

Review Article

Roles of hyperuricemia in metabolic syndrome and cardiac-kidney-vascular system diseases

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Abstract: Uric acid is the final product of purine metabolism. Hyperuricemia is defined as a condition where the level of uric acid exceeds the normal range. The most well-known disease induced by hyperuricemia is gout. However, many studies have reported that hyperuricemia also plays important roles in cardiac-kidney-vascular system diseases and metabolic syndrome. Although hyperuricemia has been known for a long time, its pathophysiology remains poorly understood. In this review, we highlight studies on advanced pathological mechanisms for injuries induced by hyperuricemia, summarize epidemiological studies on hyperuricemia and its associated diseases, and take a brief look at hyperuricemia prevention.

Keywords: Hyperuricemia, uric acid, metabolic syndrome, cardiac-kidney-vascular system diseases, pathological mechanisms

Introduction

Uric acid is the final oxidation product of purine degradation. In humans, uric acid is mainly derived from endogenous production and food intake, with 70% being excreted by the kidneys and the remainder being primarily eliminated by the intestine [1]. Hyperuricemia is defined as a condition where the serum uric acid (SUA) level exceeds 339 $\mu\text{mol/L}$ for premenopausal women and 416 $\mu\text{mol/L}$ for men and postmenopausal women [2]. Previous studies have suggested that uric acid is a metabolic waste product that forms crystalline deposits in multiple organs or tissues, causing damage such as kidney stones and gout arthritis. With deeper research, it has been recognized that uric acid exerts a strong antioxidant effect that can remove oxygen free radicals generated by oxidative stress and avoid oxidative damage [1]. Consequently, uric acid may play a preventive role against the development of neurodegenerative processes leading to dementia [3], and exert a protective effect on bone metabolism to enhance bone mass, depress bone turnover, and reduce the prevalence of vertebral fractures [4] through its antioxidant characteristic. SUA levels may also be associated with cancer mortality. Specifically, a study from Holland

found that SUA levels were associated with a lower risk of mortality from any type of cancer among males in a general population cohort followed up for 38 years, and this association was retained after adjustment for serum total cholesterol and triglyceride (TG) levels [5]. However, under hyperuricemic conditions, the beneficial effects of uric acid are replaced by deleterious effects. Hyperuricemia may be associated with metabolic syndrome (MetS) [6, 7], and may also be related to vascular diseases, such as cardiovascular disease, and kidney disease. This article reviews the role of hyperuricemia in vascular diseases and MetS, and highlights the mechanisms underlying the effects of uric acid and its associated diseases.

Hyperuricemia and cardiovascular disease

Hyperuricemia is closely associated with cardiovascular diseases [8], including hypertension, coronary atherosclerotic heart disease, atrial fibrillation (AF), and heart failure (**Figure 1**).

Hyperuricemia and hypertension

Several studies have shown that hyperuricemia is an independent risk factor for hypertension

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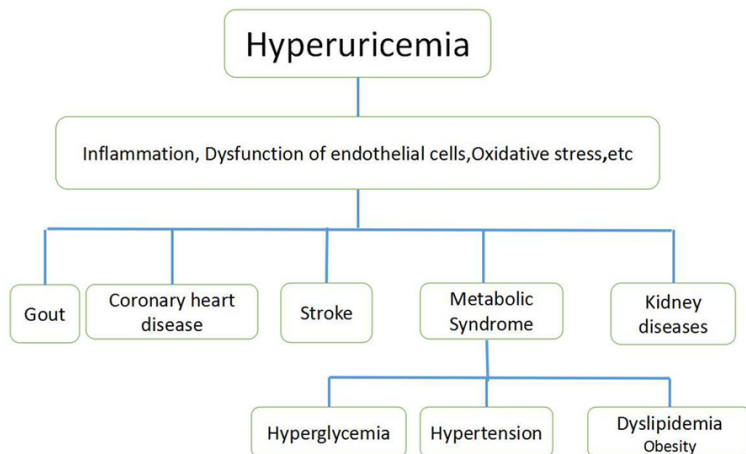


Figure 1. Hyperuricemia and its associated diseases.

[9, 10]. Wang et al. [11] described that the odds ratio (OR) for prehypertension is 1.71 in subjects with UA ≥ 322.2 $\mu\text{mol/L}$ compared with those with UA < 219.2 $\mu\text{mol/L}$ after adjusting for many confounders among 1869 Chinese young adults from Shaanxi Province, China. Another study from Japan including a total of 2335 Japanese male workers without hypertension who ranged in age from 18 to 64 years with 6 years follow-up show that, compared with the lowest quartiles (UA ≤ 303.45 $\mu\text{mol/L}$), the highest serum UA quartiles (UA > 398.65 $\mu\text{mol/L}$) were 1.65 times greater multivariable-adjusted risk of incident hypertension [12]. In a study of the Multiple Risk factors Intervention in normotensive men, the presence of SUA levels greater than 7 mg/dl increased the risk of developing hypertension by 80% [13]. A randomized study showed that SUA lowering drugs were able to reduce blood pressure values in adolescent pre-hypertensive and hypertensive individuals. All these studies demonstrate that hypertension is related with high level of uric acid [14]. The mechanisms for hyperuricemia-induced hypertension may be as follows. (1) Hyperuricemia can lead to hypertension by blocking the production of nitric oxide (NO). NO can induce vasodilation to increase blood flow, reduce vascular smooth muscle cell (VSMC) proliferation, and modulate thrombosis, so it plays an important role in protecting the vasculature under physiological concentrations [15]. The decreases in NO induced by hyperuricemia are mediated by several signaling pathways and mechanisms as follows. (i) High levels of uric acid can lead to descending of NO by in-

