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Uric acid in metabolic syndrome: From an innocent bystander to a central player

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Abstract

Uric acid, once viewed as an inert metabolic end-product of purine metabolism, has been recently incriminated in a number of chronic disease states, including hypertension, metabolic syndrome, diabetes, non-alcoholic fatty liver disease, and chronic kidney disease. Several experimental and clinical studies support a role for uric acid as a contributory causal factor in these conditions. Here we discuss some of the major mechanisms linking uric acid to metabolic and cardiovascular diseases. At this time the key to understanding the importance of uric acid in these diseases will be the conduct of large clinical trials in which the effect of lowering uric acid on hard clinical outcomes is assessed. Elevated uric acid may turn out to be one of the more important remediable risk factors for metabolic and cardiovascular diseases.

Keywords

Uric acid; Metabolic syndrome; Hypertension; Diabetes mellitus; Kidney disease; Cardiovascular disease

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1. Uric acid and metabolic syndrome

While the condition known as metabolic syndrome has been suggested to be a pathophysiological condition, studies in comparative physiology show that the syndrome, as well as many of its associated factors, is a simple consequence of excessive fat storage [1]. Indeed, most mammals and birds will store their excess fat not only in their adipose tissue, but also in their liver and serum (triglycerides), often in association with the development of insulin resistance and elevated blood pressure [1]. While the underlying mechanisms involved in fat storage involve multiple genetic and other factors, recent studies suggest a role for nucleic acid metabolism, in which stimulation of adenosine monophosphate (AMP) deaminase promotes fat storage and insulin resistance, whereas activation of AMP activated protein kinase stimulates fat degradation and decreases gluconeogenesis [2–4]. A key factor that appears to promote fat storage is the AMP deaminase product, uric acid [2,3,5,6]. Here we will briefly discuss the studies incriminating uric acid in these conditions.

2. Uric acid and hypertension

One of the earliest associations of hyperuricemia was with hypertension [7–9]. Asymptomatic hyperuricemia is both associated with [10,11], and predicts, the development of hypertension [11]. Studies in laboratory animals have been complicated by the fact that most mammals express uricase, which is an enzyme that breaks down uric acid. As a consequence, most mammals have uric acid levels of 1–3 mg/dl, whereas the great and lesser apes, and humans, have uric acid levels of 3 mg/dl or greater [12]. When rats are given a uricase inhibitor (oxonic acid), they develop mild hypertension [13]. Genetically raising uric acid by knocking down the enteric urate transporter (SLC2A9) also results in elevation in uric acid that responds to lowering of uric acid with allopurinol [14]. Animal models of metabolic syndrome also have mild hyperuricemia despite the presence of uricase, and lowering uric acid in these animals also lowers blood pressure [15,16]. Interestingly, studies suggest that over time elevated serum uric acid induces microvascular and inflammatory changes in the kidney; the latter results in enhanced sensitivity to the effects of salt. Enhanced salt sensitivity leads to salt-sensitive hypertension that occurs irrespective of serum uric acid levels [17]. This suggests that hyperuricemia is more likely playing a role in initiating hypertension, but over time microvascular alterations in the kidney maintain the hypertensive state.

Pilot studies also suggest that lowering uric acid may improve blood pressure, including in pre-hypertensive obese [18] and hypertensive adolescents [19], hypertensive children on an angiotensin converting enzyme inhibitor [20], and in adults with asymptomatic hyperuricemia [21,22], in older hypertensive adults [23,24], in subjects with gout [25], in obese prehypertensive adults [26], in some subjects with chronic kidney disease [27], and in hemodialysis patients [28]. However, not all studies have reported a lowering of blood pressure, especially in subjects with chronic kidney disease [29]. Nevertheless, the studies support the hypothesis that uric acid may be a remediable risk factor in subjects with hypertension.

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Experimental studies suggest that uric acid may raise blood pressure through several mechanisms, including impairing endothelial function [30–36], stimulating endothelin [37,38] and activating both the renal and intracellular renin angiotensin system [36,39,40] (Fig. 1). One of the more important pathogenic mechanisms by which uric acid raises blood pressure appears to be by stimulating intracellular oxidative stress by activation of NADPH oxidases both in the cytosol and mitochondria [5,40–43]. Indeed, blocking oxidative stress or improving endothelial function can lower blood pressure in hyperuricemic rats [35,44]. In addition, uric acid stimulates vascular smooth muscle cell proliferation and induces inflammatory changes in the kidney that may help perpetuate the hypertension [39,45,46].

