macrophage phagocytosis of monosodium urate crystals leads to intra-cellular hyperuricemia, hyperuricemia and consequently hypokalemia, as well as to cascade of NALP3 inflammasome activation and caspase-dependent activation of IL1β path (from proIL1β). Secretion of IL1β attracts neutrophils, which support the inflammatory response by pro-inflammatory mediators’ production and excretion [7].

As it is a well-known fact that signs and symptoms of inflammation do not follow TOPHUS (pathognomonic structure in gout patients) presence in patients with chronic gout, the following question was raised: Which is the way that leads to the resolution of the inflammatory response and pacification of crystals in TOPHUS? This question has been waiting for an answer for a long time.

According to recent *in vivo* and *in vitro* studies, the induction and resolution of gout inflammation is orchestrated by both monocytes and granulocytes. Neutrophils act not only through phagocytosis, intraphagosomal digestion and secretion of inflammatory mediators, but also through creation of the neutrophil extracellular traps (NETs), which are defined as the active cell death, different from apoptosis and necrosis [7–10]. NET histochemically represents extracellular DNA of neutrophils and proteolytic enzymes (elastase, cathepsin G, myeloperoxidase-MPO complex). NET structure limits the spread of the aggressive entity (in this case, crystal) both chemically and mechanically by inflammatory mediators’ proteolytic degradation. MSU crystals are the most powerful drivers of NETosis under almost all physiological conditions, including whole blood and plasma.

Patients with acute uric arthritis resolution are presented with robust NETosis (activation and release of NETs) in the synovial fluid as well. Furthermore, TOPHUS is traditionally associated with poorly controlled chronic disease and can actually be found in all stages of the disease. TOPHUS is composed not only of natrium sodium urate crystals, but also of extracellular DNA and neutrophil proteolytic enzymes that neutralize crystals mechanically and chemically (has, in fact, all the characteristics of the above-mentioned NET aggregate). Adenosine triphosphate disodium (ATP) and lactoferrin, which are released during the NET formation process, are extremely important for the inflammatory reaction resolution. Activation of extracellular nucleotides from mononuclear cells initiates the necrotic cell clearance, while lactoferrin serves as a specific inhibitor of the polymorphonuclear migration.

### Table 1. Echosonographic evidence in asymptomatic hyperuricemia

<table>
<thead>
<tr>
<th>Publication</th>
<th>SUA in AHU mg/dL (μmol/L)</th>
<th>US evidence</th>
<th>Joints</th>
<th>Frequency (%)</th>
<th>Controls</th>
<th>Gout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puig et al.¹</td>
<td>8.5 (505.6)</td>
<td>Tophi</td>
<td>Knees and TC</td>
<td>12/35 (34%)</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Howard et al.²</td>
<td>8 (475.8)</td>
<td>Double contour and/or tophi</td>
<td>Femoral cartilage and MTP1</td>
<td>5/17 (29%)</td>
<td>1/19 (5%)</td>
<td>7/14 (50%)</td>
</tr>
<tr>
<td>Pineda et al.³</td>
<td>8.1 (481.8)</td>
<td>Double contour</td>
<td>Knees and MTP1</td>
<td>17/100 (17%) knees; 25/100 (25%) MTP1</td>
<td>0/104 knees</td>
<td>0/104 MTP1</td>
</tr>
<tr>
<td>De Miquel et al.⁴</td>
<td>8.5 (505.6)</td>
<td>Double contour or hyperechoic spots</td>
<td>Knees and feet</td>
<td>11/26 (42%); 9/11 (81.8%) + crystal</td>
<td>/</td>
<td>/</td>
</tr>
</tbody>
</table>

SUA – serum uric acid; AHU – asymptomatic hyperuricemia; US – ultrasound; TC – talocrural joint; MTP1 – first metatarsophalangeal joint.

¹Nucleosides Nucleotides Nucleic Acids. 2008; 27:592–5;
²Arthritis Care Res. 2011; 63:1556–62;

**ULTRASONOGRAPHY IN GOUT AND ASYMPTOMATIC HYPERURICEMIA**

Owing to advanced imaging techniques (ultrasound, magnetic resonance imaging, computed tomography), asymptomatic synovial sheath inflammation can be seen in joints that have never been presented with the traditional, clinically visible gout arthritis [11–15]. It can also be presented in the so-called intercritical period (between two apparent gout arthritis attacks). Furthermore, ultrasound displays MSU crystal deposition in tissues as a structural change of the articular cartilage, showing either a double contour sign or the TOPHUS formation, and can be found not only in the inflamed joints, but also in joints that have never been affected by overt arthritis [13] (Table 1). Sensitivity of the ultrasound urate tissue deposition finding (double contour sign or TOPHUS) is variable and ranges 20–90%, which depends on previous therapy (treated or not), data availability (blinded or unblinded research), study type (prospective or retrospective), type of observed joints, etc. The specificity is 98–100%.

