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Marija Radak-Perović^{1,2}, Mirjana Zlatković-Švenda^{1,2,†}

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monosodium urate crystal deposition: to be treated or not?**

Гихт – асимптоматска хиперурикемија са асимптоматским таложењем
кристала мононатријум урата и без њега: да ли лечити?

¹University of Belgrade, Faculty of Medicine, Belgrade, Serbia;

²Institute of Rheumatology, Belgrade, Serbia

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†Correspondence to:

Mirjana ZLATKOVIĆ-ŠVENDA

Institute of Rheumatology, Resavska 69, 11000 Belgrade, Serbia

E-mail: mirjanazlatkovicsvenda@gmail.com

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

Гихт – асимптоматска хиперурикемија са асимптоматским таложењем кристала мононатријум урата и без њега: да ли лечити?

SUMMARY

Elevation of serum uric acid (SUA) level with no clinically visible arthritis (known as asymptomatic hyperuricemia – AHU) is not traditionally considered as a gout disease, but only as a possible (preceding) cause of it, even though may be accompanied with tissue uric acid crystal deposition. On the other hand, gout is traditionally recognized as a 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 the low-grade chronic inflammatory disease from the very beginning, visible only by phases of acute arthritis attacks. According to ultrasound, UA 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 recently described NETs (neutrophil extracellular traps) phenomenon. Also, HU was identified as a systemic disorder lately, 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 (Xantine oxidase-XO inhibitors and uricosurics) on hypertension and chronic kidney disease indicates possibility of their utility in asymptomatic hyperuricemia and asymptomatic gout therapy, apart from usage in clinically manifested gout treatment and for certain conditions (like tumor lysis syndrome is).

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

САЖЕТАК

Повишен ниво мокраћне киселине (МК) 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. Са друге стране, гихт се традиционално препознаје као рецидивирајући, видљиви артритис који се јавља само након дужег трајања болести због акумулације мокраћне киселине у зглобовима.

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 епизоде акутног артритиса само чини видљивим. Као што је доказано ултразвук, интраартикуларни хиперехоични агрегати кристала МК (тофуси) налазе се не само у симптоматској фази гихта, већ и у претходној- асимптоматској (латентној) фази. Нову перцепцију проблема потврдио је недавно описан феномен *NET*-озе (неутрофилних екстраћелијских замки). Такође, хиперурикемија се у последње време сматра системском болешћу, 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; гихт; имагинг студије; ултразвук; неутрофилне екстраћелијске замке

INTRODUCTION

Gout is the inflammatory rheumatic disease, characterized by monosodium urate (MSU) crystal deposition in joints and connective tissues generally, localized periarticular or subcutaneous. According to current diagnostic algorithm (New York, Rome and ACR criteria), the acute gout arthritis attack is traditionally demanded for diagnosis of gout [1]. The classical gout disease goes through four linear, but discontinual phases: 1. asymptomatic hyperuricemia phase (AHU), 2. recurrent acute arthritis phase, 3. intercritic phase (between the 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 visible gout arthritis attack (at least one) or patients with chronic, visible, tophaceous gout [3-6].

Recently discovered phenomenon of NETosis (neutrophil extracellular traps) in gout has enabled 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 [20-28]. 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 the gout development. However, only 22% of people with extremely high level of serum uric acid (SUA) (more than 535 $\mu\text{mol/L}$, e.g. 8,9 mg/dL) will develop symptomatic gout during the five years period of follow-up [4]. On the contrary, 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 those with normouricaemia. Crystal deposition depends on UA solubility (variable and mostly dependent on UA concentration), which decreases its solubility, as well as high acidity and low temperature.

