Association of Serum Uric Acid with Diabetes and Hypertension and Hyperuricemia A Causal Effect on Metabolic Syndrome

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Abstract: *Elevated serum uric acid concentration is a common laboratory finding in subjects with metabolic syndrome/obesity, hypertension, kidney disease and cardiovascular events. Hyperuricemia has been attributed to hyperinsulinemia in metabolic syndrome and to decreased uric acid excretion in kidney dysfunction and is not acknowledged as a main mediator of metabolic syndrome, renal disease, and cardiovascular disorder development. However, more recent investigations have altered this traditional view and shown by providing compelling evidence to support an independent link between hyperuricemia and increased risk of metabolic syndrome, diabetes, hypertension, kidney disease and cardiovascular disorders. However, despite these new findings, controversy regarding the exact role of uric acid in inducing these diseases remains to be unfolded. Furthermore, recent data suggest that the high-fructose diet in the United State, as a major cause of hyperuricemia, may be contributing to the metabolic syndrome/obesity epidemic, diabetes, hypertension, kidney disease and cardiovascular disorder.*
Our focus in this review is to discuss the available evidence supporting a role for uric acid in the development of metabolic syndrome, hypertension, diabetes; and the potential pathophysiology mechanisms involved.
Key Words: *serum uric acid, metabolic syndrome, hypertension, kidney disease, hyperinsulinemia*

I. Introduction

Since several million years ago, our early ancestors have lost the gene for uricase which converts uric acid into the soluble form, allantoin and uric acid remains as the final waste product of purine metabolism in humans.[1] As a consequence, humans have higher uric acid levels than most other mammals having the enzyme uricase.[2]

Although definition of hyperuricemia is arbitrary, it is usually defined as a serum uric acid level greater than 7.0 mg/dl in men and greater than 6.0 mg/dl in women. This difference has been linked to the uricosuric effect of estrogens in women.[3,4,5]

Since uric acid has the ability to act as an antioxidant, elevated plasma uric acid concentration has been considered as a beneficial phenomenon, which has a compensatory role in response to increased oxidative stress in conditions such as cardiovascular disease.[6] Although uric acid seems to have antioxidant activity in the extracellular environment, once it enters cells including vascular smooth muscle cells (VSMC) and adipocytes, it has detrimental effects. Injurious impacts of uric acid include an inhibitory effect on nitric oxide (NO) production; induction of platelet aggregation, and pro-inflammatory activity.[7]

Extending these observations, it has been proposed that hyperuricemia may predict the development of metabolic syndrome, diabetes, hypertension, kidney disease and cardiovascular disorders.[8] These findings support the notion that elevated serum uric acid levels cannot just be viewed as a secondary phenomenon in these pathologies.[9] However, it is still unclear whether uric acid plays a pathogenic role in the development and progression of these syndrome and diseases.[10]

This review will discuss available evidence supporting a role for uric acid in the onset and progression of metabolic syndrome, hypertension, and renal disease; as well as the potential pathophysiological mechanisms.[11]

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. Hyperuricemia is defined as a condition where the serum uric acid (SUA) level exceeds 5.69 mg/dl for premenopausal women and 6.99 mg/dl for men and postmenopausal women.[12] 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

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been recognized that uric acid exerts a strong antioxidant effect that can remove oxygen free radicals generated by oxidative stress and avoid oxidative damage.[13] Consequently, uric acid may play a preventive role against the development of neurodegenerative processes leading to dementia, and exert a protective effect on bone metabolism to enhance bone mass, depress bone turnover, and reduce the prevalence of vertebral fractures 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. However, under hyperuricemic conditions, the beneficial effects of uric acid are replaced by deleterious effects. Hyperuricemia may be associated with metabolic syndrome (MetS), 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.[14]

