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Review Article

Uric acid in metabolic syndrome: Does uric acid have a definitive role?

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ABSTRACT

Increased serum uric acid (SUA) levels are commonly seen in patients with metabolic syndrome and are widely accepted as risk factors for hypertension, gout, non-alcoholic fatty liver disease, chronic kidney disease (CKD), and cardiovascular diseases. Although some ambiguity for the exact role of uric acid (UA) in these diseases is still present, several pathophysiological mechanisms have been identified such as increased oxidative stress, inflammation, and apoptosis. Accumulating evidence in genomics enlightens genetic variabilities and some epigenetic changes that can contribute to hyperuricemia. Here we discuss the role of UA within metabolism and the consequences of asymptomatic hyperuricemia while providing newfound evidence for the associations between UA and gut microbiota and vitamin D. Increased SUA levels and beneficial effects of lowering SUA levels need to be elucidated more to understand its complicated function within different metabolic pathways and set optimal target levels for SUA for reducing risks for metabolic and cardiovascular diseases.

1. Introduction

The final product of purine metabolism is uric acid (UA) which is produced by xanthine oxidase (XO). Although most mammalian species can also oxidize UA to allantoin via uricase, humans are thought to lost uricase for an evolutionary advantage to maintain blood pressure under a low-salt diet with protection against oxidative damage. Therefore, humans have 3 to 10 times higher serum uric acid (SUA) levels compared to other mammals with uricase enzyme [1]. Since the discovery of gout as the "disease of kings", gout and hyperuricemia have been associated with excessive meat and alcohol consumption. Due to the spread of Western lifestyle and diet in the developed and high-income developing countries, hyperuricemia has become gradually more common. In the National Health and Nutrition Examination Survey (NHANES) 1988-1994, the prevalence of hyperuricemia was 19.1% with the mean SUA level of 5.32 mg/dL among males and 4.65 in females while in the NHANES 2007-2008, the prevalence of hyperuricemia was 21.5% with the mean SUA level of 6.14 mg/dL among males and 4.87 mg/dL among females [2,3]. It was also shown that SUA levels are linearly correlated with serum C-peptide, insulin levels, and insulin resistance [4].

Accumulating evidence demonstrated that both SUA levels and related comorbidities have significantly increased regardless of gender or ethnicity [3,5]. It is well-predicted that the increasing trend in the prevalence of hyperuricemia and the mean SUA levels will continue as more people adopt the Western lifestyle. Even though the exact reason for this trend is unknown, some potential contributing factors can be increased consumption of purine-rich foods and alcohol, increased prevalence of metabolic syndrome and obesity, aging populations with several comorbidities including diabetes and chronic kidney disease (CKD), increased use of certain medications such as loop diuretics, thiazides, and aspirin. Certain risk factors for hyperuricemia and protective factors against hyperuricemia were shown in Table 1.

Although only a few large-scale studies were comprehensively conducted, several studies have investigated the SUA level and its associations with multiple diseases. Hyperuricemia is associated with hypertension [6], heart failure, stroke [7], obesity [8], metabolic syndrome [9], insulin resistance, type 2 diabetes mellitus [10], dyslipidemia [11], CKD [12], nonalcoholic fatty liver disease [13], and cardiovascular diseases [14]. The role of UA in metabolic syndrome and its pleiotropic effects in multiple organ systems has been a matter of discussion due to its complicated and outrageous connections within cellular metabolism and between signaling pathways [15]. In this review, we focus on the effect of UA on metabolism by illustrating its complicated nature within the cellular metabolism (micro-environment) and organ systems (macro-environment).

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Table 1
Certain risk and protective factors for hyperuricemia.

Risk Factors for Hyperuricemia
Male gender
African-American origin
Hypertension
Sleep apnea
Congestive Heart Failure
Renal Failure
Myeloproliferative neoplasms
Hypercholesterolemia, hypertriglyceridemia
Diet rich in protein, purine, and fructose
High alcohol consumption
Obesity, high body-mass index
Protective Factors Against Hyperuricemia
Estrogen and progesterone combination hormonal therapy in postmenopausal females
Increased coffee and vitamin C consumption
Low-fat dairy products
Weight changes both weight gain and weight loss

