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Review article

Gout, hyperuricemia and chronic kidney disease: New treatment possibilities

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ABSTRACT

Introduction: Gout remains one of the most frequent diseases of joints and soft tissues. Apart from symptomatic gout, uric acid is also involved in pathogenesis and progression of several other diseases such as chronic kidney disease, hypertension, metabolic syndrome and cardiovascular disease.

Aim: To describe the role of uric acid in the development of chronic diseases such as chronic kidney disease, hypertension, metabolic syndrome and cardiovascular disease. We also aimed to discuss the role of uric acid in the development of gout, considered the most typical manifestation of hyperuricemia. The important task of our work was also identification of 'classical' and newest therapeutic strategies aimed to lower uric acid level and to improve the diseases that might be triggered with hyperuricemia.

Material and methods: We searched the latest literature in the field identifying studies describing the different roles of uric acid in the development of several diseases. We also found and described latest clinical trials focused on therapeutic lowering of hyperuricemia.

Discussion: Increasing evidence suggests contribution of uric acid in the development of chronic diseases, including chronic kidney disease, cardiovascular disease, hypertension and metabolic syndrome. The development of these pathologies may be controlled by effective lowering of hyperuricemia using both 'classical' drugs (i.e. allopurinol) and the newer agents (i.e. febuxostat).

Conclusions: Uric acid contributes to the development of several chronic, potentially life-threatening diseases. Hyperuricemia control should be considered as one of the strategies in their treatment.

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1. Introduction

Gout remains one of the most frequent diseases of joints and soft tissues. Its prevalence is continuously increasing, especially in the developed world. It affects up to 2% of the general adult population and is especially frequent among males over 40 years of age who concomitantly suffer from metabolic syndrome. The disease is triggered by the uric acid (UA) crystal precipitation within the tissues, that is secondary to elevated serum UA level (hyperuricemia). Acute arthritis represents the most typical clinical manifestation of gout – UA crystallizes within synovial fluid; crystal phagocytosis results in an acute inflammation.[1–3] Except for full-blown, acute and symptomatic gout, chronic and apparently asymptomatic hyperuricemia is also associated with certain health risk, resulting in increased risk for cardiovascular disease (CVD), chronic kidney disease (CKD), and kidney stone disease.

2. Aim

To describe the role of UA in the development of such chronic diseases such as CKD, hypertension, metabolic syndrome and CVD. We also aimed to discuss the role of UA in the development of gout, considered the most typical manifestation of hyperuricemia. The important task of our work was also identification of 'classical' and newest therapeutic strategies aimed to lower UA level and to improve the diseases that might be triggered with hyperuricemia.

3. Material and methods

We searched the latest literature in the field identifying studies describing the different roles of UA in the development of several diseases. We also found and described the latest clinical trials focused on therapeutic lowering of hyperuricemia.

4. Discussion

4.1. *Hyperuricemia vs. gout*

UA represents the end-product of purine metabolism. One-third of UA is ingested with diet, whereas remaining two-thirds are generated endogenously. Purine turnover takes place using several enzymes (with a key enzyme xanthine oxidase) – they are metabolized via inosine and guanine into hypoxanthine, xanthine, and finally UA. In man and other primates purine metabolism ends up at this level (i.e. with UA as a final product). In most mammals, however, another step of metabolism is present, namely further conversion of UA into much more water-soluble allantoin (using an enzyme uricase – urate oxidase).[2]

UA is excreted from the body in up to 70% with urine and with feces. UA as a small molecule is completely filtered in glomeruli, but later on the proximal tubular resorption and re-secretion occur. These processes result in effective UA clearance equalling 10–12% of the amount filtered initially in the glomeruli.[4,5] Urate anion transporter URAT1, belonging to the organic anion transporter protein superfamily constitutes the key pathway of this reabsorption; it exchanges UA for several anions, such as lactate, β-hydroxybutyrate, acetoacetate and certain drugs (such as salicylates, pyrazinamide). In turn, drugs such as benzbromarone, losartan, or fenofibrate can inhibit this transporter.[6]