Uric Acid and Metabolic Syndrome

Hyperuricemia is commonly observed in metabolic syndrome and numerous epidemiological investigations have confirmed the association of hyperuricemia with metabolic syndrome. While it has been suggested that uric acid may simply be a consequence of the increased uric acid absorption in the proximal tubule secondary to hyperinsulinemia, there is growing data that uric acid may predict the development of metabolic syndrome, obesity and diabetes.[15]

In a study by Chen et al[16], hyperuricemic subjects had an odd ratio of 1.6-fold higher for developing metabolic syndrome. Also, Sui et al demonstrated this predictive role of uric acid even in human subjects who were free of all features of metabolic syndrome at baseline. In addition, it was illustrated that the correlation between elevated uric acid and metabolic syndrome was independent of estimated glomerular filtration rate (eGFR). In fact, this emphasizes that the status of renal function does not provide justification for the observed link between elevated uric acid levels and the development of metabolic syndrome. A recent human study also supports the premise that insulin resistance has an important role in the causal relationship between metabolic syndrome, and hyperuricemia. Similarly, Osgood and colleagues proposed that the serum uric acid not only correlates with concomitant insulin action, blood pressure, and lipid profile; it also predicts future insulin resistance and type 2 diabetes.[17]

A fructose-rich diet can raise uric acid production and induce the components of metabolic syndrome through mechanisms independent of energy intake or weight gain. These effects are not observed with glucose-rich diet. Use of an animal model of metabolic syndrome induced by consumption of a high fructose diet has contributed the discovery of a causal role for hyperuricemia in the context of insulin resistance states. In this regard, elegant study by Nakagawa and colleagues have provided support for this association by feeding rats a fructose-rich diet, with or without the uric acid-lowering drugs, allopurinol (a xanthine oxidase inhibitor) or benzbromarone (uricase inhibitor). The group of rats that did not receive the drugs developed hyperininsulinemia, hypertriglyceridemia, systolic hypertension, and increased body weight. In contrast, treatment of animals with drugs that lowered serum uric acid levels significantly blunted the features of metabolic syndrome. In particular, when allopurinol was initiated early, it prevented weight gain, insulin resistance, hypertriglyceridemia, and hypertension. Nakagawa et al. also found that uric acid impaired endothelial function.[18]

Apparently, fructose-induced insulin resistance occurs as a result of fructose-induced hyperuricemia. Further, as demonstrated in humans, insulin resistance has been shown to play a potentially key role in the causal relationship between metabolic syndrome, diabetes type 2 and hyperuricemia.[19]

The proposed mechanisms related to these findings may include effect of uric acid on endothelial dysfunction and overproduction of reactive oxygen species (ROS). Uric acid inactivates production of NO in the animal. The recent data also support an association between hyperuricemia and endothelial dysfunction in human and importantly, that this endothelial dysfunction can be reversed by administration of allopurinol in animal model as well as in human subjects. In addition to the above mechanism, hyperuricemia induces intracellular ROS production and decreases NO bioavailability in adipose cells. Since oxidative stress in adipocytes has been considered as a major factor of insulin resistance, hyperuricemia-induced oxidative stress in adipose tissue might play a key role in these dysregulations.[20]

If uric acid plays a pivotal role in the development of metabolic syndrome, then it is critical to understand what stimuli are involved in augmenting serum uric acid levels. This is important since these processes themselves might play an active role in contributing to the development/progression of metabolic syndrome. For example, excessive alcohol intake or thiazide diuretics have been shown to result in all components of metabolic syndrome. Reungjui et al. have demonstrated that thiazides exacerbate the features of metabolic syndrome in the fructose-fed rat model and allopurinol therapy ameliorates hypertension, insulin resistance, hyperglycemia, and hypertriglyceridemia.[21]

In summary, although a strong relationship between hyperuricemia and metabolic syndrome has been established through animal and epidemiological studies, the potential pathophysiological mechanisms by which uric acid contributes to this disease state are just beginning to be clarified. It is clear that further investigations are needed to fully understand the role(s) of uric acid in metabolic syndrome.[22]