ducing reactive oxygen species (ROS). Li et al. [16] found that hyperuricemia can induce ROS accumulation in Human umbilical vein endothelial cells (HUVECs), thereby increasing phosphorylation of eNOS at Thr495 but not at Ser1177 (phosphorylation at Thr495 can reduce eNOS activity; on contrary, phosphorylation at Ser1177 can enhance eNOS activity), that eNOS phosphorylation at Thr495 is mediated by the PKC signaling pathway, and that inhibition of PKC activity can decrease uric acid-induced eNOS phosphorylation

at Thr495, suggesting that uric acid induces phosphorylation of eNOS at Thr495 through a PKC-dependent pathway (**Figure 2**). Li et al. [16] also found that eNOS phosphorylation at Thr495 can reduce the interaction between eNOS and calmodulin, because eNOS activity is triggered by calmodulin binding [17, 18] (**Figure 2**). In addition, the antioxidant can improve uric acid-induced eNOS inhibition and NO production. (ii) Hyperuricemia can reduce production of NO by impairing insulin receptor (IR) signaling pathway. As well-known, the binding of insulin and IR can activate two signaling pathway including the PI3K/Akt signaling pathway which promotes metabolic effects, and the MAPK-related signaling pathway which promotes cellular proliferation, differentiation, and gene expression. Choi et al. [19] revealed that uric acid can inhibit insulin-stimulated eNOS phosphorylation at Ser1177 in a time-dependent manner and reduced production of NO in endothelial cells mediated by the PI3K/Akt pathway. Afterwards Eliezer et al. [20] observed that high levels of uric acid can recruit ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), a plasma membrane enzyme which is expressed in all major insulin target tissues to inhibit the function of insulin receptor thus impacting eNOS phosphorylation via PI3K/Akt signaling pathway (**Figure 2**). These results demonstrated that high uric acid level can decrease NO production independent of its ability to increase the oxidative stress burden at cellular level. Meanwhile, Chao et al. [21] found that uric acid can increase the level of ET-1 by stimulating ET-1 gene expression

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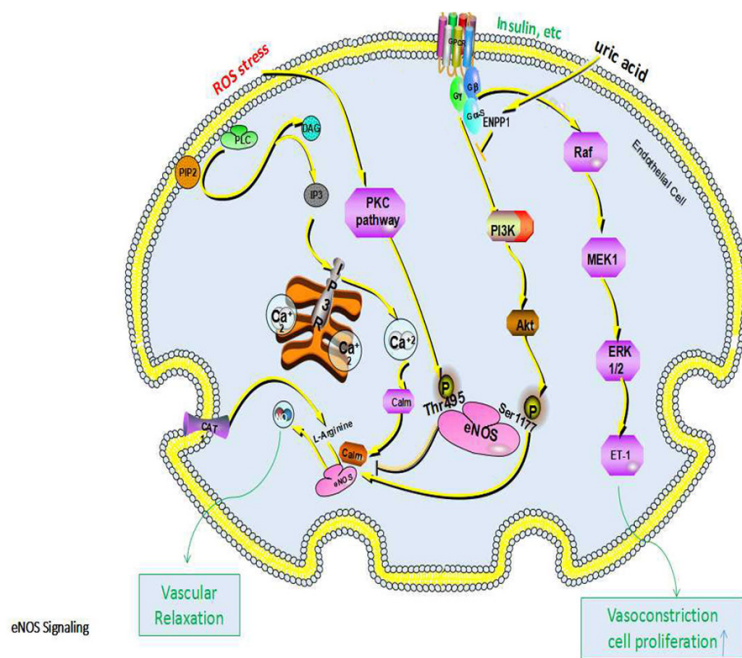


Figure 2. Mechanisms and pathways for the decrease in NO induced by uric acid.

through insulin receptor signaling pathway which involves mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway (**Figure 2**). A balanced action of insulin for endothelial production of NO and endothelin (ET)-1 (one of the most powerful vasoconstrictor substances) is critical for maintaining hemodynamic homeostasis under healthy conditions [22]. High levels of uric acid can inhibit insulin-induced vasodilatation and promote insulin-induced vasoconstriction [20, 21, 23]. (iii) NO is primarily synthesized from L-arginine in endothelial cells by eNOS, and plasma L-arginine is transported in endothelial cells and stored in an arginine pool through the cation amino acid transporter (CAT) on the cell membrane, meaning that eNOS activity and L-arginine transmembrane transport are two rate-limiting steps for NO production (**Figure 2**). L-arginine is the only substrate for NO synthesis by eNOS, and is metabolized by several pathways including intracellular arginase, which is the final enzyme in the L-arginine-urea cycle. Some researchers found that high levels of uric acid can enhance L-arginine-arginase enzymatic activity by attenuating stimulated cGMP production in pulmonary arterial endothelial cells, leading to catabolism of arginine [17]. Schwartz et al. [24] found that hyperuricemia can reduce