2. Pathophysiology of UA-induced injury

2.1. The paradox of oxidant versus anti-oxidant properties

Anti-oxidant effects of UA have been demonstrated in certain neurological conditions such as stroke, multiple sclerosis, and Parkinson's disease which have been confirmed in both human participants and animal studies conducted with rats and mice [7,16]. UA acts as an antioxidant molecule in several conditions; however, it has been also linked to oxidative stress due to the over activity of XO enzyme. The balance between pro-oxidant and anti-oxidant properties of UA depends upon various factors including genetic polymorphisms, environmental conditions, presence of other pro or anti-oxidant molecules, cell type, and certain signaling pathways. The anti-oxidant property of UA is more prominent in the extracellular space as it can scavenge oxygen radicals such as hydroxyl, peroxyl, and singlet oxygen radicals and provide beneficial production of cells and organs from external oxidative stress. On the other hand, the pro-oxidant property of UA is more prominent intracellularly as enhanced activity of XO is directly linked to increased UA levels inside the cells and XO is one of the main ROS producers [1]. Also, elevated UA levels lead to activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase via translocation of regulatory components from the cytoplasm to the cell membrane, thus, forming the active holoenzyme [17]. Therefore, XO and NADPH oxidase can promote each other forming a vicious cycle and produces more ROS when intracellular UA levels increase. Moreover, UA may contribute to oxidative stress through the generation of mitochondrial reactive oxygen species (ROS) in response to mitochondrial DNA damage, decreased levels of cytochrome C, and succinate dehydrogenase [18,19].

UA has a variable role in oxidative status as an inducer of oxidative stress intracellularly by the inhibition of nitric oxide and adiponectin synthesis and disruption of a tricarboxylic acid cycle in contrast to its role extracellularly as a suppressor of oxidative stress through chelation of metal ions and neutralization of certain radicals [20,21]. The pro-oxidant character of UA with increased stress of ROS can contribute the progression of several diseases including CV and metabolic diseases while beneficial effects of UA at the central nervous system may be attributable to the blockage of the blood-brain barrier due to a decline in nitric oxide production at endothelial cells and a decrease in neutrophilic infiltration [22,23]. Future studies are needed for a better understanding of the balance between the pro and anti-oxidant effects of UA.

2.2. The augmentation of inflammation

UA displays pro-inflammatory properties via several mechanisms as illustrated in Fig. 1.

(i) **The activation of the mitogen-activated protein kinase (MAPK) pathway.** The MAPK pathway is among the most important pathways linking extracellular signals with an intracellular response. UA was shown to activate p38 MAPK and extracellular signal-regulated kinase (ERK) both of which are involved in the secretion of inflammatory cytokines, adhesion factors, chemokines, and cellular proliferation and migration [24,25].

(ii) **The suppression of the adenosine monophosphate-activated protein kinase (AMPK) pathway.** AMPK pathway is crucial for the regulation of cellular energy metabolism while the suppression of the AMPK pathway is a stress signal for cells and results in the secretion of inflammatory cytokines and the activation of the nucleotide-binding domain and leucine-rich repeat protein-3 (NLRP3) inflammasome [26]. UA was shown to suppress the AMPK pathway while fructose also leads an inflammatory response and oxidative stress by suppressing the AMPK pathway [27,28].

(iii) **The activation of the phosphatidylinositol-3 kinase (PI3K)-Akt pathway.** PI3K-Akt pathway has been linked to cell proliferation, migration, differentiation, and cellular energy metabolism. UA phosphorylates Akt and activates mTOR which blocks autophagy and promotes inflammation and angiogenesis via hypoxia-inducible factor (HIF)-1α [29,30]. Additionally, the activation of mTOR by UA results in mitochondrial damage which causes elevated levels of mitochondrial ROS and release of cytochrome c which is involved in the intrinsic pathway of apoptosis and cellular senescence [31].

(iv) **The decline in nitric oxide (NO) synthesis.** Elevated SUA levels lead to the dephosphorylation, and thus inhibition of endothelial nitric oxide synthase and decline in NO production. This finding has further been validated by the demonstration of increased expression of high mobility group box 1 (HMGB1) protein and its receptor, namely receptor for advanced glycation end products (RAGE), and attenuation of those effects by benzbromarone which is a urate transport inhibitor [32]. The decline in NO levels and increase in HMGB1 levels have pro-inflammatory outcomes in human tissues.

(v) **Other pro-inflammatory properties.** Elevated SUA levels are linked to increased production of a protease called calpain-1 that leads to endoplasmic reticulum stress [33]. Additionally, the renin-angiotensin-aldosterone system (RAAS) and inflammasome pathway are involved in UA-mediated cellular response [34].

2.3. Apoptosis

High SUA levels lead to downregulation of B-cell lymphoma 2 (Bcl-2) expression in pancreatic β-cells which results in an imbalance between Bcl-2-associated X protein (Bax)/Bcl-2 [35]. Additionally, calpain-1 induced ER stress and mitochondrial damage-induced cytochrome c release are the potential apoptotic mechanisms involving UA-induced apoptosis. Another important consequence of ER stress in response to hyperuricemia is the overexpression of various lipogenic enzymes such as acetyl-CoA carboxylase-1, fatty acid synthase, and stearoyl-CoA desaturase-1 through activation of sterol regulatory element-binding proteins (SREBP)-1c all of which results in lipogenesis, especially in the liver leading to non-alcoholic fatty liver disease [36].