Uric Acid and Hypertension

Hyperuricemia is commonly associated with arterial hypertension.In an early study, hyperuricemia was repoted in 25–40% of untreated hypertensive and 75% of malignant hypertensive subjects. In more recent investigations, it has been suggested that the serum uric acid level is an independent risk factor for the development of hypertension. Uric acid has also been shown to be an independent risk factor for a non-dipper circadian pattern of hypertension. Interestingly, serum uric acid levels of 5.5 mg/dL or higher indicated an increased likelihood of preeclampsia in hypertensive pregnant patients.[23]

Mazzali et al. reported that rats with elevated serum uric acid concentrationdeveloped hypertension with a direct relationship between the level of blood pressure and uric acid. In fact, hyperuricemia was demonstrated to cause hypertension via pathways that involved a reduction in nitric oxide synthase in the macula densa of the kidney, stimulation of renin-angiotensin system (RAAS), and reduction of renal perfusion. Importantly, each of these effects was ameliorated by uric acid lowering drugs. Similarly, using a fructose-induced metabolic syndrome animal model, it has been shown that elevation of uric acid is associated with stimulation of the RAAS and in turn, hypertension.[24] Increased synthesis of Ang II in adipocytes appears to be secondary to hyperuricemia. Similarly, a relationship between serum uric acid levels and activation of the RAAS has been shown in humans.

In addition, in a recent clinical study, an increase in uric acid levels>5.5 mg/dL was found in 90% of hypertensive adolescent subjects, while uric acid levels were significantly lower in controls. Furthermore, reduction of uric acid normalized blood pressure in 66% of hyperuricemic adolescents with hypertension as compared to 3% in the control individuals. These studies involving children and adolescents may be of benefit in elucidating the causative role of uric acid in hypertension as confounding factors prevalent in adults do not exist.[25]

Based on available data, serum uric acid could be a potential novel target for preventing or reversing a rise in blood pressure in patients. At this point, losartan is the only drug amongst antihypertensive medications that has a hypouricemic effect; therefore, prescribing losartan in hypertensive patients with hyperuricemia might be considered by physicians. As most diuretics elevate serum uric acid, developing uricosuric diuretics might be an exciting area of research.[26]