arginine uptake in endothelial cells, suggesting that uric acid can affect NO production through alterations in arginine isolated from eNOS activity (**Figure 2**). (2) Hyperuricemia-induced hypertension may be associated with the RAS. Zheng H et al. [25] carried out an experiment to investigate the relationship between hyperuricemia and atherosclerosis in an experimental rabbit model, they found that compared to the control, uric acid, plasma renin and plasma angiotensin II activities were enhanced ($P < 0.001$) in the hyperuricemia groups, smooth muscle cell (SMC) proliferating cell nuclear antigen expression increased strongly and intima thickness and intima areas elevated significantly, all these reactions can be blocked by losartan (a

kind of angiotensin II receptor antagonist) at the dose of 30 mg/kg per day. Kirca et al. [26] observed that vascular smooth muscle cell (VSMCs) of rat aorta underwent proliferation in the condition of hyperuricemia which could be inhibited by losartan, and the proliferative pathways involved phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK), p44/42 mitogen-activated protein kinase (p44/42 MAPK) and platelet-derived growth factor receptor β (PDGFR β). Several observational studies in humans have investigated the positive correlation between uric acid levels and RAS activity in humans [27, 28]. (3) As mentioned above, NO can relax vascular smooth muscle, and its effect is antagonistic to the sympathetic nervous system and the vasoconstrictor action of the vascular renin-angiotensin system (RAS) that together maintain the function of blood vessels. Excess uric acid reacts directly with NO to produce unstable nitrosouric acid and finally produces stable 6-aminouracil [2]; this weakens the role of NO in relaxing blood vessels and inhibiting proliferation of smooth muscle, causing the sympathetic nervous system and the RAS to act in a relatively hyperfunctional manner. (4) It is well known that the renal epithelial sodium channel (ENaC) is responsible for the rate-limiting step of sodium

reabsorption and thus plays an important role in the maintenance of sodium balance, extracellular fluid volume, and blood pressure. Xu et al. demonstrated that hyperuricemia induces hypertension through activation of ENaC, and also found that the expressions of α -, β -, and γ -ENaC were significantly increased in hyperuricemic rats to enhance the absorption of sodium ions in the renal tubules, leading to an increase in blood volume that can cause hypertension [30]. (5) Uric acid crystals can be deposited in vascular endothelial cells to induce vascular endothelial damage directly, followed by lipid deposition from blood under the endothelium that damages endothelial cells, thereby inducing vascular endothelial injury and atherosclerosis. In addition, by acting as a barrier, endothelial cells have an anticoagulant effect, and damage to these cells not only weakens the anticoagulant effect, but also exposes subendothelial collagen to induce platelet aggregation and adhesion, thus promoting thrombus formation. Taken together, these two mechanisms can lead to the occurrence and development of hypertension. (6) Hyperuricemia may affect blood pressure by decreasing the production of adiponectin. Adiponectin, which is produced in adipose tissue, has many functions including anti-atherogenesis, insulin sensitization, lipid oxidation enhancement, regulation of platelet activation and vasodilatation [31, 32]. Brzeska et al. [33] found that adiponectin was negatively correlated with uric acid. Nishizawa et al. [32] carried out a clinical trial to investigate the effect of febuxostat on circulating adiponectin in hyperuricemic patients, they found that plasma levels of adiponectin were lower in hyperuricemic patients than in normouricemic controls and the adiponectin increased significantly after only 6 months of febuxostat treatment. Other research has proven that high levels of uric acid can reduce adiponectin production both *in vivo* [34] and *in vitro* [35].

Hyperuricemia and coronary atherosclerotic heart disease

There are some complex correlations between hyperuricemia and coronary heart disease (CHD). A study carried by Kim et al. [36] illustrates the relationship between uric acid and coronary artery calcification (CAC). They conducted a cross-sectional retrospective single-

center study involving 4884 participants without overt coronary artery disease and obtained their CAC scores. The CAC score showed a significant positive association with the SUA level, with retention of statistical significance after adjusting for confounding factors. CAC score was reported to be useful for identifying individuals at high risk for CHD and a strong predictor for all-cause mortality [37, 38]. Choi et al. [39] conducted the first study on the effects of SUA on arterial stiffness. For this, all of their participants underwent brachial-ankle pulse wave velocity (baPWV) assessment to detect arterial stiffness. They found that elevated SUA was independently associated with increased baPWV. A study from China involving 6347 middle-aged and elderly Chinese patients revealed that the 10-year CHD risk was increased by 2.76 times in patients with hyperuricemia compared with patients without hyperuricemia in the female population [40]. Hyperuricemia may promote the development and progression of CHD by forming uric acid crystals, inducing NO production, exerting oxidative stress, promoting inflammatory reactions, promoting oxidation modification of low-density lipoprotein-cholesterol (LDL-C), stimulating proliferation of VSMCs through the RAS [39, 40], and reducing adiponectin production [41].

Hyperuricemia and atrial fibrillation

Atrial fibrillation (AF) is a common cardiac arrhythmia associated with the risks of heart failure and stroke, and can increase the risks of mortality and morbidity [42]. A large-scale epidemiological study involving 90,117 subjects carried by Kuwabara et al. [42] analyzed 49,292 subjects without competing risk factors (hypertension, type 2 diabetes mellitus, cardiovascular disease, chronic kidney disease, heart failure) and observed that hyperuricemia was an independent competing risk factor for AF in an apparently healthy general population. A meta-analysis of cohort studies produced a similar result [43]. The mechanism for hyperuricemia-induced AF may be as follows. (1) Hyperuricemia-induced AF may associate with increased calpain-1 expression and activation. Yan M et al. [44] described the expression and activation of calpain-1, which has been reported to participate in several pathological conditions affecting the cardiovascular system, was increased in the cardiac tissue of hyperuricemic rats inducing cardiomyocyte ER stress and sub-