3. . UA and genetic variations

Hyperuricemia may develop in response to various mechanisms including the over-degradation of purine nucleotides and under-excretion of UA from the intestines and kidneys (See Fig. 2). Genetic variations in the proteins involved in the UA absorption or excretion

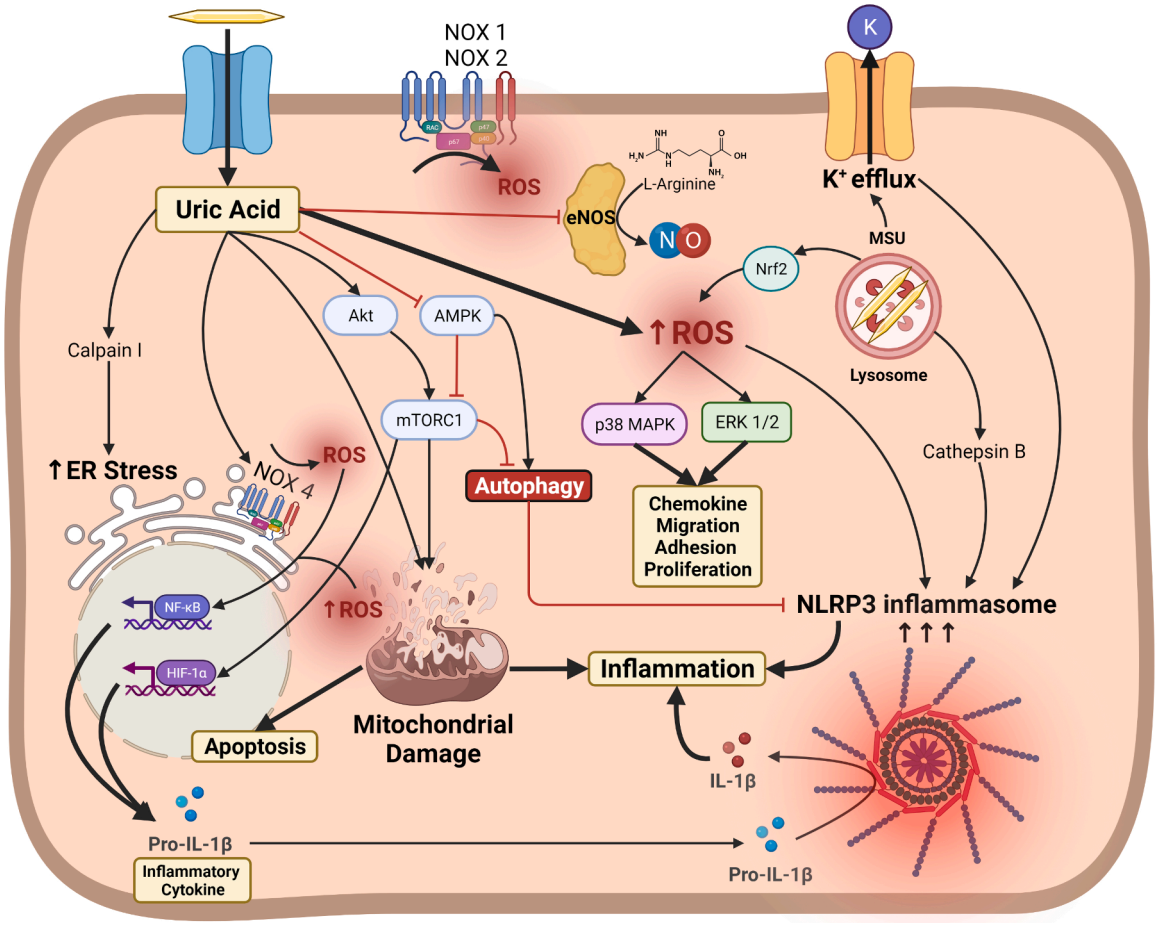

Fig. 1. The effect of uric acid on intracellular signaling pathways in the pathogenesis of UA-induced injury & inflammation. Uric Acid promotes the production of reactive oxygen species (ROS) and activates several inflammatory signaling pathways, intracellularly. Black arrows illustrate promotion while red lines illustrate inhibition. ER, endoplasmic reticulum; NOX, NADPH oxidase; eNOS, endothelial NO synthase; MSU, monosodium urate; AMPK, AMP-activated kinase; Nrf2, Nuclear factor-erythroid 2-related factor 2; mTORC1, mammalian target of rapamycin complex 1; p38 MAPK, p38 mitogen-activated protein kinase; ERK, extracellular signaling-regulated kinase; HIF-1α, Hypoxia Inducible Factor 1α; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL, interleukin.

from the intestine such as ATP-binding cassette transporter (ABC) G2 or from kidneys either located at basolateral membrane such as organic anion transporter (OAT)-1/2/3 or glucose transporter (GLUT)-9 or at apical membrane such as OAT4, urate transporter (URAT) 1, GLUT9, ABCG2, ABCG4, and NPT1 have been linked to hyperuricemia [37,38]. High purine diet, high phosphoribosyl pyrophosphate (PRPP) synthetase activity, hypoxanthine phosphoribosyltransferase (HPRT) deficiency which is referred to as Lesch-Nyhan syndrome, adenine phosphoribosyltransferase deficiency, xanthine dehydrogenase deficiency, which is also referred to as xanthinuria, increased cell turnover can lead to hyperuricemia due to increased purine breakdown.