Initiated by UA serum supersaturation, joint and connective tissue localised crystallization leads to activation of cytokines and other inflammatory mediators. Interleukin 1β is the principal and the most important proinflammatory cytokine, produced by residential cells of connective tissue, after the NALP3 inflammasome activation. Macrophage phagocytosis of monosodium urate crystals leads to intracellular hypernatremia, hypervolemia and consequently hypokalemia as well as to cascade of NALP3 inflammasome activation and caspase-dependent activation of $IL1\beta$ path (from pro $IL1\beta$). Secretion of $IL1\beta$ attracts neutrophils, which support the inflammatory response by proinflammatory 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 question was raised: Which is the way that leads to 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 monocytes and granulocytes, both. Neutrophils act not only through phagocytosis, intraphagosomal digestion and secretion of inflammatory mediators, but also through creation of the neutrophil extracellular traps (NETs) [7-10], which are defined as the active cell death, different from apoptosis and necrosis. 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. Monosodium urate crystals (MSU) 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 sodium urate crystals, but also of extracellular DNA and neutrophil proteolytic enzymes that neutralize crystals mechanically and chemically (has all characteristics of the above-mentioned NET aggregate, actually). 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.

ULTRASONOGRAPHY IN GOUT AND ASYMPTOMATIC HYPERURICEMIA

Owing to advanced imaging techniques (ultrasound, MRI, CT) [11-15], asymptomatic synovial sheath inflammation can be seen in joints that have never been presented with the traditional, clinically visible gout arthritis. It can also be presented in the so-called

intercritical period (between the two apparent gout arthritis attacks). Furthermore, ultrasound (US) displays MSU crystal deposition in tissues as structural change of the articular cartilage, showing either a double contour sign (please, see ref 20) or the TOPHUS formation, and can be found not only in the inflamed joints, but also in joints that have never been affected by an overt arthritis [13] (Table 1). Sensitivity of the ultrasound urate tissue deposition finding (double contour sign or tophus) is variable and ranges from 20% to 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 US examination standard recommendation [11], which demands evaluation of 6 anatomic structures bilaterally and simultaneously (12 regions): 3 structures for TOPHUS hyperechoic aggregates: 1 joint-radiocarpal and 2 tendons -patellar ligament and the triceps muscle tendon AND 3 cartilages for the DOUBLE CONTOUR sign: first metatarsophalangeal joint, second metacarpophalangeal joint and calcaneal or femoral condylus cartilage. The sensitivity of Naredo's examination is 85%, specificity 83%, positive predictive value 92% and negative predictive value 71% [11].

New possibilities of the US examination utility have substantially changed the perception of gout, which seems to be the 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 the 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.

HYPERURICAEMIA: THE PRINCIPAL RISK FACTOR FOR METABOLIC SYNDROME, HYPERTENSION AND RENAL FAILURE OCCURENCE

UA has been identified as not only the marker, but also a mediator of hypertension, cardiovascular morbidity and progressive declinment 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 latest data, paradigm of the causative association between hyperuricemia and cardiovascular and chronic kidney disease seems to have progressed from skepticism to a true evidence of relationship [17,18]. However, therapy remains controversial [19].

Uric acid 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 (LDL and membranes) [16]. Cirillo et al. have noticed elevated serum uric acid level in patients with metabolic syndrome [20], 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-NO production (also known as the endothelium derived relaxing factor-EDRF), which leads to endovascular inflammation and inflammatory mediators cascade reaction primarily. LDL oxidation and vasoconstriction lead to stable atherosclerotic plaque formation, which becomes unstable in time, resulting in a well-known diversity of cardiovascular events.

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 declinment and UA serum level incresement. 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).

Impact of hypo-uricaemic therapy on cardiovascular events occurrence risk has not been fully understood yet. 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, vasodilatation enabled by XO inhibitors improves the blood flow. Indeed, significant blood pressure declinment was observed in patients who received antihypertensive therapy combined with Allopurinol, as compared to antihypertensives alone [25]. Finally, 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 improvement of the endothelial function. Also, recent investigations advice caution when using Allopurinol, since it can have ceratin side effects, such are induced gout attacks, elevated aminotransferases and cytopenias) [19]. On the other side, uricosuric agents such as Probenecide and Benzbromarone did not show similar benefit on endothelial function [28].