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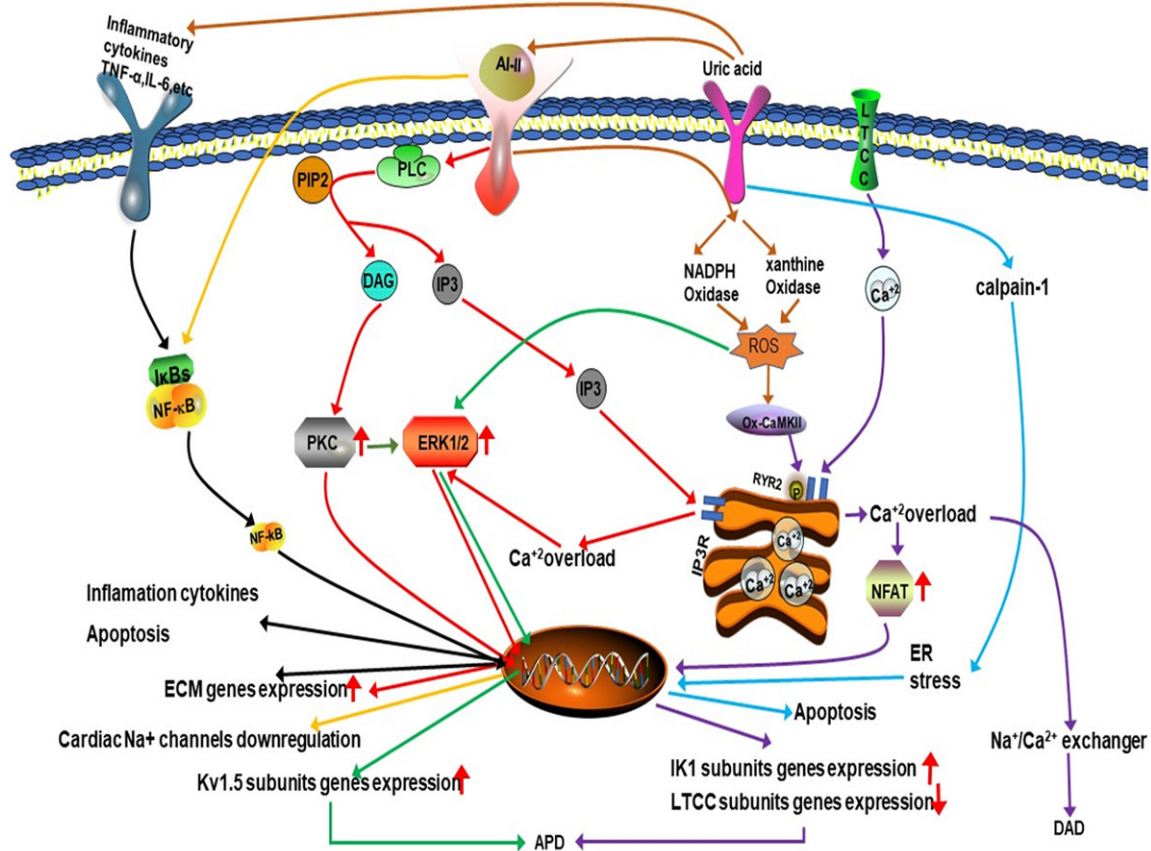


Figure 3. The mechanism of hyperuricemia-induced atrial fibrillation.

sequent apoptosis as well as interstitial fibrosis, and the allopurinol pretreatment mitigated all the above changes induced by hyperuricemia (**Figure 3**). (2) Hyperuricemia-induced AF may associate with inflammation. As mentioned above, high dose UA increased expression of inflammation cytokines [45]. Inflammatory cytokine such as Interleukin-6 (IL-6), Interleukin-8 (IL-8), Interleukin-10 (IL-10) and tumor necrosis factor (TNF- α) et al. can activate nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B) signaling pathway causing extracellular matrix (ECM) proteins deposition, thus inducing fibrotic remodeling [46] (**Figure 3**). (2) The ROS generation induced by activation of xanthine oxidases and NADPH oxidases plays an important role in hyperuricemia-induced-atrial fibrillation. Korantzopoulos et al. [47] reported that increased SUA was accompanied by an increase in cardiac tissue xanthine oxidase activation. ROS production through activation of xanthine oxidase may contribute to the pathological consequences of

AF such as thrombosis, inflammation, and tissue remodeling [48, 49]. A series of researchers demonstrated that allopurinol therapy decreased atrial vulnerability by inhibiting atrial remodeling [49, 50]. The activation of NADPH oxidases also exert similar effect on cardiac myocyte [51, 52]. The ROS can shorten the atrial action potentials (APD) and promote delayed after depolarizations (DAD) by altering various ion channels such as L-type Ca^{2+} -channel (LTCC) [53] and IK1 channel, both of which involved in nuclear factor of activated T cell (NFAT) signaling pathway and Kv1.5 channel, which involved in ERK1/2 signaling pathway [51] (**Figure 3**). (3) Hyperuricemia can activate the RAS system to increase the risk of AF. The RAS plays an significant role in the development of various cardiovascular diseases, including atrial fibrillation (AF). Just as mentioned above [25], hyperuricemia can increase the angiotensin II level. A recent study found that mice treated with angiotensin II showed increased neutrophil infiltration into their atrial