In total 250–750 mg of UA is synthesized from endogenous purines and ingested from diet over 24 h; hence the same amount must become excreted. If the daily supply exceeds physiologic UA elimination capacity or there is any impairment in such an elimination, hyperuricemia develops.[5]

Serum UA concentration of around 6.8 mg/dL is considered as a saturation point of monosodium urate (MSU) (above this level sodium urate crystals may start to precipitate, with possible deposition within soft tissues, joint cartilages and synovial fluid).[7] Lowering pH or temperature may trigger precipitation in lower concentration. Thus the body regions that are at the highest risk for exposure to crystals include peripheral tissues with reduced temperature and relatively reduced perfusion (such as tendons, cartilages, distal parts of extremities).[2,5] The amount of 1 600 mg of UA can be dissolved in 1 L of urine with pH of 7.0; this value falls down to as low as 60 mg/dL in pH 5.0.[8]

MSU precipitates and accumulates predominantly in synovial fluid; the deposits are called 'tophi.' Their accumulation within the joints leads to the destruction of articular cartilages with development of erosions. Crystals are also subjected to phagocytosis by monocytes – interleukin 1β (IL-1β) released during this process is considered the key inflammatory cytokine mediating joint damage in gout. IL-1β interacts with respective receptor and it leads to synthesis and release other proinflammatory mediators (including tumor necrosis factor α and prostaglandin PGE2). They activate migration of neutrophils – neutrophils that phagocyte apoptotic cells and crystals accumulate in synovial fluid and this finding is considered typical for gouty arthropathy. Proinflammatory cytokines promote chronic damage of articular surfaces by means of chondrocyte apoptosis, inhibition of collagen synthesis, increased synthesis and release of metalloproteinases and osteoclast activation. Inflammatory reaction may be recurrent, with periods of flares and remissions.[1,5,9,10]

4.2. *Risk factors for development of gout*

Among modifiable risk factors for the development of gout the most important factors include diet, alcohol consumption, certain drugs, obesity and hyperlipidemia, diabetes, hypertension and smoking. Age, male sex, genetic background and to some extent CKD constitute the most important non-modifiable factors.[5,11–13]

Hyperuricemia may result from excess intake/endogenous synthesis of UA and impaired UA excretion. High dietary consumption of purine-rich products has been known for decades a key factor for development of gout. Alcohol not only leads to increased endogenous generation of UA, but also impairs its excretion via interaction with proximal tubules. Excess drinking of beverages sweetened with fructose syrup may also trigger synthesis of UA. Fructose metabolism consumes ATP and leads to accumulation of adenosine

monophosphate (AMP); AMP is further metabolized into UA. This metabolic process is not controlled in a negative feedback loop – fructose turnover depends mainly on the amount of substrate. Hence the increased fructose intake directly translates into increased UA synthesis.[14–16]

Excess of purine may also result from increased breakdown of cells and tissues. This is especially the case in hemato-oncologic disorders (after treatment initiation, with development of tumor lysis syndrome). Nucleic acids released from damaged cells are metabolized to UA; concomitant release of excess phosphate and potassium, and profound secondary hypocalcemia may lead to life-threatening acute kidney injury. Quite similar situation may develop in the course of massive rhabdomyolysis.[17–20] Among drugs that significantly impact on UA elimination and may lead to hyperuricemia, the most important ones are thiazide diuretics; these drugs reduce renal excretion of UA.[5,21] Drugs used in almost all immunosuppressive protocols in organ transplant recipients and some autoimmune diseases, i.e. calcineurin inhibitors (tacrolimus, cyclosporine) also impair UA elimination.[3] Other drugs that may increase serum UA include L-DOPA, nicotinic acid and tuberculostatic agents (ethambutol, pyrazinamide).[3,10,22]