The most acceptable balance of sensitivity and specificity was reached by Naredo et al. [11] ultrasound examination standard recommendation, which demands evaluation of six anatomic structures bilaterally and simultaneously (12 regions): three structures for TOPHUS hyperechoic aggregates – one joint (radiocarpal) and two tendons (patellar ligament and the triceps muscle tendon) – and three cartilages for the double contour sign – first metatarsophalangeal joint, second metacarpophalangeal joint and calcaneal or femoral condylus cartilage. The sensitivity of Naredo et al. [11] examination was 85%, specificity 83%, positive predictive value 92%, and negative predictive value 71%.

The new possibilities of ultrasound examination have substantially changed the perception of gout, which seems to be a chronic inflammatory disease from the very beginning, only expressed by different levels of activity (visible or not). Acute, vigorous gout arthritis is just a tip of the iceberg which enables us to see gout (Figure 1), just like an
HYPERURICAEMIA: THE PRINCIPAL RISK FACTOR FOR METABOLIC SYNDROME, HYPERTENSION, AND RENAL FAILURE OCCURRENCE

UA has been identified as not only the marker, but also a mediator of hypertension, cardiovascular morbidity and progressive decline in renal function by a number of recently reported studies from animal models, clinical retro and prospective observational studies, and randomized intervention trials [16–27]. According to the latest data, the paradigm of the causative association between hyperuricemia and cardiovascular and chronic kidney disease seems to have progressed from skepticism to true evidence of relationship [17, 18]. However, therapy remains controversial [19].

UA is known as the major antioxidant agent in human plasma. However, its antioxidant nature comes to its own opposite within the cell, where it paradoxically converts to pro-oxidant agent, which mostly targets lipids [low-density lipoproteins (LDL) and membranes] [16]. Cirillo et al. [20] have noticed elevated SUA level in patients with metabolic syndrome and have concluded that uric acid is not just a link in the metabolic syndrome chain, but plays a crucial role in its development. UA-caused adipose tissue fat cell oxidation promotes insulin resistance that leads to hypertension, visceral obesity, hypertriglyceridemia, dyslipidemia and hyperglycemia.

In addition to LDL oxidation caused by the prooxidant SUA effect, the atherosclerotic process is started by the nitric oxide production (also known as the endothelium-derived relaxing factor – EDRF), which leads to endothelial function [28]. However, its antioxidant nature comes to its own within the cell, where it paradoxically converts to pro-oxidant agent, which mostly targets lipids [low-density lipoproteins (LDL) and membranes] [16]. Cirillo et al. [20] have noticed elevated SUA level in patients with metabolic syndrome and have concluded that uric acid is not just a link in the metabolic syndrome chain, but plays a crucial role in its development. UA-caused adipose tissue fat cell oxidation promotes insulin resistance that leads to hypertension, visceral obesity, hypertriglyceridemia, dyslipidemia and hyperglycemia.

Furthermore, hyperuricemia-activated renin-angiotensin-aldosterone system adds to hypertension development. Kidney UA crystal deposition promotes stone occurrence, tubulointerstitial nephritis and fibrosis which additionally leads to hypertension, renal function decline and UA serum level increase. It is not exactly known which process serves as a trigger factor in the newly created Circulus vitiosus, but certainly there is a chain that should be interrupted (Figure 2).

The impact of hypo-uricaemic therapy on the cardiovascular events’ occurrence risk is not fully understood yet. An improvement of endothelial function has been shown by a small number of interventional trials using XO inhibitors. In patients with chronic heart failure and HU, vasodilation enabled by XO inhibitors improves the blood flow. Indeed, significant blood pressure decline was observed in patients who received antihypertensive therapy combined with allopurinol, as compared to antihypertensives alone [25]. Finally, a significant reduction in cardiovascular morbidity and mortality was shown in gout patients on higher allopurinol dosage and with lower SUA level, according to a large retrospective cohort study [26].