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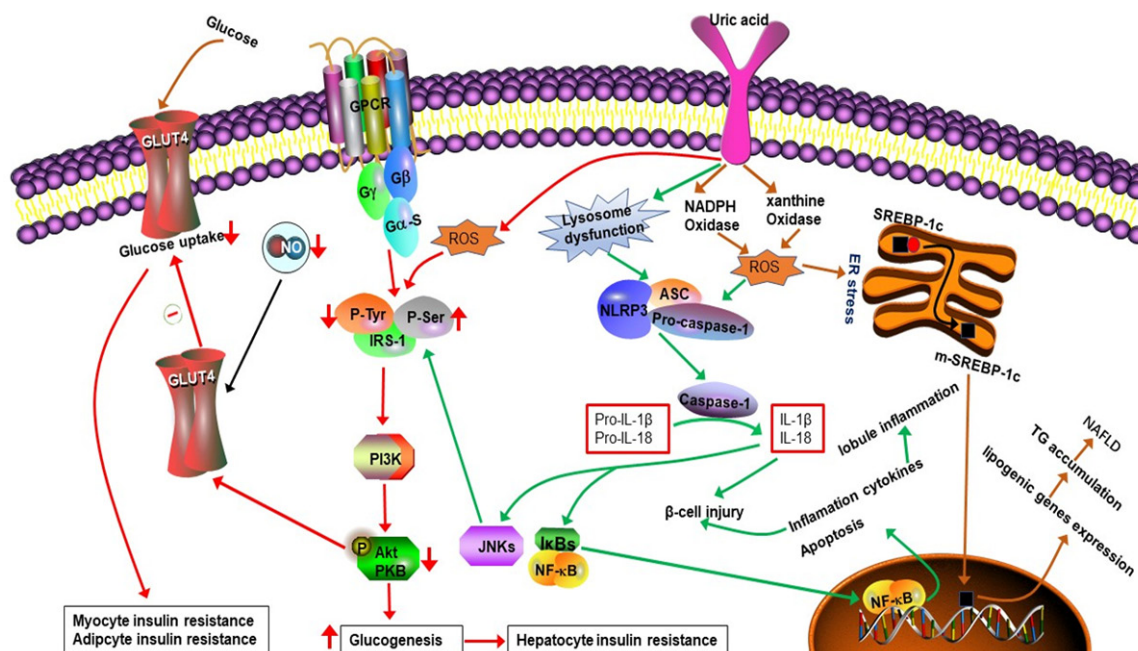


Figure 4. The mechanism of hyperuricemia-induced insulin resistance and Nonalcoholic fatty liver.

tissue [54]. In clinical settings, the angiotensin receptor blocker losartan showed a 33% reduction in the incidence of new-onset AF, suggesting that losartan may decrease the risk of AF by abolishing the RAS system activation induced by hyperuricemia [55]. The arrhythmogenic effects of angiotensin II are associated with atrial fibrosis induced by increased production of the extracellular matrix (ECM) proteins which involved PKC pathway, ERK1/2 pathway and NF- κ B pathway, and with the alteration of various ion channels induced by oxidative stress and inflammation [47, 52, 53], thus resulting in electrical and fibrotic remodeling (**Figure 3**). Taken together, hyperuricemia is involved in the pathogenesis of AF through electrical and structural remodeling.

Hyperuricemia and hyperglycemia

Hyperuricemia is strongly associated with insulin resistance and abnormal glucose metabolism. Several studies reported that high uric acid level showed a negative effect on islet beta cells and glucose regulation [56-59], and allopurinol lowers uric acid and improves insulin resistance and systemic inflammation in asymptomatic hyperuricemia [60]. (1) Zhu et al. [61] found that increased ROS can be generated in an hyperuricemia mouse model, that the

produced ROS can increase phosphorylation of insulin receptor substrate at a serine residue and decrease its phosphorylation at a tyrosine residue, and that two reactions block the phosphorylation of protein kinase B at a serine residue, leading to failure of downstream signaling and resulting in insulin resistance (**Figure 4**). (2) Hyperuricemia-induced-insulin resistance is associated with decrease of endothelial NO levels. As mentioned above, hyperuricemia can reduce the endothelial NO production. NO is a key regulator for insulin sensitivity of peripheral tissues for NO leads to increase blood flow and to enhance glucose uptake by cells [62] (**Figure 4**). (3) Hyperuricemia can induce insulin resistance and beta cell apoptosis through the activation of the NLRP3 pathway. High Uric acid level can cause lysosomal dysfunction and activate NLRP3 pathway producing inflammatory factors (IL-1 β , IL-18), thus activating JNKs pathway inducing insulin resistance and NF- κ B pathway initiating the procedure of apoptosis in islet B cells [63, 64] (**Figure 4**). (2) Hyperuricemia can set negative effect on pancreatic β -cell growth and insulin secretion through activation of adenosine monophosphate-activated protein kinase (AMPK) which could be induced by ROS and inflammation. Zhang et al. [65] revealed the presence of increased ROS at high levels in uric acid-treat-