Hyperuricemia and hypertension

Several studies have shown that hyperuricemia is an independent risk factor for hypertension. Wang et al. described that the odds ratio (OR) for prehypertension is 1.71 in subjects with UA ≥ 5.41 mg/dl compared with those with UA < 3.685 mg/dl 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 ≤ 5.10 mg/dl), the highest serum UA quartiles (UA > 6.70 mg/dl) were 1.65 times greater multivariable-adjusted risk of incident hypertension. 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%. 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. 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. 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 inducing reactive oxygen species (ROS). Li et al. found that hyperuricemia can induce ROS accumulation in Human umbilical vein endothelial cells (HUVECs), thereby increasing phosphorylation of eNOS(nitric oxide synthasePC) 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(Protein Kinase C) 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. Li et al. also found that eNOS phosphorylation at Thr495 can reduce the interaction between eNOS and calmodulin, because eNOS activity is triggered by calmodulin binding. 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.[27] 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. 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. 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. found that uric acid can increase the level of ET-1(endothelin 1) by stimulating ET-1 gene expression through insulin receptor signaling pathway which involves mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway.[28] 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. High levels of uric acid can inhibit insulin-induced vasodilatation and promote insulin-induced vasoconstriction. (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. 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. Schwartz et al. 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. (2) Hyperuricemia-induced hypertension may be associated with the RAS. Zheng H et al. 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 at the dose of 30 mg/kg per day. Kirca et al. 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 (PDGFRβ). Several observational studies in humans have investigated the positive correlation between uric acid levels and RAS activity in humans. (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; 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. (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. Brzeska et al. found that adiponectin was negatively correlated with uric acid. Nishizawa et al. 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* and in vitro.[29]
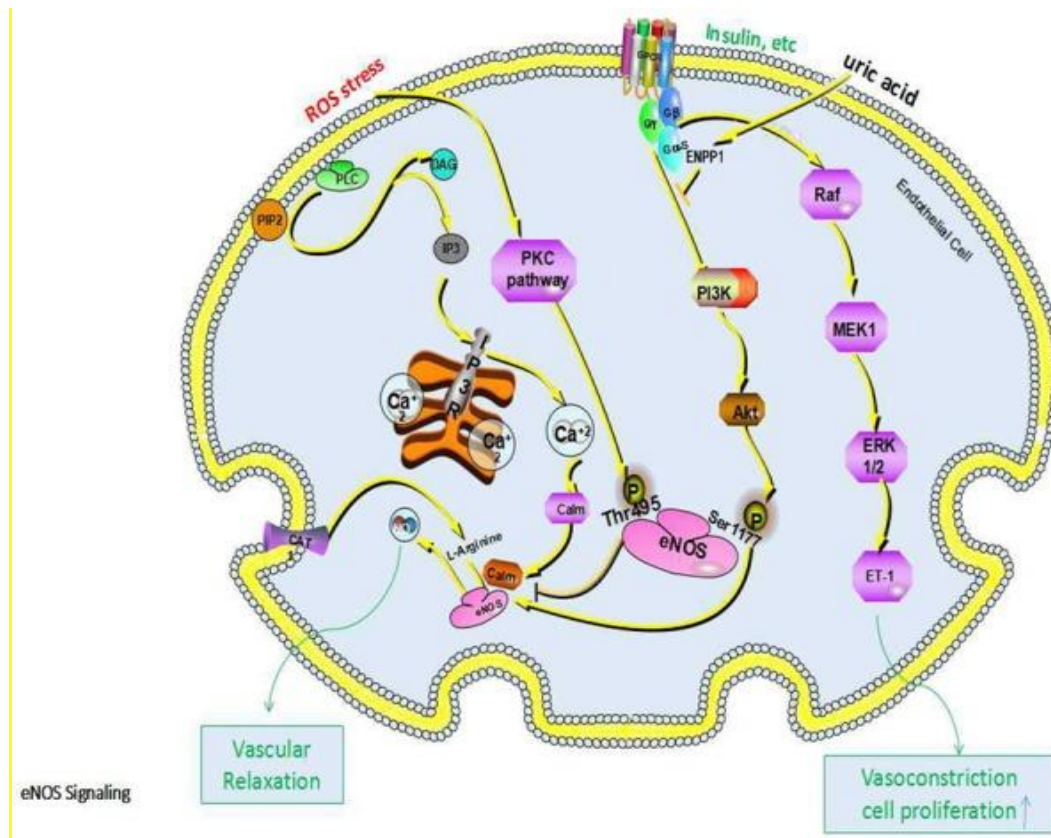