3. Uric acid and diabetes

Hyperuricemia has been linked with diabetes since the 1800s [47] and was associated with metabolic syndrome by the early 1920s [48]. Today there is overwhelming epidemiological evidence that shows that hyperuricemia is both present and predicts the development of insulin resistance and type 2 diabetes (reviewed in [49]). Historically, hyperuricemia was attributed as a secondary consequence to insulin resistance [50], but more recent studies suggest it may have a contributory causal role [49], especially since an elevated serum uric acid often precedes the development of insulin resistance [51]. A study of 5012 young adults found that baseline elevated serum uric acid predicted the onset of both diabetes (HR 1.87, CI 1.33–2.62) and insulin resistance (HR 1.36, CI 1.23–1.51). The elevation in baseline serum uric acid was not associated with plasma insulin concentration suggesting that serum uric acid is in fact an independent risk factor in the development of insulin resistance and subsequent diabetes [51]. Indeed, insulin resistance in models of metabolic syndrome can be improved by lowering serum uric acid [15,16], and uric acid has been shown to block AMP-activated protein kinase and to stimulate gluconeogenesis [3]. Uric acid also blocks insulin mediated endothelial nitric oxide release [43] that is critical for insulin action [52]. Furthermore, uric acid induces oxidative stress in adipocytes, leading to lower adiponectin synthesis [41]. Reducing uric acid can improve circulating adiponectin levels and insulin resistance in mice with metabolic syndrome [16]. Furthermore, uric acid has also been shown to induce oxidative stress in islet cells, and upregulation of urate transporters have been identified in islets of rats with sugar-induced diabetes [53]. Scott, et al. [54] also reported that serum insulin was decreased by 26% in rats in which uricase was inhibited after 4weeks in association with an increase in serum glucose by 24–38%. Finally, pancreatic islet cells from neonatal rats incubated with uric acid but not oxonate (the uricase inhibitor) reduced insulin secretion by 65%. Removing the uric acid from the medium rapidly restored insulin secretion suggesting uric acid could have a cytostatic or cytotoxic effect on β-cells in the pancreas.

The effect of lowering uric acid on insulin resistance in human studies is limited. However, insulin resistance (HOMA index) has been reported to be improved by benzbromarone [55] and allopurinol [56] in two small randomized trials. In addition, one study reported an improvement in hemoglobin A1C levels in normotensive diabetic subjects treated with allopurinol [57].

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While the evidence that uric acid may have a causal role in type 2 diabetes is mounting, the primary argument against this relationship has been the use of Mendelian randomization studies in which genetic polymorphisms that predict an increase in uric acid can be used to predict the risk for gout but not diabetes [58,59] Again, the limitation of these studies is that they are evaluating serum (extracellular) uric acid as a risk factor when the metabolic mechanisms are mediated by intracellular uric acid, and by the fact that the polymorphisms involve urate transport and explain only 4–6% of the overall variance of serum uric acid levels [60].

4. Uric acid and fat storage (adipose and liver)

An elevated serum uric acid is also a potent predictor for the development of obesity [61] and fatty liver [62–67]. Experimentally uric acid has been shown to increase triglyceride accumulation in cultured liver cells [5,6] and hyperuricemia also increases triglyceride levels in the liver of rats [68]. The mechanism has been shown to be mediated by intracellular and mitochondrial oxidative stress [5,69]. The oxidative stress is associated with inhibition of aconitase in the Krebs cycle that leads to citrate accumulation and the stimulation of ATP citrate lyase resulting in increased fat synthesis, as well as an inhibition of enoyl CoA hydratase resulting in impaired beta fatty acid oxidation that is also potentiated by the inhibition of AMPK-activated protein kinase [2,5,70]. Lowering uric acid has been shown to reduce liver fat in several animal models of metabolic syndrome and also in alcohol-induced fatty liver [5,70,71]. To date we are unaware of any clinical trials to determine if lowering uric acid can reduce adiposity or hepatic steatosis in humans. However, one clinical trial found that allopurinol use resulted in less weight gain in adolescents compared to placebo treated controls [18]. More recently, another study reported that allopurinol treatment resulted in weight loss in obese, prehypertensive adults that was independent of energy intake [26].

5. Role of diet in uric acid mediated effects

Uric acid can be increased in the circulation by high purine foods (such as beer) and by fructose. Classically the focus has been on high purine foods as risk factors for gout [72], of which most purine-rich foods fall in the umami-class of foods that are increasingly recognized as risk factors for metabolic syndrome [73]. High fat diets can also increase serum uric acid [74]. In western cultures, a major dietary source for increasing uric acid is fructose present in added sugars [75]. Indeed, there is remarkable evidence that sugary beverages play a major role in the epidemic of obesity and metabolic syndrome [76–78] and experimental studies show that it is likely the fructose component which is primarily responsible for uric acid elevation and subsequent development of metabolic syndrome[79–81] (Fig. 2). Experimental studies also suggest that a primary mechanism by which fructose induces metabolic syndrome is through its ability to increase intracellular uric acid [5,15,68,70,82]. Clinical studies also show that fructose can raise serum uric acid and induce features of metabolic syndrome [83–88]. In one study, high doses of fructose (200 g/day) were given to healthy adult males for two weeks with or without allopurinol [89]. In this study many of the features of metabolic syndrome were induced rapidly despite the short duration of the study. However, lowering uric acid was associated with prevention of the rise

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in blood pressure but no improvement in insulin resistance. Whether this is because of the high doses of fructose given, or whether this suggests the beneficial effects of lowering uric acid is unknown [89].