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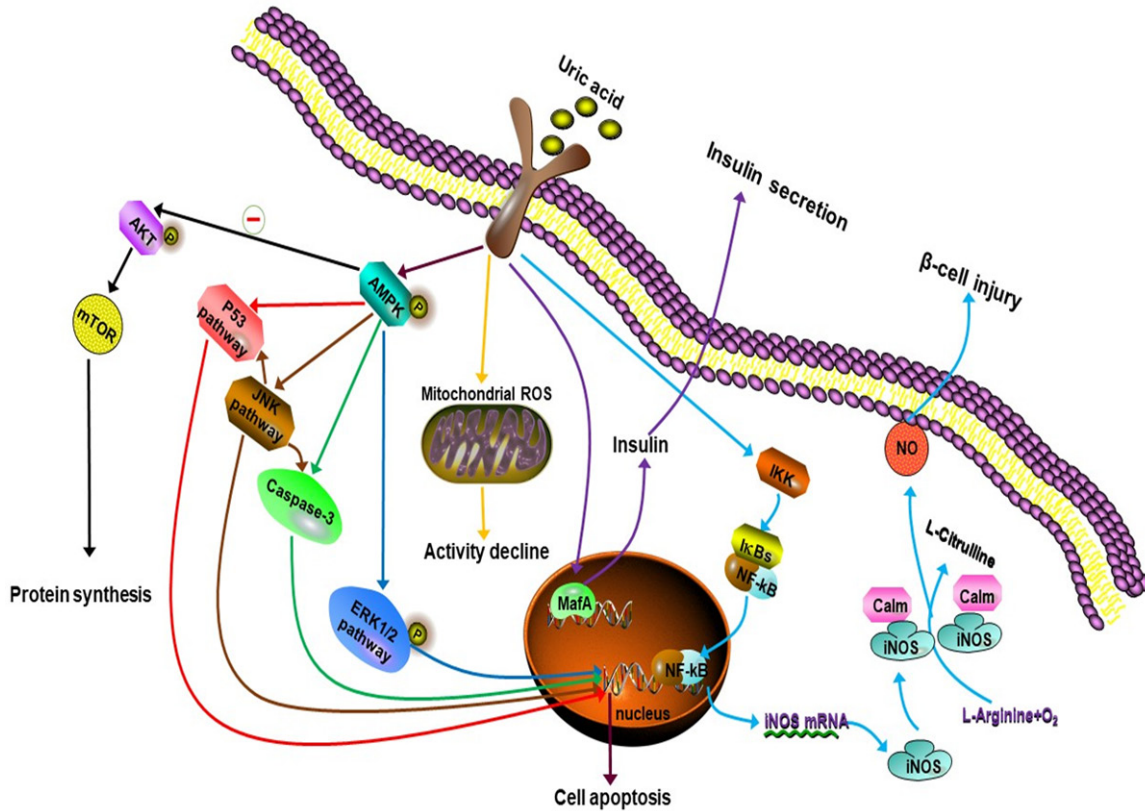


Figure 5. Mechanisms of hyperuricemia-induced β -Cell injury and dysfunction.

ed β -cells. As a target for oxidative stress, it is known that adenosine monophosphate-activated protein kinase (AMPK) can be phosphorylated by the actions of ROS. In the cited study, the authors found the effects of high levels of uric acid on β -cells through oxidative damage and growth inhibition are mediated by activation of the AMPK and ERK signaling pathways, and found that ERK is a downstream target of AMPK in uric acid-treated β -cells. Other researchers also observed that the activation of AMPK caused by ROS and inflammation can induce β -cells injury and apoptosis [66-69]. As well known, AMPK contributes to the salutary effects of adipokines on fatty acid oxidation, glucose utilization and insulin sensitivity, relatively short-term activation of AMPK has been regarded as a therapeutic strategy for obesity and T2DM [67], however, sustained activation of the enzyme can lead to programmed cell death and this process may involve in various signaling pathway [66] (**Figure 5**). (3) The activation of nuclear factor (NF)- κ B and subsequent production of NO by inducible nitric oxide synthase (iNOS) have been proven to be responsible for β -cell damage and death. In the

study by Jia et al. [70], hyperuricemia was observed to cause pancreatic β -cell death and dysfunction through the NF- κ B-iNOS-NO signaling axis. In addition, they found that high levels of uric acid enhanced the degradation of musculoaponeurotic fibrosarcoma oncogene homolog A (MafA) protein (one of the transcription factors for insulin synthesis), thereby reducing glucose-stimulated insulin synthesis and secretion (**Figure 5**). (4) Hyperuricemia can increase insulin resistance by increasing the production of monocyte chemoattractant protein (MCP)-1 and reducing adiponectin production. MCP-1, a chemotactic factor that causes aggregation of monocytes in tissues, has an important role in inflammatory processes. MCP-1 was reported to be significantly increased in patients with type 2 diabetes, and has been suggested as a possible molecular marker for this disease [70, 71]. Yang L et al. described MCP-1 can decrease the function and quantity of islet β cells and induce insulin resistance by contributing to macrophage infiltration into islet β cells and the target tissue of insulin [72]. Another important factor affecting insulin resistance is adiponectin, which is mainly produced in adi-

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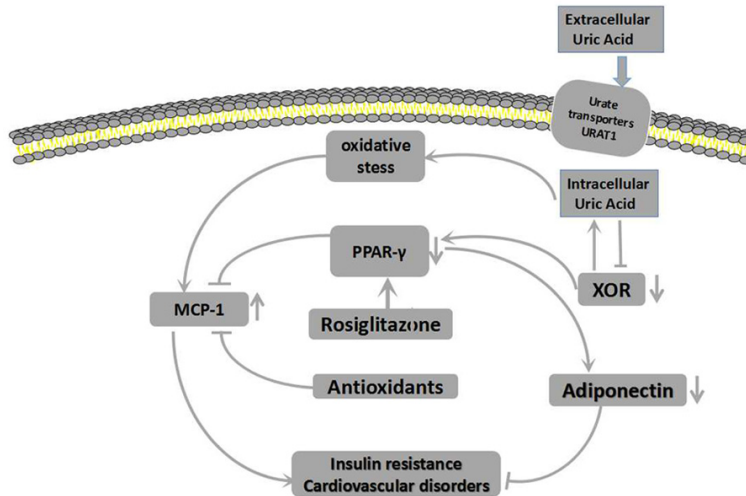