Management of asymptomatic hyperuricemia was approved in Japan only, for people with SUA level more than 9 mg/dL [29]. This subject is very complex, since there are no reliable data to make strong international recommendations yet. The last EULAR evidence-based recommendations for the management of gout stated that recent studies have yielded conflicting results regarding asymptomatic hyperuricemia treatment [3].

Indeed, genetic evidence based on conventional and novel Mendelian randomisation approaches suggest a modest, if any, causal effect of serum uric acid 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 data should be given by the end of 2019 [thanks to prof Richette Pascal].

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 HU on hypertension, cardiovascular disease and renal disease. Further studies identifying guidelines for the therapy regime for asymptomatic hyperuricaemia would be beneficial.

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Table 1. Echasonographic evidence in asymptomatic hyperuricemia

Publication	SUA in AHU mg/dl ($\mu\text{mol/L}$)	US evidence	Joints	Frequency (%)	Controls	Gout
Puig et al. ¹	8.5 (505.6)	Tophi	Knees and TC	12/35 (34%)	/	/
Howard et al. ²	8.0 (475.8)	Double contour and/or tophi	Femoral cartilage and MTP1	5/17 (29%)	1/19 (5%)	7/14 (50%)
Pineda et al. ³	8.1 (481.8)	Double contour	Knees and MTP1	17/100 (17%) knees; 25/100 (25%) MTP1	0/104 knees 0/104 MTP1	/
De Miquel et al. ⁴	8.5 (505.6)	Double contour or hyperechoic spots	Knees and feet	11/26 (42%); 9/11 (81.8%) + crystal	/	/

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

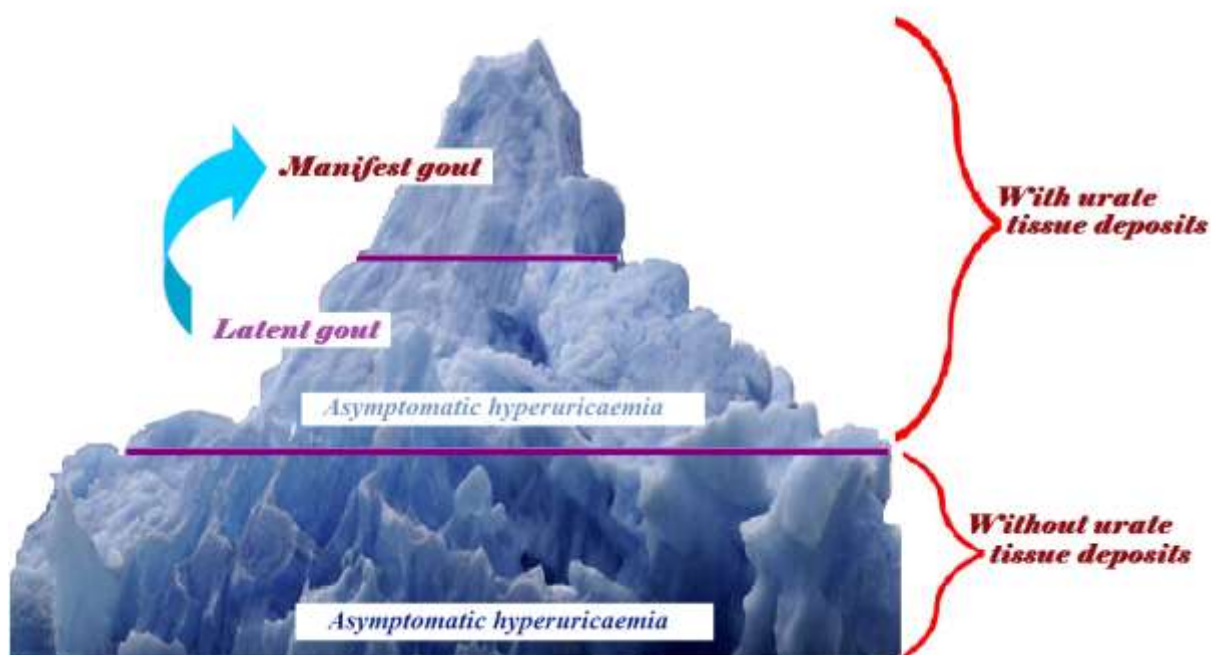
¹Nucleosides Nucleotides Nucleic Acids 2008;27:592-5;

