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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