Figure 6. Mechanisms for the increase in MCP-1 and decrease in adiponectin induced by uric acid.

pose tissue [41] and controlled by peroxisome proliferator-activated receptor- γ (PPAR- γ) [73, 74]. As adiponectin receptors are expressed in both fat and muscle tissues in humans, adiponectin can exert a potent insulin-sensitizing effect [75]. Baldwin et al. [35] observed a significant increase in the abundance of MCP-1 mRNA and a gradual decrease in adiponectin mRNA in dose-dependent and time-dependent manners in differentiated mouse 3T3-L1 adipocytes cultured with high levels of uric acid. They further found that the uric acid-induced increase in MCP-1 production could be inhibited by antioxidants and rosiglitazone (a PPAR- γ agonist), suggesting that activation of MCP-1 expression and secretion in adipocytes is mediated by superoxide-dependent ROS and a mechanism involving PPAR- γ . However, the effect of uric acid on adiponectin production was not prevented by antioxidants, but could be abrogated by rosiglitazone, suggesting that uric acid-induced inhibition of adiponectin production is not mediated by redox-dependent signaling, but rather by a mechanism involving PPAR- γ . They also found that uric acid could induce downregulation of PPAR- γ by affecting xanthine oxidoreductase (an enzyme producing uric acid that acts as a crucial upstream regulator of PPAR- γ activity) [35] via a negative feedback mechanism (**Figure 6**).

Hyperuricemia and obesity, NAFLD and dyslipidemia

A previous study showed that increased uric acid levels are associated with MetS compo-

nents, such as hypertriglyceridemia, insulin resistance, elevated blood pressure, and low high-density lipoprotein-cholesterol (HDL-C), but the relationship between uric acid and hypertriglyceridemia was the strongest and most stable [76]. Zheng X et al. reported that elevated uric acid level shows independently positive associations with the prevalence of Non-alcoholic fatty liver disease (NAFLD) and the severity of fatty liver [77]. Sirota et al. [78] got the similar results and found that the positive association between SUA and NAFLD was independent of insulin resistance. Yang C et

al. [79] observed that hyperuricemic subjects had significant higher TC and TG levels, compared to obese and non-obese normouricemic subjects. Kuwabara, et al. [80] reported that an elevated SUA increases the risk for developing high LDL cholesterol, as well as hypertriglyceridemia. The hyperuricemia-induced abnormal storage of fat may be related to the following mechanisms. (1) High uric acid level can induce insulin resistance resulting hyperinsulinemia [61, 72], high level of insulin promotes lipolysis in the adipocyte and increases free fatty acids (FFAs) delivered to the liver, where subsequent accumulation of the triglycerides may lead to hepatic steatosis. (2) SUA levels contribute to NAFLD pathogenesis through their association with ROS and subsequent ER stress [81, 82]. High uric acid level activates NADPH Oxidase (NOX) after entering into hepatocytes and induces membranous NOX-dependent ROS production, which stimulates ER stress. ER stress stimulates sterol regulatory element-binding protein-1c (SREBP-1c) cleavage into mature form, which is translocated into nucleus and activates the transcription of lipogenic genes (lipogenic Enzymes). Metformin, an inhibitor of SREBP-1c, and antioxidants can blocked hepatic fat accumulation. NOX-dependent ROS further activates mitochondrial ROS production, which can also be activated by ER stress. Mitochondrial ROS is also reported to be an important mechanism of TG accumulation in hepatocyte [82] (**Figure 4**). (3) The prevalence rates of high NAFLD activity score (NAS) and lobule inflammation tended to increase

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with increases in the SUA level, which suggested that the inflammation of NAFLD tended to increase as the SUA level increased [83], the inflammation development of NAFLD may involve in NLRP3 inflammasome-dependent mechanism [63] (**Figure 4**). (4) Hyperuricemia-induced high TG levels may be associated with a decreased activity in glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a protein that is known to be one of the major targets of ROS [84]. Given that GAPDH is a key enzyme in the glycolysis pathway and the central link for glucose metabolism, a decrease in its activity will lead to inhibition of glycolysis, which can lead to accumulation of not only glucose, but also large amounts of glyceraldehyde 3-phosphate, thus promoting its isomerization or transformation of dihydroxyphosphate acetone into glycerol. As glycerol is an important material for TG synthesis, this can in turn lead to an increase in TG synthesis. (5) Hyperuricemia may affect lipid metabolism by reducing the activity of lipoprotein lipase through inflammation. Some researchers described that IL-1 β , a product of NLRP3 inflammasome pathway, could inhibit lipoprotein lipase [64]. It is known that lipoprotein lipase can break down the core of lipoproteins (TG), and that a decrease in the expression of this enzyme can lead to a decrease in TG catabolism. (6) Hyperuricemia can induce dyslipidemia by reducing adiponectin production. Some researchers reported that adiponectin was positively associated with HDL-C and lipoprotein lipase and negatively associated with LDL-C and TG concentrations [85]. Similar correlations among adiponectin, HDL-C, and TG were also observed in postmenopausal women and female adolescents [41] and, as previously mentioned, hyperuricemia can decrease adiponectin production. (7) Obesity is associated with infiltration of monocytes into adipose tissue, which can lead to activation of inflammation pathways, reduction in lipid turnover, and deposition of fat in ectopic locations [86]. As mentioned above, hyperuricemia can lead to elevated MCP-1 levels in adipose tissue, which cause aggregation of monocytes in adipose tissues, and in turn, these accumulated monocytes in adipose tissues secrete inflammatory cytokines, such as TNF- α , IL-6, and MCP-1 [87]. These effects create a vicious circle that aggravates the metabolic disorder in adipose tissues.

