

Hyperuricemia, Type 2 Diabetes Mellitus, and Hypertension: an Emerging Association

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Abstract Uric acid is the final oxidation product of purine metabolism in circulation and has been associated with the occurrence of gout and kidney stones. Type 2 diabetes mellitus and hypertension are two important public health challenges, and both are linked to increased risk of cardiovascular events. Hyperuricemia has recently emerged as an independent risk factor in the development of type 2 diabetes mellitus and hypertension through several proposed mechanisms. Few clinical trials investigated the use of uric acid lowering agents in the management of these two disease entities; however, their results provided encouraging evidence to a potential role for these agents in fighting disease burden. Larger randomized controlled trials are therefore warranted to establish the role of uric acid as a promising target for novel therapeutic interventions in the management of type 2 diabetes mellitus and hypertension.

Keywords Diabetes · Uric acid · Chronic kidney disease · Hyperuricemia

Introduction

Uric acid (UA) is the final breakdown product of purine compounds. It is generated in the liver, and mainly excreted by the kidneys (65–75%) and the gastrointestinal tract (25–35%) [1, 2].

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Hyperuricemia (HUA) is widely known to cause gout which is the most common inflammatory arthritis characterized by painful disabling acute attacks [3]. However, recent evidence suggests an emerging association between HUA, hypertension (HTN), and type 2 diabetes mellitus (T2DM) [4]. HTN remains a major cause of cardiovascular diseases and a leading risk factor for global disease burden, with almost 30% of the Western adult population affected with the disease [5]. Likewise, T2DM, a major lifestyle disease, has become a global burden, with more than 640 million adults expected to be affected by the disease by 2040 [6]. It is therefore necessary to develop new therapeutic interventions to limit the burden of both of these disease entities. Following an overview of UA homeostasis, on HUA and its prevalence, we will discuss recent evidence on the association between HUA, HTN, and T2DM with a focus on the effects of UA lowering therapies on cardiovascular events.

Uric Acid Homeostasis

UA is generated in the liver from the breakdown of dietary and endogenously synthesized purine nucleotides. Dietary intake, including purine rich products, glucose, and fructose, constitutes the exogenous pool of UA. The suggested association between fructose ingestion and HUA is of particular interest. Upon consumption of fructose, it is absorbed and phosphorylated resulting in a depletion of adenosine triphosphate and increase in adenosine monophosphate, leading to HUA. However, some trials attributed this association to the hypercaloric state rather than to fructose in particular, so additional studies are warranted to confirm the association [7]. On the other hand, the endogenous pool of UA is mostly regulated by the enzyme xanthine oxidase which irreversibly oxidizes xanthine into UA, a normal intracellular fluid

compound [8, 9•]. Normal serum UA level is about 6.8 mg/dL [10], with adult males having higher levels than females [2].

UA degradation by the microbiota of the gut, known as intestinal uricolysis, eliminates almost one third of body urate. Complex interchange between secretion and reabsorption at the proximal tubules of the kidneys is responsible for the daily excretion of the remaining two thirds of total UA [9•, 10, 11]. The resultant effect of these mechanisms is a normal UA excretion of almost 10% [9•].

Several plasma membranes contribute to UA disposal by the kidneys. The ATP-binding cassette subfamily G membrane 2 (ABCG2) mediates urate entry to the intestines and is also found in the epithelium of proximal renal tubules. Furthermore, the major UA reabsorptive transporters in the renal tubule are the urate anion exchanger 1 (URAT1) and the glucose transporter type 9 (GLUT9). Any polymorphism involving the expression of these renal UA transporters may result in HUA and gout [10, 12, 13].

Current pharmacological agents aiming to decrease serum UA work by interfering with UA production via inhibition of the enzyme xanthine oxidase (such as allopurinol), decreasing UA reabsorption by targeting URAT1 (such as probenecid) or enhancing metabolism of UA into allantoin by uricase [14]. Moreover, SGLT2 inhibitors have been shown to decrease UA levels by interfering with GLUT9, and the angiotensin receptor blocker losartan was found to lower serum UA by inhibiting URAT1 [15].