Diabetes, arterial hypertension and obesity are generally accepted, modifiable risk factors for hyperuricemia. Hyperinsulinemia with insulin resistance decrease clearance of UA, which may result in hyperuricemia in subjects with impaired glucose tolerance, before the onset of diabetes. Obesity and even moderate increase of body weight above the 'ideal' one comprise risk factors for hyperuricemia. It has been demonstrated that even BMI over 23 kg/m^2 is already associated with higher likelihood of developing gout.[23] Hypertension and hyperuricemia interact one with another – hypertension increases risk of hyperuricemia, and in turn – hyperuricemia leads to blood pressure increase. Prevalence of hyperuricemia in hypertensive patients exceeds its prevalence in normotensive patients several times. It has been demonstrated in a large, population-based study from the Framingham cohort that increased serum UA is an independent risk factor for development of hypertension.[2,12,23,24]

Hyperuricemia was also shown to increase the risk of metabolic syndrome, de novo type 2 diabetes, CKD, CVD and cardiovascular events. UA excess contributes to endothelial dysfunction and increased plasma renin activity.[2,22]

4.3. *Hyperuricemia and CKD*

Considering the link between hyperuricemia and CKD we face the 'chicken or egg' dilemma. Kidney plays a fundamental role in UA elimination (with predominant role of proximal tubules). This is why in chronic kidney problems that primarily affect tubulointerstitial compartment earlier and more pronounced rise in serum UA might be expected. On the other hand, hyperuricemia as a primary event leads to increased UA concentration within renal tissue (interstitium), tubules, and urinary tract. This may lead to precipitation of UA which may trigger local, chronic inflammation (and – less frequently – may result in acute kidney injury).[1] Inflammation in response to microtophi is not a single mechanism of kidney injury. Hyperuricemia also stimulates renin release, inhibits nitric oxide synthesis, promotes inflammation at the level of renal microcirculation, activates platelets and may lead to intraglomerular hypertension. When acting in a prolonged manner hyperuricemia may result in hypertrophy and sclerosis of glomeruli, and interstitial fibrosis.[2,22]

Given the crucial role of the kidneys in an elimination of UA one can expect hyperuricemia and its adverse impact on kidneys in most of CKD patients. However in the setting of CKD UA elimination by single nephron significantly increases, together with increased loss of UA via gastrointestinal tract. Owing to these compensatory mechanisms many patients with CKD still have normal serum UA. This is best illustrated by the fact that elevated serum UA is found in around 50% of end-stage renal disease patients.[25]

Elevated serum UA in patients suffering from diabetes has also certain adverse effects on the kidney. Diabetic patients with chronic hyperuricosuria are more prone to develop diabetic nephropathy with albuminuria and higher rate of glomerural filtration rate (GFR) loss. It has been shown in type 1 diabetics that even high normal level of UA is a strong predictor of renal complications.[22,25,26]

In the RISK trial, a Polish study on hypertension it has been demonstrated that hyperuricemia in hypertensive subjects is linked to development and progression of CKD.[24] High UA was also shown to predict progression of CKD in subjects with primary glomerular disease, for example with IgA nephropathy.[22] In many observations an independent impact of UA on CKD progression (including end-stage renal disease) has been documented.[25]

The opposite data, however, can also be found. In some studies hyperuricemia was not an independent risk factor for further progression of CKD in patients with CKD stages 3 and 4 (although it remained a predictor of adverse cardiovascular outcome in this patient group).[22,27]

Hyperuricosuria is also a risk factor for stone formation – development of UA-containing stones depends more on UA excretion with urine rather than on hyperuricemia.[1]

Stones may develop also in normouricemic subjects who have hyperuricosuria, especially those with chronically lowered urine pH.[7]

Another issue concerning UA in relations to kidney disease should be mentioned, namely hyperuricemia and gout in organ transplant recipients. It is estimated that up to 85% of kidney transplant recipients may suffer from hyperuricemia. Cyclosporine use, impaired graft function and infections following transplantation are among the key factors leading to elevate serum UA. Posttransplant gout may include many joints already at the disease onset, but the clinical symptoms may be masked with immunosuppressive drugs used.[3]