The rs7442295 single nucleotide polymorphism or loss-of-function mutation in the solute carrier family (SLC) 2, facilitated glucose transporter member 9 (SLC2A9) gene encoding for GLUT9 which results in reduced secretion of urate into urine and increased absorption into the bloodstream [39,40]. A similar pattern of hyperuricemia has been reported in the rs475688, rs3825016, and rs11726117 polymorphisms of the SLC22A12 gene encoding for URAT1 which results in renal hypouricemia type 1 [41,42]. A similar outcome has been observed with the rs2231142 single nucleotide polymorphism of the BCRP gene encoding for ABCG2 in addition to defective intestinal urate excretion [43,44]. Rare cases of OAT4 or OAT10 gene mutations have been identified in the literature as potential etiological factors for hyperuricemia [45,46].

Additional rare mutations that have been linked to hyperuricemia are identified including REN, which is involved in autosomal dominant tubulointerstitial kidney disease, glucose-6-phosphatase catalytic subunit leading to glycogen storage disorder type 1a, mitochondrial seryl-tRNA synthetase leading to splicing defects, uromodulin and lactate dehydrogenase [47,48]. New genetic polymorphisms on multiple genes are expected to be identified in the upcoming years with growing research involving UA metabolism.

Multiple genetic polymorphisms of xanthine oxidoreductase and xanthine dehydrogenase, enzymes involved in the metabolism of uric acid, have been identified. A study conducted on Japanese subjects demonstrates clear association between three single nucleotide polymorphisms of xanthine dehydrogenase (47686C>T at exon 22, 69901A>C at intron 31,and 67873A>C at exon 31) and hypertension while only one has been linked to carotid atherosclerosis (69901A>C at intron 31) and one with chronic kidney disease (66292C>G) [49,50]. Similarly, multiple genetic polymorphisms at xanthine oxidoreductase have been linked to oxidative stress, hypertension and cardiovascular events [51,52].

4. UA and epigenetic reprogramming

Accumulating evidence is not enough to fully explain the underlying mechanisms of hyperuricemia-induced pathological alterations despite the presence of strong associations between certain genes and the risk for hyperuricemia and gout. Trained immunity, a term referring to an altered and enhanced non-specific innate immune response to a PAMP or DAMP after a previous encounter, is mediated via immunometabolism and epigenetic reprogramming [53,54]. After a demonstration of

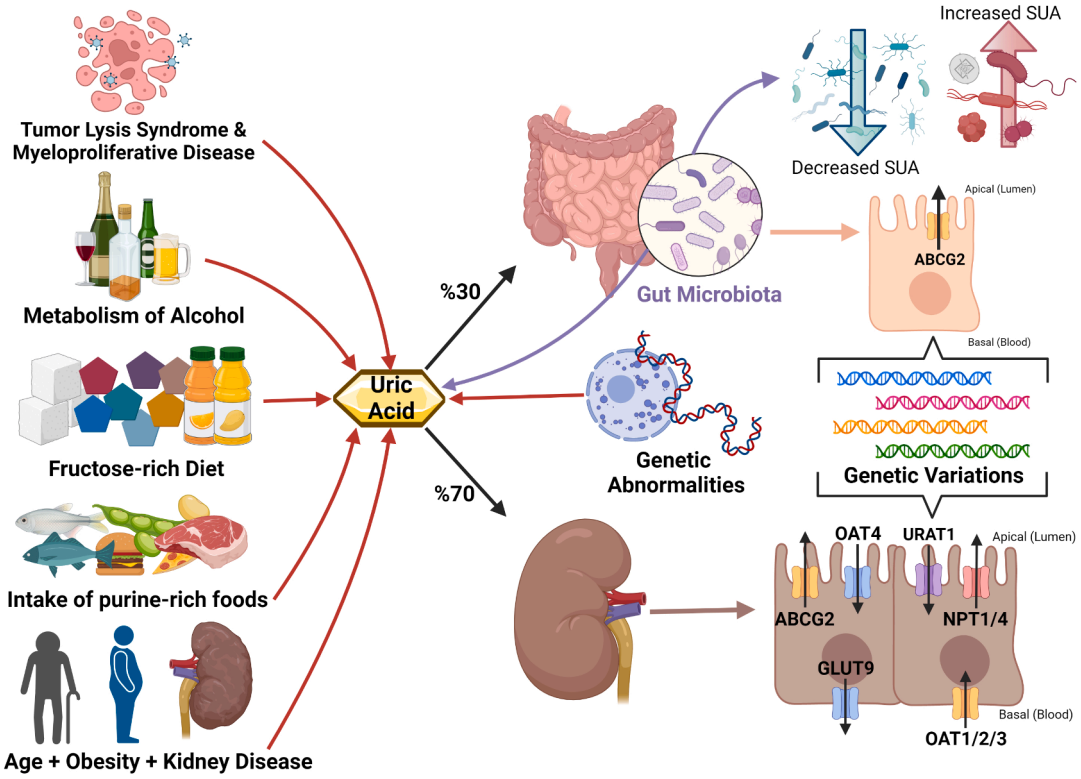

Fig. 2. The cause of elevated high serum uric acid (SUA) levels and excretion paths of uric acid with relations to genetic variations and gut microbiome. ABCG2, ATP-binding cassette transporter G2; OAT, organic anion transporter; GLUT 9, glucose transporter 9; URAT1, urate transporter 1.