Hyperuricemia Definition and Epidemiology

HUA is practically defined as UA levels greater than 6.8 mg/dL, which corresponds to its solubility point [16]. Some clinical trials define HUA as UA greater than 7 mg/dL in males and UA greater than 6 mg/dL in females [17••].

HUA has been associated with several known risk factors including alcohol consumption, diet rich in fructose, meat or seafood, certain medications, namely, diuretics, angiotensin converting enzyme, as well as obesity and hypertension [18, 19]. The prevalence of HUA in the USA attained 13% of the general population as defined by a serum UA >7 mg/dL and 21% as defined by a serum UA >7 mg/dL in males and >5.7 mg/dL in females [20]. HUA in females is more common after menopause due to the inhibitory effect of estrogen on urate reabsorption [21]. This finding is further corroborated by other studies showing decreased UA levels among postmenopausal women on hormone replacement therapy [22].

Hyperuricemia and Type 2 Diabetes Mellitus

Emerging evidence suggests that HUA is an independent risk factor for developing T2DM. In a systematic review

of eight prospective cohort studies, including a total of 32,016 participants and 2930 incident T2DM, the risk of T2DM was increased by 6% for every 1 mg/dL increase in serum UA [23••]. A meta-analysis of 12 cohort studies assessed the correlation between UA levels and incident T2DM and impaired fasting glucose (IFG). The study included 6340 cases, and a total of 62,834 participants were analyzed. Findings from this meta-analysis revealed that a positive nonlinear relationship exists between serum UA levels and incident T2DM and IFG. The findings were also applicable to the incidence of T2DM alone [24]. Kim et al. prospectively examined the incidence of T2DM among 54,075 gout and 162,225 osteoarthritis patients over a mean follow-up of 1.9 years. Incidence rate of T2DM was almost 2% among gout patients versus 0.98% among osteoarthritis patients after controlling for potential confounders including age, comorbidities, medications, and health care use patterns [25]. In another prospective cohort study investigating the association between serum UA and incident IFG, 13,328 women and 41,350 men without diabetes were followed up for 4 years. Results suggested that any abnormality in UA concentrations is associated with an increased risk for the development of IFG in men, independent of other known risk factors. In women, such association was not present [26]. Although the reason for this gender difference is still uncertain, sex hormones may play a role, especially that estrogen facilitates excretion of UA during the reproductive period [27]. A retrospective cohort study examined the risk of new-onset diabetes among 1923 male patients with HUA and no prior evidence of diabetes. The risk was positively correlated with serum UA levels, reaching up to 27% for serum UA > 9 mg/dL, after adjusting for confounding factors [28].

Data from experimental studies reveal that HUA mediates increased insulin resistance and decreased insulin release, eventually leading to T2DM through different potential pathogenic factors. Indeed, UA emerged as a pro-inflammatory substance: Infusion of UA into mice increases TNF- α levels and activates phospholipase A2 and nuclear factor kappa-light-chain-enhancer of activated B cells [29]. UA also activates inflammasome in mice, which leads to a decrease in insulin sensitivity [30]. Furthermore, UA enhances production of reactive oxygen species which can lead to the loss of transcription factors needed for insulin gene expression, leading to decreased insulin production and secretion [31].

A small number of studies assessed the effects of pharmacologic lowering of UA on T2DM.