4.4. *Hyperuricemia – treatment options*

Treatment of gout should address several aspects of the disease and deal with underlying predisposing factors as well as consequences and symptoms of organ damage triggered by UA. According to the guidelines issued by the European League Against Rheumatism (EULAR) in the year 2006 the following strategies should be employed:

- non-pharmacological methods,
- treatment of acute gout attacks,

– prophylaxis against acute gout attacks,
– use of long term urate lowering therapy,
– attention to comorbidities.[28]

These guidelines mentioned the recommended target serum level of UA which should be achieved and later on not exceeded; it has been defined as less than or equal to 6 mg/dL. Recommendations of the British Society for Rheumatology even suggest a target level of UA below 5 mg/dL.[29]

Concerning the pharmacological approach, two drug categories should be distinguished, namely drugs that are used to control an acute, symptomatic attack of gout (used for the short time) and long-lasting treatment aimed to prevent attacks and to keep serum UA concentration within desired target.

4.5. *Treatment of asymptomatic hyperuricemia*

EULAR and the American College of Rheumatology (ACR) guidelines suggest starting pharmacological treatment in case of symptomatic gout with recurrent exacerbations, arthropathy, tophi formation, or gout found on the X-ray imaging of joints. Additional indications for such a treatment according to ACR include CKD stage 2 or higher and uric acid stone formation.[28,30] Asymptomatic hyperuricemia should be treated by means of non-pharmacological strategies. Similar approach has been accepted by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on diagnosis and treatment of CKD, published in the year 2013. The KDIGO experts shared the opinion that existing evidence does not support routine use of UA lowering drugs in symptomatic or asymptomatic hyperuricemia in order to slow down the progression of CKD.[31] According to some authors serum UA should be lowered – even if asymptomatic – when it exceeds the level of 12 mg/dL (714 μmol/L).[1]

4.6. *Non-pharmacologic approach*

All known non-pharmacologic interventions should be applied in patients with hyperuricemia (or to prevent hyperuricemia) before pharmacological UA lowering treatment is considered. Risk factors should be carefully identified and treated accordingly; these include optimal metabolic control of diabetes, obesity, hyperlipidemia, and arterial hypertension. Drugs that may increase UA should be withdrawn if possible. Low-purine diet should be introduced, with cessation of alcohol intake, body weight reduction should be achieved. To gain therapeutic success education concerning lifestyle modification should be implemented.[5,28,30,32]

4.7. *Approach to acute attacks of gout*

Colchicine, non-steroidal anti-inflammatory drugs (NSAID), and steroids are key drugs used to stop acute attack of gout. Recommended starting dose of colchicine is 1.0 mg, but later on dose should be tapered to 0.5 mg (given up to three times per day). Higher doses, used previously, were characterized with very similar efficacy but much higher frequency of side effects.[1,5] NSAID, also including selective cyclooxygenase 2 inhibitors, should be used in the highest tolerable doses. Steroids can be given orally, but intra-articular injections can also be used. Steroids are especially useful in organ transplant recipients, since colchicine and NSAID may be nephrotoxic and may interact with calcineurin inhibitors. Recommended initial dose of prednisone is 0.5 mg/kg a day (usually for 5–10 days, with subsequent tapering).[3,30] New promising approach in the treatment of acute gout may be using 'biologic' drugs that inhibit IL-1 or TNF; the ongoing studies test anakinra, canakinumab and rilonacept in this indication.[9,33]

4.8. *Prophylaxis of acute attacks of gout*

After initiation of UA-lowering therapy exacerbation of symptoms may be expected since UA may be released from tissues; hence adding colchicine 0.5 mg bid or NSAID may be needed for a few months.[28]