²Arthritis Care Res 2011;63:1456-62;

³Arthritis Res Ther 2011;13(1):R4;

⁴Ann Rheum Dis 2012;71:157-8

Figure 1. The course of the gout disease (iceberg)

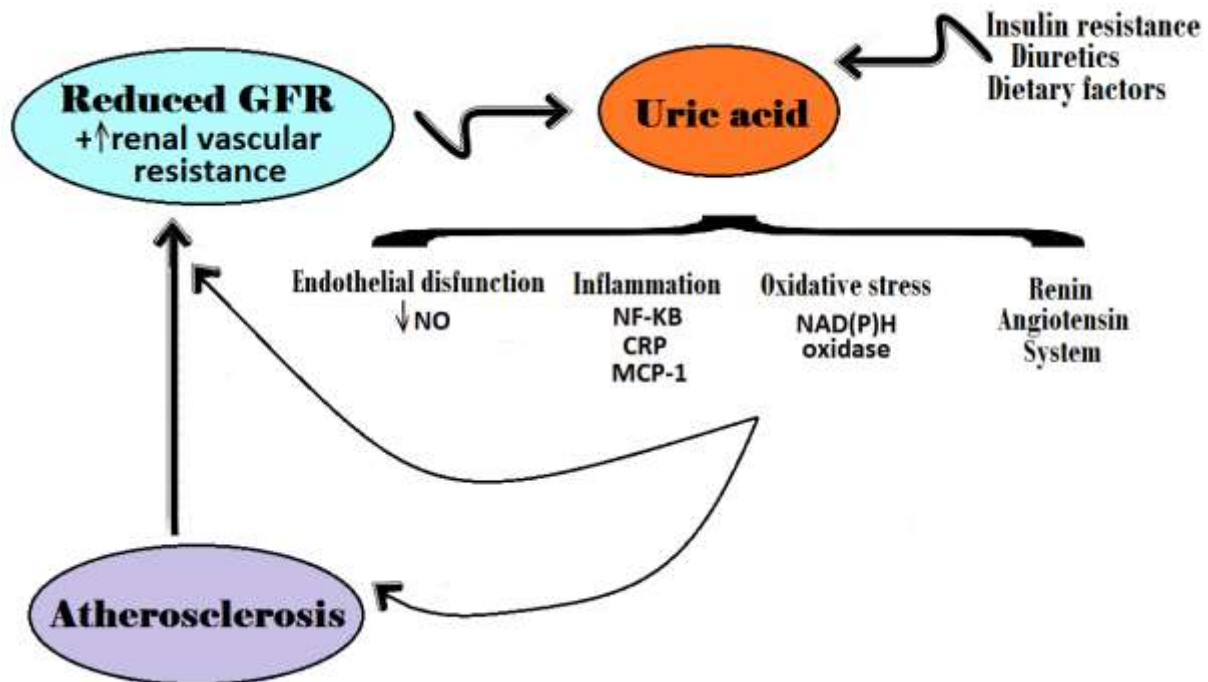


TIP: symptomatic disease, traditionally presented with clinically visible arthritis with/without monosodium urate crystal deposition

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 promotive 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



GFR – glomerular filtration rate; NO – nitric oxide; NF-KB – nuclear factor kappa-light-chain-enhancer of activated B cells; CRP – C-reactive protein; MCP-1 – monocyte chemotactic protein-1; NAD(P)H – nicotinamide adenine dinucleotide phosphate-oxidase

Source: Am J Kidney Dis 2012 The National Kidney Foundation