Figure 1: eNOS signaling

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, and allopurinol lowers uric acid and improves insulin resistance and systemic inflammation in asymptomatic hyperuricemia. (1) Zhu et al. 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. (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.[30] (3) Hyperuricemia can induce insulin resistance and beta cell apoptosis through the activation of the NLRP3(nucleotide-binding domain and leucine-rich repeat containing (NLR) proteins3) pathway. High Uric acid level can cause lysosomal dysfunction and activate NLRP3 pathway producing inflammatory factors (IL-1β, IL-18), thus activating JNks pathway (c-Jun N-terminal kinases) inducing insulin resistance and NF- kappa B pathway (nuclear factor kappa-light-chain-enhancer of activated B cells) initiating the procedure of apoptosis in islet B cells. 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., revealed the presence of increased ROS at high levels in uric acid-treated 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 (extracellular-signal-regulated kinase (*ERK*) *pathway)*, 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. 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, however, sustained activation of the enzyme can lead to programmed cell death and this process may involve in various signaling pathways.[31] (3) The activation of nuclear factor (NF)-κB 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. hyperuricemia was observed to cause pancreatic β-cell death and dysfunction through the NF-κB-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. (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. 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. Another important factor affecting insulin resistance is adiponectin, which is mainly produced in adipose tissue and controlled by peroxisome proliferator-activated receptor-γ (PPAR-γ). As adiponectin receptors are expressed in both fat and muscle tissues in humans, adiponectin can exert a potent insulin-sensitizing effect. Baldwin et al.[32] 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) via a negative feedback mechanism.[33]
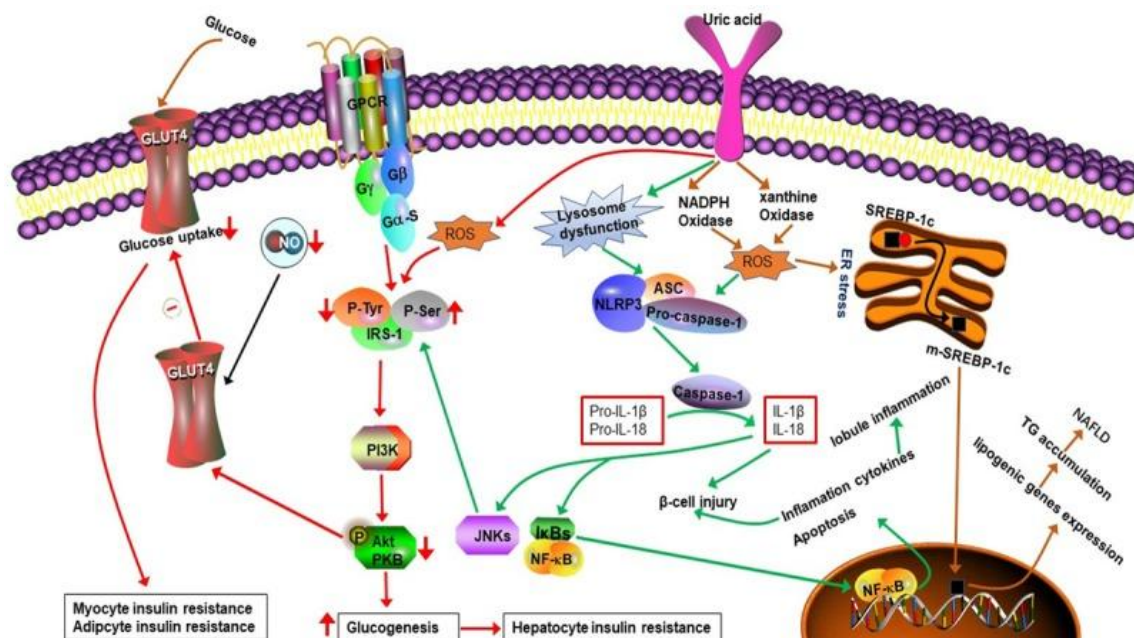