4.9. *Long-term UA-lowering therapies*

In patients with diagnosis of gout the treatment goal should be set at the UA level of 6.0 mg/dL and the treatment should be introduced to keep UA below this value. When tophi are present, serum UA not exceeding 5.0 mg/dL is desired. In principle, three therapeutic strategies may be used to control UA below certain threshold: drugs that limit its synthesis, drugs that improve its elimination, or using an enzyme that facilitates its further metabolism to allantoine.[28,32]

4.10. *Xanthine oxidase inhibitors*

According to the EULAR and ACR guidelines xanthine oxidase inhibitors are considered the first-line pharmacological approach in the long-term treatment of gout. In document released in 2006 allopurinol has been mentioned as an exclusive member of this drug group; in the 2012 American guidelines two drugs are listed as equivalent: allopurinol and febuxostat.[28,32]

Allopurinol, present on the pharmaceutical market from the sixties is a purine analogue and non-selective inhibitor of xanthine oxidase (with oxipurinol as an active metabolite). Allopurinol and oxipurinol are substrates for xanthine oxidase, but also other enzymes participating in metabolism of purines and pyrimidines. Inhibiting these enzymes is reversible, so action of allopurinol is transient. Urine is a predominant way of drug elimination; hence dose lowering is recommended in CKD.[6,28,34,35]

Febuxostat has been registered and approved in the year 2008 in Europe. This drug is a strong, non-purine inhibitor of xanthine oxidase, blocking the active sites of this enzyme. Febuxostat does not block other enzymes of purine and pyrimidine metabolism (hence it is considered selective inhibitor of xanthine oxidase). Drug is excreted with urine and feces in equal parts, so in mild to moderate CKD dose reduction is not necessary.[34,36]

Efficacy of both dugs was compared in the series of prospective multicenter studies (known under acronyms APEX, FACT and CONFIRMS) that comprised in total of 4 101 patients.[34,37,38] Different doses of febuxostat (40–240 mg) and allopurinol (100–300 mg) were used in these trials. It has been

demonstrated that febuxostat 40 mg was comparable with allopurinol 200 mg in lowering serum UA level below 6 mg/dL (proportion of patients reaching values below this threshold equalled 42% and 45%, respectively). Febuxostat 80 mg was, however, more efficient, increasing this proportion to 67%.[38] In subjects starting treatment with very high serum UA (i.e. higher than or equal to 10 mg/dL), percentage of subjects reaching the target level was 41% in those taking febuxostat 80 mg, 48% in patients on 120 mg dose and only 9% following allopurinol 100–300 mg.[34,37]

The comparative studies were also performed in CKD patients (GFR range between 30 and 59 mL/min); in these studies allopurinol was used in a maximum dose of 200 mg and febuxostat – 40 mg and 80 mg. Both doses of febuxostat were more efficient in achieving treatment goal below 6 mg/dL as compared with allopurinol.[38]

It has been documented in a recent Japanese study that febuxostat is also effective and safe in advanced CKD (allows for achieving target UA below 6 mg/dL in more than 70% of patients). Along with UA lowering trends toward improvement in GFR and reduction of proteinuria were observed.[39] In another trial from Japan low dose of febuxostat (mean 15.9 mg) was more efficient than allopurinol in lowering serum UA in patients with GFR below 30 mL/min and in addition allowed for improvement of renal function.[40] It is also effective and safe in patients with severe CKD and associated CVD.[41] Febuxostat was also successfully used in kidney transplant recipients. Using 10 mg dose allowed to reduce serum UA below 6 mg/dL in 73% of patients, with satisfactory safety profile.[42]