the production of higher amounts of pro-inflammatory cytokines, namely interleukin (IL)-1β and IL-6, and lower amounts of anti-inflammatory cytokines such as IL-1Ra from harvested peripheral blood mononuclear cells of hyperuricemic patients compared to normouricemic individuals following an ex-vivo stimulation, suspicion has been raised regarding the potential urate-induced epigenetic response [55]. A similar pattern has been observed when those cells are pre-treated in a medium with high UA content [55,56]. Variations in terms of DNA methylation including various inflammation-associated genes such as IL-23R and IL-17, transcription factors such as a nuclear factor of activated T-cells, cytoplasmic 2 (NFATC2) and myocyte enhancer factor (MEF) 2C, and gout-associated genes such as SLC2A9 and ABCC9 have been reported in a study conducted with 16 gout patients and 14 controls [57]. Both transcription factors have been hypomethylated in gout patients and are involved in the expression of inflammatory and anti-inflammatory genes [58]. NFATC2 has been involved in both acute and chronic inflammation through modulation of interferon regulatory factor-1 (IRF-1), MYC, and signal transducer and activator of transcription (STAT) genes in myeloid cells and suppression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) hyperactivation, thus resulting in macrophage M1 polarization [59,60]. Additionally, hypomethylation of chemokine (C-C motif) ligand 2 (CCL2) promoter has been reported in the Chinese Han male population with gout [61]. Inhibition of epigenetic modifications may alter the production of certain cytokines as evident by the decline in cytokine release in response to romidepsin, a class I histone deacetylase inhibitor [62]. Treatment with romidepsin results in the upregulation of the suppressor of cytokine signaling (SOCS) 1 gene, which is involved in the proteasomal degradation pathway, thus, the effect of romidepsin is reversible with bortezomib treatment, a proteasome inhibitor [63,64]. Similarly, a short-chain fatty acid, butyrate, has an inhibitory effect on histone deacetylation and results in comparable secretion patterns [65,66] Despite such altered epigenetic modifications in response to hyperuricemia, the underlying mechanism of those changes are unknown so far with limited number of studies demonstrating no association with two common mechanisms, namely trimethylation of lysine 4 of histone 3 (H3K4me3) and acetylation of lysine 27 of histone 3 (H3K27ac) [56]. Although more comprehensive genetics and epigenetics studies are required for the better understanding of the role of DNA or histone methylation or acetylation in gout pathophysiology, we expect an exponential growth in this area of research in the upcoming years.

5. Consequences of asymptomatic hyperuricemia

Guidelines or consensus statements regarding the management of hyperuricemia and gout recommend urate-lowering therapy in cases with recurrent attacks, urate nephrolithiasis, arthropathy, tophi, and in patients with multiple comorbidities while strong variations exist in asymptomatic cases in terms of the cut-off value, even whether to treat under any circumstances. The cutoff value for increased comorbidity risk is variable across studies such as 6.0 mg/dl in the NHANES III study in both sexes and 7.5 mg/dL in men and 6.2 mg/dL in women in another large scale study . 1 mg/dl increase in SUA level is linked to 20 mg/dl increase in serum total cholesterol levels and 10 mm Hg increase in systolic blood pressure [67].

The balance between pro and anti-oxidant effects of UA appears to be concentration-dependent [68]. High SUA levels are associated with increased endoplasmic reticulum stress which results in cardiomyocyte apoptosis [33,69]. Also, hyperuricemia leads to the secretion of pro-inflammatory and vasoconstrictive cytokines such as IL-1, IL-6, tumor necrosis factor-alpha, endothelin-1 and thromboxane A2 macrophage M1/M2 differentiation [14,70]. Macrophage M1 releases pro-inflammatory cytokines while macrophage M2 leads to myocardial fibrosis. All such alterations are evident even in asymptomatic individuals with hyperuricemia and contribute to endothelial dysfunction.

Hyperuricemia is linked to insulin resistance which is mediated via direct cytotoxicity towards pancreatic beta cells, reduction in insulin secretion and insulin receptor sensitivity while insulin resistance may also result in hyperuricemia vice versa through increased expression of URAT1 at the renal cortex [71,72].