Figure 2: The mechanism of hyperuricemia-induced insulin resistance and Nonalcoholic fatty liver.
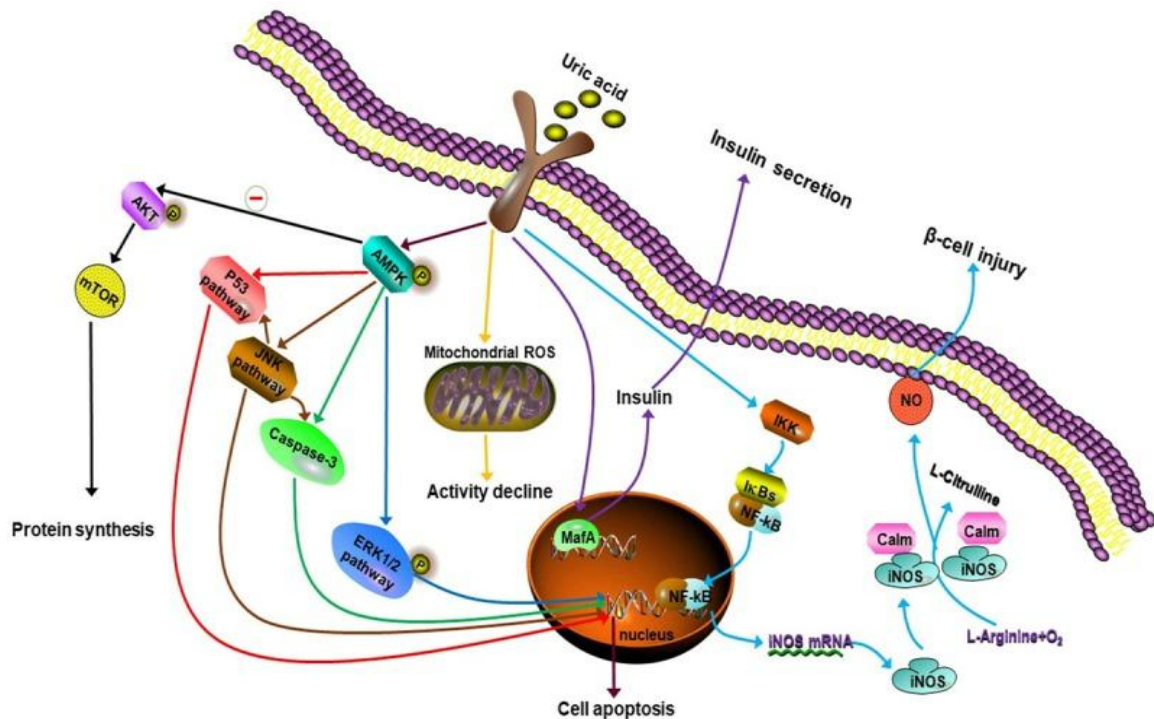
Figure 3: Mechanisms of hyperuricemia-induced β-Cell injury and dysfunction.
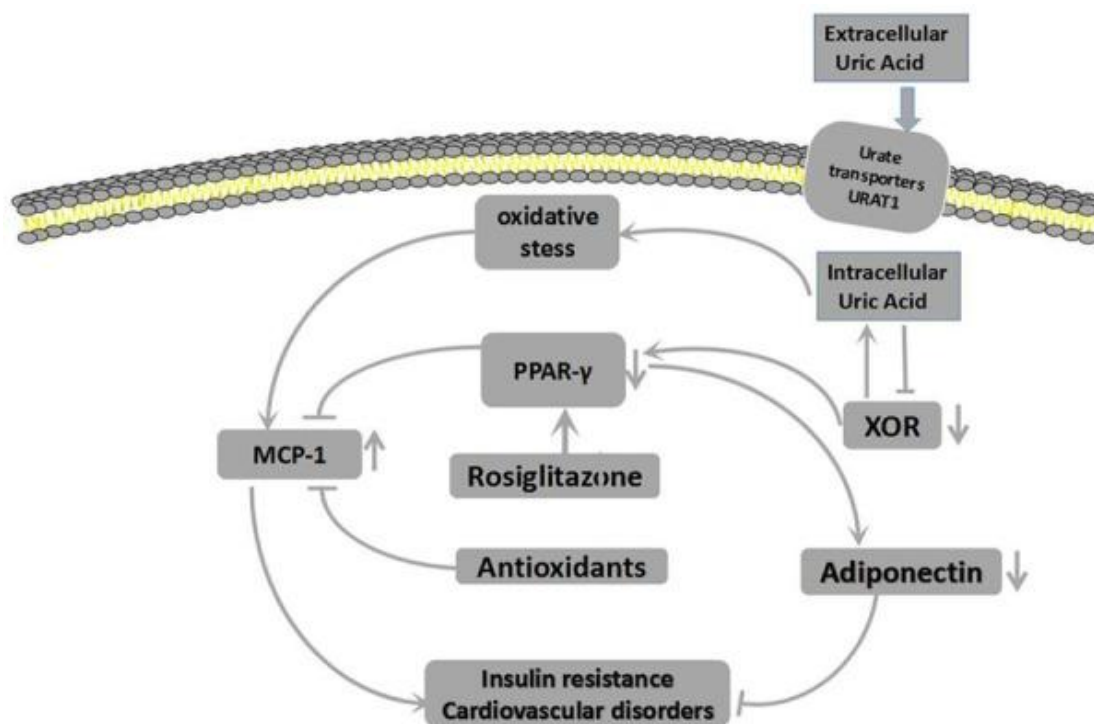