Allopurinol-achieved low SUA level is not always correlated with an improvement of the endothelial function. Also, recent investigations advised caution when using allopurinol, since it can have side effects, such as induced gout attacks, elevated aminotransferases, and cytopenia) [19]. On the other hand, uricosuric agents such as probenecid and benzbromarone did not show similar benefit on endothelial function [28].

Management of asymptomatic hyperuricemia has been approved in Japan only, for people with SUA level more than 9 mg/dL [29]. This subject is very complex, since osteoporotic fracture makes the osteoporosis visible. Since the advanced imaging techniques have enabled diagnosis of gout in its subclinical, latent, inapparent form, the question of the asymptomatic disease therapy was raised. Here, we have offered some arguments that asymptomatic hyperuricemia with MSU crystal deposition could be regarded and treated as the gout disease.

Figure 1. The course of the gout disease (iceberg);
Tip: symptomatic disease, traditionally presented with clinically visible arthritis with/without monosodium urate crystal deposition;
Middle: latent gout, presented as asymptomatic hyperuricemia and monosodium urate crystal deposition (as seen by advanced imaging techniques) that could be considered as gout as well, thus raising the question of therapy (further described in the text);
Basis: asymptomatic hyperuricemia without urate tissue depositions leads to controversies in terms of therapy, due to a potential effect of this state on cardiovascular events and decline in renal function

Figure 2. Circulus vitiosus made of high serum uric acid level, atherosclerosis, and renal function decline;
there is no reliable data to make strong international recommendations yet. The most recent European League Against Rheumatism evidence-based recommendations for the management of the gout state that recent studies have yielded conflict the results regarding asymptomatic hyperuricemia treatment [3].

Indeed, genetic evidence based on conventional and novel Mendelian randomization approaches suggest a modest, if any, causal effect of SUA concentration on the development of cardiovascular disease [30]. A collaborative group from Europe, New Zealand, United States, etc. has collected more than 400,000 samples from gout patients to perform the largest genome-wide associated study ever conducted in people with gout and the data should be available by the end of 2019 (thanks to prof Richette Pascal).

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CONCLUSION

Here we have offered arguments that asymptomatic hyperuricemia with tissue urate crystal deposition (latent gout) could be regarded as gout and treated accordingly, bearing in mind the promotive effects of hyperuricemia on hypertension, cardiovascular disease, and renal disease. Further studies identifying the guidelines for the therapy regime for asymptomatic hyperuricemia would be beneficial.

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ГИХТ – АСИМПТОМАТСКА ХИПЕРУРИКЕМИЈА СА АСИМПТОМАТСКИМ ТАЛОЖЕЊЕМ КРИСТАЛА МОНОНАТРИЈУМ-УРАТА И БЕЗ ЊЕГА: ДА ЛИ ЛЕЧИТИ?

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САЖЕТАК
Повишен ниво мокраћне киселине у серуму без клиничких знакова артритиса (познат као асимптоматска хиперурикемија) традиционално се не схвата као гихт, већ само као могућа (претходна) фаза ове болести, мада може бити повезан са депозицијом кристала мокраћне киселине у ткивима. С друге стране, гихт се традиционално препознаје као рецидивирајући, видљиви артритис који се јавља само после дужег трајања болести због акумулације мокраћне киселине у зglobовима. Напредне технике снимања суштински су промениле перцепцију овог проблема, показавши да је гихт од самог почетка хронично инфламаторно обољење ниског степена активности, а да га епизода акутног артритиса само чини видљивим. Као што је доказано ултразвуком, интраартикуларни хиперекоични агрегати кристала мокраћне киселине (тофуси) налазе се не само у симптоматској фази гихта већ и у претходној – асимптоматској (патентној) фази. Нову перцепцију проблема потврдио је недавно описан феномен NET-озе (неутрофилних екстрацилијских замки). Такође, хиперурикемија се у последње време сматра системском болесном, одговорном не само за видљив напад артритиса већ и за настанак и прогресију реналних и кардиоваскуларних болести.

Позитиван утицај лекова који смањују ниво мокраћне киселине у серуму (инхибитора ксантин-оксидазе и урикозурика) на хипертензију и хроничну бубрежну болест индикује могућност њихове примене у лечењу асимптоматске хиперурикемије и асимптоматског гихта, поред редовне употребе код клинички манифестног гихта и у одређеним стањима (као што је синдром лизе тумора).

Кључне речи: асимптоматска хиперурикемија; таложење кристала мокраћне киселине; ултразвук; неутрофилне екстрацилијске замке