Treatment with allopurinol results in an improvement in insulin resistance in a study conducted on 73 subjects with asymptomatic hyperuricemia [73,74]. As expected from this bidirectional relationship, sodium-glucose cotransporter-2 (SGLT-2) inhibitors result in a decrease in SUA levels [75]. In a randomized open parallel-controlled study conducted with 176 patients with type II diabetes mellitus and asymptomatic hyperuricemia, allopurinol treatment for 3 years results in a decline in SUA levels, insulin resistance, carotid intima-media thickness, systolic and diastolic blood pressure and serum high-sensitivity C-reactive protein level [76].

6. Association between SUA and atrial fibrillation

Elevated SUA levels even in the absence of any comorbid condition have been linked to atrial fibrillation (AF), the most common type of cardiac arrhythmia with increasing prevalence, in multiple clinical studies [77,78]. A large scale prospective cohort study conducted with 123.238 Chinese participants over an eight-year period demonstrate that high baseline SUA levels or elevation of SUA levels over time have been positively correlated with AF [79]. Multiple pathophysiological mechanisms have been postulated in order to explain the underlying mechanism of SUA-associated AF. A key finding of the ectopic signal producing center in patients with AF is the upregulation of ROS formation which is enhanced in hyperuricemic patients with the activity of XO enzyme, potentially reversible effect by XO inhibitors such as allopurinol [80]. Additionally, intracellular accumulation of uric acid leads to alteration of ion channels located on cardiac myocytes such as hyperuricemia-induced MAPK-ERK (Mitogen-activated protein kinase-Extracellular signal-regulated kinase) signaling resulting in the upregulation of Kv1.5 channel that leads to an increase in the ultra-lipid delayed-rectifier current and shortening of atrial action potential [81,82]. Another mechanism contributing the altered ion channel dynamic is the change in the expression of heat shock proteins. Furthermore, accumulation of monosodium urate crystals at cardiac tissue induces NLRP3 inflammasome which is composed of NLRP3, ASC and pro-caspase 1 and leads to pro-inflammatory response through activation of IL-1β and IL-18 [83,84]. Increased activity of NLRP3 inflammasome has been illustrated on atrial cardiomyocyte in patients with AF [85].

7. UA and gut microbiota

Almost 25% of UA is secreted into the intestine and metabolized by gut microbiota such as Escherichia coli, Clostridium, and Pseudomonas bacteria [86,87]. Even though the role of UA and its metabolism in the kidney and liver are widely elucidated, there have been a few studies that focused on the relationship between UA and intestine with its microbiota. The UA levels can be reduced by gut microbiota which induces the catabolism of purines and intestinal UA transporters for more UA excretion [87]. Accumulating evidence indicated that dysbiosis of gut microbiota is related to several metabolic, cardiovascular, and inflammatory bowel diseases. Several studies also suggested possible links between intestinal dysbiosis and hyperuricemia as high SUA levels could change the environment within the intestinal tract, damage the intestinal barrier, and alter the gut microbiota [88,89]. Zhang et al showed that diabetic patients with high SUA levels had significantly lower gut microbiota diversity compared to diabetic patients with normal SUA levels and stated that diabetic patients with high SUA levels had higher Escherichia–Shigella genus and lower Faecalibacterium, Oscillospiraceae_UCG−002, and Oscillospiraceae_UCG−005 genus in their gut microbiota [90]. Also, they suggested that gut microbiota regulates lipopolysaccharide synthesis which may affect SUA levels by showing enhanced lipopolysaccharide biosynthesis in the gut microbiota of diabetic patients with high UA levels.

In a recent mice study, UA was shown as a culprit mediator of colitis by directly increasing intestinal permeability. Rhein treatment to these mice with colitis was shown to decrease SUA levels by increasing Lactobacillus as researchers showed that Lactobacillus level inversely correlated with SUA levels [91]. By protecting the intestinal barrier, gut microbiota can alleviate chronic inflammation which is also a significant pathological process in hyperuricemia. In another study, fecal microbiota transplantation from mice with hyperuricemia to normal mice caused an increase in SUA content in normal mice suggesting that the gut microbiota can be directly associated with the pathogenesis of hyperuricemia [92]. It was also shown that gut microbiota can be changed after hyperuricemia treatment with allopurinol in male rats [93]. As the effects of UA are not confined to an organ, the gut microbiota has multiple effects on different organs. One of the well-known enhancers of UA production in the body is fructose which also causes dysbiosis in the small intestines. Due to high fructose intake, endotoxemia and gut permeability caused by UA can worsen lipogenesis in the liver and contribute to non-alcoholic fatty liver disease [94]. All of these findings suggest that UA may be a central mediator between the intestines, liver and kidney for metabolic changes. Protecting healthy gut microbiota and supporting it via probiotics or prebiotics seem to be a safe and effective way to manage SUA levels and alleviate metabolic syndrome. Nevertheless, the beneficial strains for lowering SUA and regulatory pathways in which gut microbiota and UA interacts are still needed by elucidated in the future for a better understanding of the role of UA in metabolic syndrome.