Figure 4: Mechanisms for the increase in MCP-1 and decrease in adiponectin induced by uric acid.

Humans and great apes have higher serum uric acid due to mutations that reduced activity and then silenced the uricase gene about 15 million years ago. Uricase degrades intracellular urate in the liver, resulting in low serum uric acid.[34] Parallel silencing of uricase occurred in lesser apes, suggesting natural selection for higher serum uric acid.[35] Uric acid is an antioxidant in the extracellular environment, reacting with superoxide (to make allantoin) and with peroxynitrite (to make triuret). These antioxidant properties of uric acid were proposed to be beneficial by protecting against aging and cancer-associated oxidative stress.[36-41]

A different hypothesis has also been proposed.[42] The uricase mutation occurred during a period of global cooling that caused seasonal famines for ancestral apes living in Europe due to loss of fruit availability

during winter months. The primary food for these ancestral apes was fruit rich in fructose, a nutrient that predisposes to increased hepatic and visceral fat stores and insulin resistance due to its unique metabolism in which transient ATP depletion occurs. The nucleotide turnover generates urate intracellularly with a rise in serum uric acid.[43] The intracellular urate causes mitochondrial oxidative stress and inhibits AMPK, resulting in liver fat accumulation, gluconeogenesis, and metabolic syndrome.[44] Inhibition of uricase amplifies the effects of fructose to induce metabolic syndrome, whereas expressing the ancestral uricase in human liver cells blocks the effects of fructose to induce fat accumulation and gluconeogenesis. This suggests uric acid may be a survival factor that enhances the metabolic effects of fructose during famine.[45]

The introduction of diets rich in sugar and umami (purine-rich) foods has led to a remarkable rise in serum uric acid and a widespread increase in obesity and diabetes.[46] Elevated serum uric acid consistently predicts the development of obesity and diabetes. Lowering serum uric acid prevents insulin resistance in fructose-dependent and fructose-independent animal models of metabolic syndrome.[47] A pilot randomized clinical study reported that lowering uric acid with a uricosuric agent improves insulin resistance, and we completed a randomized trial that showed that lowering uric acid with allopurinol also improves insulin resistance in hyperuricemic individuals. In contrast, we did not show improvement in insulin resistance by lowering serum uric acid in subjects administered fructose, but this may relate to the high doses (200 g/day) administered.[48]

In this issue of *Diabetes*, Sluijs et al.[49] challenge the uric acid-insulin resistance hypothesis using a genetic epidemiological approach known as Mendelian randomization. A "genetic score" consisting of 24 single nucleotide polymorphisms identified from genome-wide association studies was developed that explained 4% of the variance in serum uric acid. Using two studies that included over 40,000 subjects with diabetes, they show that the genetic score predicts serum uric acid as expected, but not diabetes. They conclude that serum uric acid is not causal in diabetes and that "uric acid–lowering therapies may therefore not be beneficial in lowering diabetes risk".[50]

II. Conclusion

SUA levels were higher in non-diabetic individuals, but a decreasing trend was observed in prediabetic and diabetic individuals. This finding supports the hypothesis that SUA might be involved in the early stages of metabolic imbalance leading to prediabetes and to a lesser extent in the advanced stages of diabetes is diagnosed. So, SUA might be a determinant in altered glucose metabolism but not a potential predictor of diabetes. Further studies with large sample size are needed to examine the reliability of using SUA to predict diabetes.

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