In a randomized open parallel-controlled study, 176 patients with T2DM and asymptomatic HUA were randomly assigned to the conventional or allopurinol treatment groups. After a 3-year follow-up period, the homeostasis assessment for insulin resistance (HOMA-IR) index

mean value was significantly lower in the allopurinol group as compared to the conventional group (3.49 in the allopurinol group versus 3.57 in the conventional group), although there were no statistically significant differences in the baseline values between the two treatment groups. The authors therefore concluded that long-term effective control of serum UA by allopurinol may actually ameliorate insulin resistance [32]. This finding was also seen in a prospective cohort study involving 73 subjects with asymptomatic HUA placed on allopurinol or control with a follow-up period of 3 months. Allopurinol-treated subjects exhibited a significant improvement in HOMA-IR index, fasting blood glucose, fasting insulin as compared to the control group [33]. An experimental study investigating the effects of allopurinol in experimentally induced insulin-resistant rats showed that allopurinol plays a protective role against vascular complications of insulin resistance partly attributed to its effect on increasing insulin secretion [34].

Hyperuricemia and Hypertension

Several studies have demonstrated an association between serum UA and HTN. Incident HTN increases by 13% per 1 mg/dL increment in serum UA level based on the results of a systematic review of 18 prospective cohort studies involving 55,607 subjects [35••]. In a retrospective study including 315 hypertensive patients and 181 individuals without hypertension, HUA was observed in 6.7% of patients with newly diagnosed hypertension. A positive correlation between serum creatinine and UA and negative correlation between UA and eGFR were also demonstrated in this study [36]. In a longitudinal cohort of healthy subjects, a baseline UA level greater than 6.5 mg/dL was associated with a 25% increase in the risk of HTN [37]. A prospective study including subjects without any baseline cardiovascular disease showed that increased serum UA was highly associated with more intima media thickness leading to the incidence of HTN [38].

Different pathophysiological mechanisms have been proposed to understand the association between HTN and HUA.

A HUA rat model was created by adding oxonic acid, a uricase inhibitor, to the diet leading to almost twofold increase in serum UA. Three weeks later, blood pressure measurements were significantly elevated among hyperuricemic rats in comparison to controls. Interestingly, this finding was not dependent on oxonic acid, since lowering UA by a uricosuric agent or a xanthine oxidase inhibitor could not prevent HTN. Moreover, these rats demonstrated increased renin levels and decreased nitric oxide synthase in the macula densa, as well as

tubulointerstitial injury, highlighting important pathological findings relating HUA to HTN and kidney disease [39•]. In another experimental study on human endothelial cells, HUA was associated with an increase in reactive oxygen species and angiotensin II, which causes efferent arteriole constriction leading to HTN, as well as in reactive oxygen species, known to significantly contribute to the incidence of HTN, cardiovascular diseases, and kidney diseases [40].

Few clinical trials looked for a possible role for UA reduction in the management of HTN.

In a randomized crossover study involving 30 adolescents (aged 11–17 years) with HUA and newly diagnosed essential HTN, treatment with allopurinol resulted in a 6.8 mmHg decrease in the 24-h systolic blood pressure [41••]. In another randomized, double-blinded, placebo-controlled trial, prehypertensive adolescents, aged 11 to 17 years, were randomized to receive the allopurinol, probenecid, or placebo. Subjects treated with urate-lowering therapy experienced a marked reduction in clinic systolic blood pressure of 10.2 mmHg and diastolic blood pressure of 9.0 mmHg [42]. In a prospective trial investigating the benefits of allopurinol treatment in hyperuricemic patients with normal renal function, allopurinol 300 mg/day was given to 48 patients with HUA and included 34 patients with HTN. Three months later, it was seen that noted that allopurinol resulted in a significant decrease in mean blood pressure from 135.4/80.2 to 131.5/78.3 mmHg [43••].

Conclusion

Substantial data from epidemiologic and experimental studies indicate an emerging association between HUA, T2DM, and HTN. Pharmacologic agents lowering serum UA proved to play a promising role in the management of T2DM and HTN. Nevertheless, large prospective randomized, controlled trials are warranted to determine direct effects between UA lowering and long-term clinical outcomes. Moreover, further studies are required to validate the utility of UA levels for the primary prevention of T2DM and HTN and to clarify the serum UA level at which intervention is needed.

Compliance with Ethical Standards

Conflict of Interest Dr. Mortada declares no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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