8. UA and vitamin D

A recent meta-analysis including 32 studies concluded that vitamin D deficiency was related to hyperuricemia and suggested a bidirectional association between UA and vitamin D [95]. Another meta-analysis including 9 studies showed that patients with primary hyperparathyroidism had increased SUA levels [96]. It was also shown that vitamin D supplementation can reduce SUA levels in patients with prediabetes and hyperuricemia supporting a causal association between UA and vitamin D [97].

UA can reduce the conversion of 25(OH)D into $1,25(OH)_2D$ by suppressing the expression of the CYP27B1 gene which encodes for 1α-hydroxylase in the kidney, so UA can contribute to hyperparathyroidism which inhibits ATP-binding cassette transporter G2 transporter and results in reduced UA excretion [98]. This vicious cycle between vitamin D, PTH, and UA is noteworthy and illustrated in Fig. 3 as vitamin D deficiency in the settings of hyperuricemia can further exacerbate bone resorption and lead to significant osteoporosis. UA increases bone resorption by stimulating osteoclast and decreases bone formation by inhibiting osteoblast because of its pro-oxidant properties intracellularly which promotes oxidative stress and inflammation [99].

Although we cannot establish a concrete relationship between vitamin D and metabolic syndrome, several observational studies suggested an inverse relationship between vitamin D and hyperglycemia and some concluded that vitamin D decreases insulin resistance, the severity of T2D, and metabolic syndrome [100]. Future studies for assessing the relationship between vitamin D deficiency and metabolic syndrome to find out whether hypovitaminosis D worsens metabolic syndrome and correction would alleviate it.

9. The target level for UA level

Although no consensus on the optimal range for SUA levels is present, SUA levels of <6.0 mg/dL in women and <7.0 g/dL in men have been widely accepted as the goal of treatment in hyperuricemia patients [1]. However, some studies showed an increased risk for hypertension,