Both drugs, i.e. allopurinol and febuxostat, have several side effects (AEs). In case of allopurinol the most frequent include mild hypersensitivity reactions and gastrointestinal intolerance. More severe and potentially life threatening allopurinol hypersensitivity syndrome (AHS) is rare; it may manifest with fever, exfoliating dermatitis, eosinophilia, hepatic injury and interstitial nephritis. Very severe complication secondary to allopurinol use is the Stevens-Johnson syndrome (patients with HLA-B58 are at the highest risk for its development).[2,43,44] Such severe adverse effects were not observed following treatment with febuxostat. Most frequently observed AEs include abnormal liver tests, nausea, diarrhea, headache, skin rash and edema. Both drugs at the beginning of treatment may increase the frequency of gout attacks. Overall, comparison of two drugs did not show any significant differences in frequency and severity of side effects. Treatment with febuxostat was more frequently associated with elevated liver enzymes, without hyperbilirubinemia nor clinical symptoms.[38,45,46] In two studies mentioned above (APEX and FACT), slightly higher rate of cardiovascular events was observed (0.7 events in 100 patient-years among febuxostat users vs. 0.6 events in 100 patient-years among subjects on allopurinol).[34,37] Observed differences were not statistically significant and the cause-effect relationship between febuxostat use and the onset of events could not be established. Nevertheless, febuxostat at present is not indicated in patients with concomitant ischemic heart disease and heart failure; in turn it should be considered a first choice treatment of hyperuricemia in patients with CKD.[2,33,34,37,38,45,46]

4.11. *Uricosuric drugs*

Another treatment strategy to lower UA is using uricosuric drugs. They are not considered a first-line therapy and should be usually used together with xanthine oxidase inhibitors (or when the drugs from the latter group are contraindicated).[28,32] In general, uricosuric drugs inhibit UA reabsorption in proximal tubules. Probenecid and sulfinpyrazone, representing uricosuric agents, may be used in patients with normal kidney function. The key contraindications for their use include history of UA-containing kidney stones, UA excretion with urine exceeding 700 mg per 24 h and age above 65 years.[2] Benzbromarone (structurally resembling amiodarone) is an effective uricosuric drug which can be used in patients with mild-to-moderate CKD; its use is however limited with potential hepatotoxicity. Proper hydration is mandatory and the prolonged urine alkalinization should be achieved when using uricosuric drugs.[1,3] Weak uricosuric properties are also attributable to fibrates, atorvastatin and losartan, so these drugs may be preferentially used in patients with hyperuricemia and, respectively – hyperlipidemia and hypertension.[1,2,9]

4.12. *Uricase*

Uricase (urate oxidase) represents the novel approach to the treatment of hyperuricemia. This enzyme transforms UA to allantoin. Rasburicase, exogenous uricase which was a first drug introduced to the therapy, due to its immunogenicity and short action is not useful in long-term treatment of gout. Hence the pegylated form of the enzyme has been developed (pegloticase) which is characterized with improved pharmacokinetic properties and less pronounced side effects. Pegloticase contains mammalian recombinant uricase obtained from *Escherichia coli*, linked to polyethylene glycol.[47] The drug is used as an intravenous infusion every 2–4 weeks and thus may be used in a long-term for refractory gout. Its use may, however, be complicated with exacerbations of gout, allergic reactions (including anaphylaxis), hemolysis; decreased efficacy may also be expected with time since neutralizing antibodies may develop. High cost of a drug is also an important limitation for its use.[2,33,47]

5. Conclusions

1. Hyperuricemia results not only in gout, but also – in broad spectrum of other health consequences. It contributes to cardiovascular disease in patients with metabolic syndrome, diabetes and CKD. In patients suffering from diabetes and hypertension UA may promote development and progression of CKD. CKD (of any etiology) may progress if hyperuricemia persists.
2. Given the multidirectional association between UA, CKD and other diseases the drugs that would safely and effectively decrease hyperuricemia are of potential significance in therapy. For decades allopurinol remained a key substance in this indication, although it is not always effective in achieving defined serum UA targets and several safety concerns may be raised against its prolonged use (especially with patients with CKD).

3. Febuxostat, a new compound in the field may be successfully and safely used, also in patients with CKD (even in advanced stages).
4. Uricosuric drugs and recombinant uricase did not become true alternatives for xanthine oxidase inhibitors due to their side effects and/or high price, although uricase may be of therapeutic value in an acute tumor lysis syndrome following chemotherapy.

Conflict of interest

None declared.

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