Hyperuricemia and kidney diseases

Hyperuricemia is associated with chronic kidney disease (CKD). A prospective cohort study involving 18,778 men who participated in a health checkup program was carried out to test the relationship between elevated SUA levels and risk of developing CKD over a 4-year follow-up period. It was found that a high SUA level was significantly associated with an increased likelihood for development of CKD after adjusting for well-known independent risk factors for CKD development such as age, baseline estimated glomerular filtration rate (eGFR), systolic blood pressure, homeostasis model assessment of insulin resistance, TG, body mass index, alcohol intake, smoking status, regular exercise, hypertension, and diabetes mellitus [87]. Weiner et al. [88] revealed that the risk of developing CKD increased by 7-11% per 1 mg/dL uric acid.

Hyperuricemia may also increase mortality among CKD patients undergoing hemodialysis. In a study aiming to determine the impact of hyperuricemia on long-term (19.5 years) survival of CKD patients, it was observed that the mortality of normouricemic patients (50%) was lower than that of hyperuricemic patients (82.4%) [89].

Elevated SUA levels can delay renal recovery in living kidney donors. A study carried by Bravo et al. [90] analyzed the association between pre-donation SUA level in 291 live kidney donors and residual renal function at 6 months and 1 year after nephrectomy. They showed that females in the highest tertile (SUA > 4.5 mg/dL) had a significantly lower eGFR and a significantly higher percentage of donors with eGFR < 60 mL/min/1.73 m² compared with those in the lower tertiles at 6 months and 1 year post-donation. Furthermore, a logistic regression showed that SUA was a significant independent predictor for development of eGFR < 60 mL/min/1.73 m² at 1 year after donation in female donors. Other researchers reported that a 59.5 μ mol/L increase in baseline SUA was associated with a 1.7-fold higher risk of a > 25% decrease in eGFR in women [91]. These findings suggest that pre-donation SUA is predictive of delayed renal recovery post-nephrectomy in female donors.

Hyperuricemia and its associated diseases

Hyperuricemia plays an important role in the development of all-cause (peritonitis, non-compliance, operational problem, ultrafiltration insufficiency, dialysis inadequacy, mechanical problems, structural defect, surgical procedure, tunnel infection, other reason, unknown) and peritonitis-related technique failure in patients starting continuous ambulatory peritoneal dialysis (CAPD) as renal replacement therapy. Hsieh et al. [92] conducted a retrospective study involving 371 participants on CAPD. During the study period, technique failure occurred in 34.4% patients in the hyperuricemia group compared with 19.4% in the normouricemia group. (5) Hyperuricemia is a major risk factor for contrast induced-acute kidney injury (CI-AKI). A meta-analysis including 18 relevant studies involving a total of 13,084 patients presented compelling evidence that higher SUA was associated with a 1.68-fold higher risk for CI-AKI compared with lower SUA [93]. It was also observed that patients with hyperuricemia had higher in-hospital mortality and higher risk for renal replacement therapy after coronary angiography and/or percutaneous coronary intervention. Another meta-analysis including 10 studies with 10,427 patients revealed that higher SUA conferred a 2-fold higher risk for CI-AKI compared with lower SUA, and that administration of allopurinol may help to reduce the risk of CI-AKI among patients with hyperuricemia undergoing coronary procedures [94]. As hyperuricemia is a major risk factor for CI-AKI, its levels can be measured to assess the risk of CI-AKI development and short-term clinical outcomes before cardiac procedures. The impact of hyperuricemia in CKD and acute kidney injury may be related to the following mechanisms. First, as mentioned above, a high level of uric acid can activate the RAAS, inducing strong vascular contraction and VSMC proliferation, and further diminish the renal blood flow as well as increase renal vascular resistance, especially in afferent arterioles [25, 26]. Second, hyperuricemia can enhance oxidative stress induced by nicotinamide adenine dinucleotide phosphate (NADP) oxidase and xanthine oxidase [95-97] and reduce NO production and bioavailability, inducing further endothelial dysfunction [20]. Third, uric acid can increase the production of many inflammatory factors, including IL-1, IL-6 and C-reactive protein, thereby stimulating the inflammatory response and inducing tubular injury and leading

to glomerular hypertrophy and renal tubular interstitial fibrosis [97, 98]. Fourth, uric acid crystals can directly injure tubules.

Sufficient attention should be paid to the damage induced by hyperuricemia. The incidence of hyperuricemia can be reduced by eating less foods containing high purine levels, such as seafood, animal offal, and increasing intake of vegetables, fruits, milk, and eggs. Health education can be carried out to improve people's awareness of hyperuricemia, which may contribute to a reduction or delay in the occurrence and development of hyperuricemia and its complications.

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Disclosure of conflict of interest

None.

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