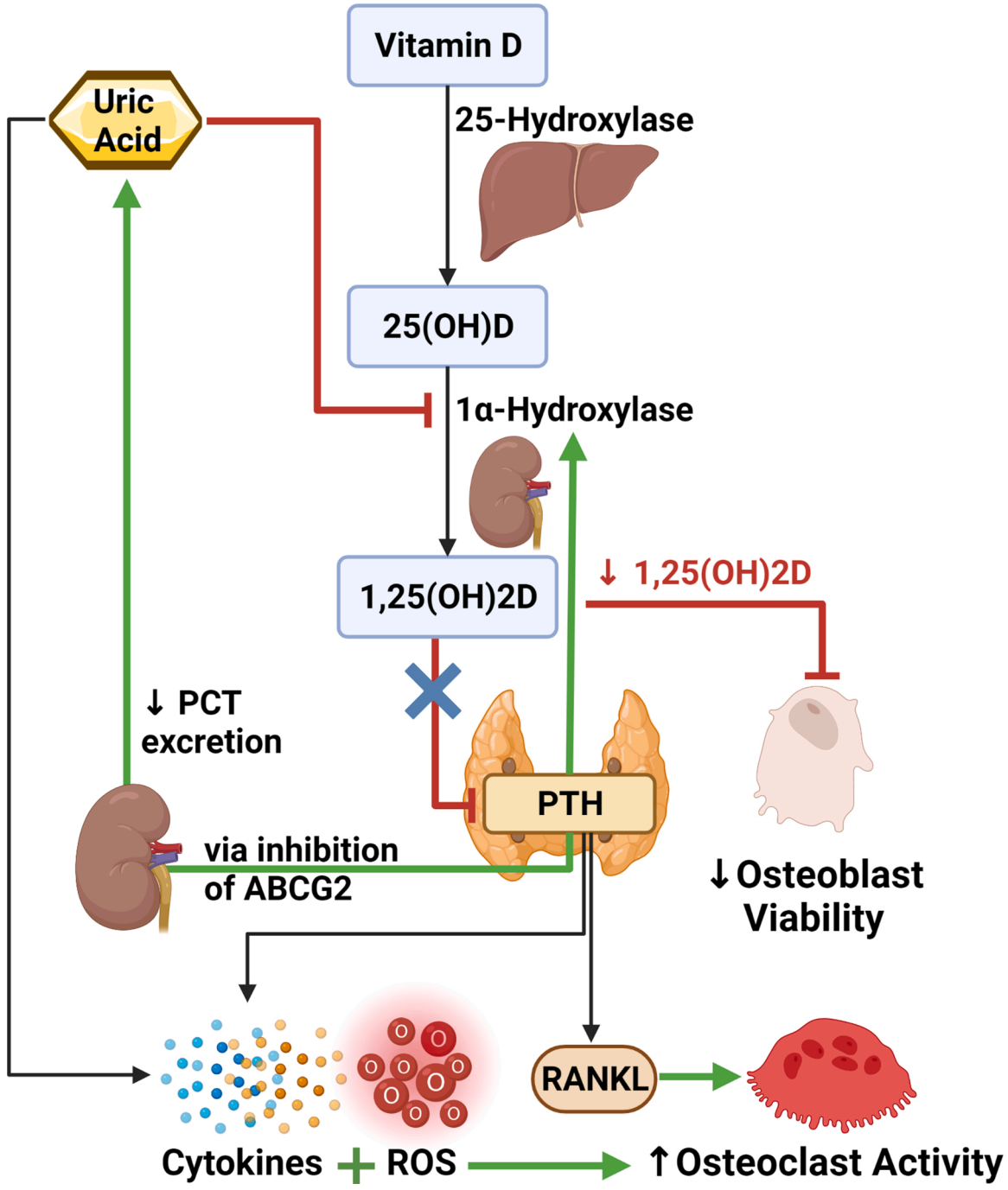

Fig. 3. The vicious cycle between uric acid, vitamin D, and parathyroid hormone leading to bone loss. ABCG2, ATP-binding cassette transporter G2; PTH, parathyroid hormone; ROS, reactive oxygen species; RANKL, receptor activator of nuclear factor kappa beta.

dyslipidemia, and CKD for patients with high SUA levels even in the normal range. For decreasing the risk for cardiometabolic disease in a healthy population, Kuwabara et al suggested that SUA levels of <5 mg/dL in men and 2-4 mg/dL in women as the optimal range [101]. Even though there is no evidence to suggest treating asymptomatic hyperuricemia for healthy people, lifestyle changes like decreasing consumption of meat, alcohol and fructose for reducing SUA levels can be suggested asymptomatic hyperuricemia.

Another important aspect after the demonstration of strong association between SUA levels and cardiovascular health is to determine certain cut-off values which may help identify the patients at risk and patients that require either therapeutic intervention or close follow-up. A nationwide multicenter large scale observational cohort study conducted in Italy with a total of 23.247 participants between age 18 and 95, referred as The Uric Acid Right for Heart Health (URRAH) study, aims to determine specific cut-off values. This study demonstrates clear association between elevated SUA levels and the risk of fatal myocardial infarction after adjustment of multiple confounding factors. SUA level over 5.26 mg/dl in females is shown to be clear cut-off value after statistical analysis, whereas, no such clear cut-off value has been validated in males [102]. Virdis A. et al. also suggested cutoff values of SUA for distinguishing total mortality (4.7 mg/dL [95% CI, 4.3-5.1 mg/dL]) and cardiovascular mortality (5.6 mg/dL [95% CI, 4.99-6.21 mg/dL]) analyzing the same database of the URRAH study [103]. Another study conducted on 3.047 participants with a mean follow-up period of 68.85 months demonstrated U-shaped curve regarding the association

between SUA levels and cardiovascular disease and all-cause mortality. SUA levels above 370.5 μmol/L in males and above 327.65 μmol/L in females have been linked to higher all-cause and cardiovascular disease mortality, as well as SUA levels below 180.5 μmol/L in males and 165.7 μmol/L in females [104]. Future studies to elucidate the necessity of targeting these cutoff values of SUA as a treatment goal in asymptomatic patients still are needed.

A U-shaped association between SUA and cardiometabolic disease was suggested because not only hyperuricemia but also hypouricemia defined as SUA levels <2 mg/dL can increase potential adverse effects [105]. Accumulating evidence suggested that very low SUA levels were associated with a decline in cognitive functions and the progression of dementia despite the lack of large-scale cohort studies on the effects of hypouricemia.

10. Future perspective

Uric acid, which was once forgotten and did not attract much attention except for gout and kidney stones, has been shown to be one of the most important metabolic agents by the findings of numerous studies conducted in recent years. Although there is no doubt about the critical role of uric acid in various diseases as a risk factor for metabolic and cardiovascular diseases, there is no consensus on how to use the available information for better patient care. Because metabolism itself is not a single entity and varies greatly from patient to patient, there is no simple prescription or recommendation for adjusting serum uric acid levels to suit all patients.

UA may be a long-awaited key for regulating harmful sides of metabolism and preventing harmful metabolic pathways; however, we do not have enough data to understand how to use it for our patients. Therefore, large-scale clinical trials with well-defined inclusion and exclusion criteria are needed to translate preclinical UA data into patient care. UA also has the potential to become one of the main agents for personalized medicine in the future with its massive connections between different organ systems as a reduction in SUA levels can be beneficial for the prevention and treatment of hypertension, insulin resistance, obesity, metabolic syndrome, non-alcoholic fatty liver disease, and cardiovascular diseases.

While accumulating data suggest that UA can be both the initiator of detrimental metabolic processes and the result of metabolism, this unclear nature of UA further damages the functioning of healthy organ systems, leading to vicious cycles between different organ systems via metabolism. This cause-effect relationship of UA is similar to a chicken and egg problem due to its role in different metabolic processes. Therefore, we also need well-prepared new randomized controlled trials to resolve the UA paradoxes in metabolisms. Increasing use of e-health and studies using big data at population levels can provide the necessary guidance for solving this unclear nature of UA and lead to better patient care.

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Data availability statement

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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