6. Uric acid and thrifty genes

Most mammals have low serum uric acid (1–2 mg/dl) due to the presence of uricase, an enzyme that degrades uric acid [90]. However, uricase activity was progressively attenuated (25 to 15 million years ago) and then silenced about 15 million years ago in apes and prehominids [91]. There is increasing evidence that the mutation may have provided survival advantages to the ancestral apes at the time, by increasing their ability to store fat in response to a decrease in food (fruit) availability that resulted from global cooling [92,93]. Indeed, studies of the resurrected ancestral uricase gene suggested that it was able to blunt the effect of uric acid to increase fat in response to fructose and to stimulate gluconeogenesis [3,91]. Other potential benefits of uric acid may include its ability to block oxidative stress (extracellularly) [94] and to stimulate foraging behavior [95].

Studies of modern apes and humans living on native diets suggest that the mutation of uricase only resulted in an increase of serum uric acid to the 3 to 4 mg/dl range [12]. However, with the introduction of western diet, serum uric acid has increased progressively over the last century [12]. The rise in western diet, coupled with the loss of uricase may account for why there is a world epidemic of obesity, diabetes and cardiovascular disease. Interestingly, Pacific Islanders have higher uric acid levels that appear to be genetic and which preceded the introduction of western diets [96]. We have postulated that the higher uric acid levels in this population may explain their higher frequency of obesity and diabetes compared to other peoples throughout the world [97].

7. Cardiovascular disease

Uric acid has been associated with cardiovascular disease for decades [98]. For a long period, uric acid was thought to be purely secondary to obesity and hypertension, and was not considered a true cardiovascular risk factor [99,100]. A major problem with these early studies is that the assumption was that the relationship of uric acid with cardiovascular disease had to be direct, and the possibility that it increased cardiovascular disease as a consequence of causing hypertension, insulin resistance or kidney disease was not considered [101,102] (Fig. 3). The reawakening that uric acid might have a role in heart disease is now a hot topic, and can be best assessed by clinical trials. Early trials suggest benefits of lowering uric acid on carotid intimal thickness [23], angina [103], left ventricular hypertrophy [104], arterial stiffness [105] and cardiovascular events in subjects with and without chronic kidney disease [29,105–108].

8. Arguments against uric acid as a cardiovascular or metabolic risk factor

There are several arguments that suggest that uric acid may not be a true risk factor for metabolic or cardiovascular disease. First is the observation that acutely raising uric acid in the blood by infusing uric acid improves endothelial function [94,109]. The improvement in endothelial function is thought to be due to the ability of uric acid to function as an

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antioxidant [94]. However, uric acid is expected to be an antioxidant in the extracellular environment. However, numerous studies have shown that uric acid is a pro-oxidant in the intracellular environment [5,40–42,53,69]. Moreover, while uric acid inactivates peroxynitrite, it generates two urate-based radicals in the process [110,111], so the ffects of uric acid as an antioxidant are not without some radical generation.

Uric acid has also been proposed to be one reason that chlorthalidone was beneficial in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study possibly due to its antioxidant properties [112]. However, this is unlikely, as in our experimental models thiazides lower blood pressure in metabolic syndrome, but the addition of allopurinol completely corrects the hypertension while at the same time improving endothelial function [113].

Some have also argued that the benefit of allopurinol on blood pressure may be via its effects to block oxidants generated during the reaction of xanthine with xanthine oxidase [114]; however, this fails to explain why probenecid (a uricosuric) lowered blood pressure in the trial by Soletsky et al [18]. In addition, the effect of xanthine oxidase inhibition to block fat accumulation in hepatocytes in response to fructose can be prevented by adding back uric acid to the culture media [5]. Finally some genetic studies have failed to link polymorphisms that raise uric acid with hypertension [26–28] whereas others have shown such a link [115,116]. However, the genetic studies have relied highly on polymorphisms in genes that alter urate transport, and hence may alter the normal relationship of serum with intracellular urate levels [60]. The complexity associated with assessing polymorphisms of urate transporters is best observed by noting that knocking down *SLC2A9* in the liver results in hyperuricemia without hypertension, whereas blocking the same gene in the intestine results in hyperuricemia with hypertension that can be treated by lowering uric acid levels [14,117].

9. Summary

We have entered a new exciting period in the history of uric acid. While uric acid was once the lonely dinner conversation for those suffering from gout or kidney stones, it is now being evaluated as a potential master conductor in the worldwide symphony of obesity, diabetes, and cardiorenal disease. However, at this time, it is still premature to lower uric acid as a means for reducing metabolic and cardiovascular disease. Rather, it is time to recommend definitive, large-scale clinical trials to determine whether lowering uric acid can be beneficial in the prevention and treatment of hypertension, insulin resistance, obesity, fatty liver, and cardiovascular disease.

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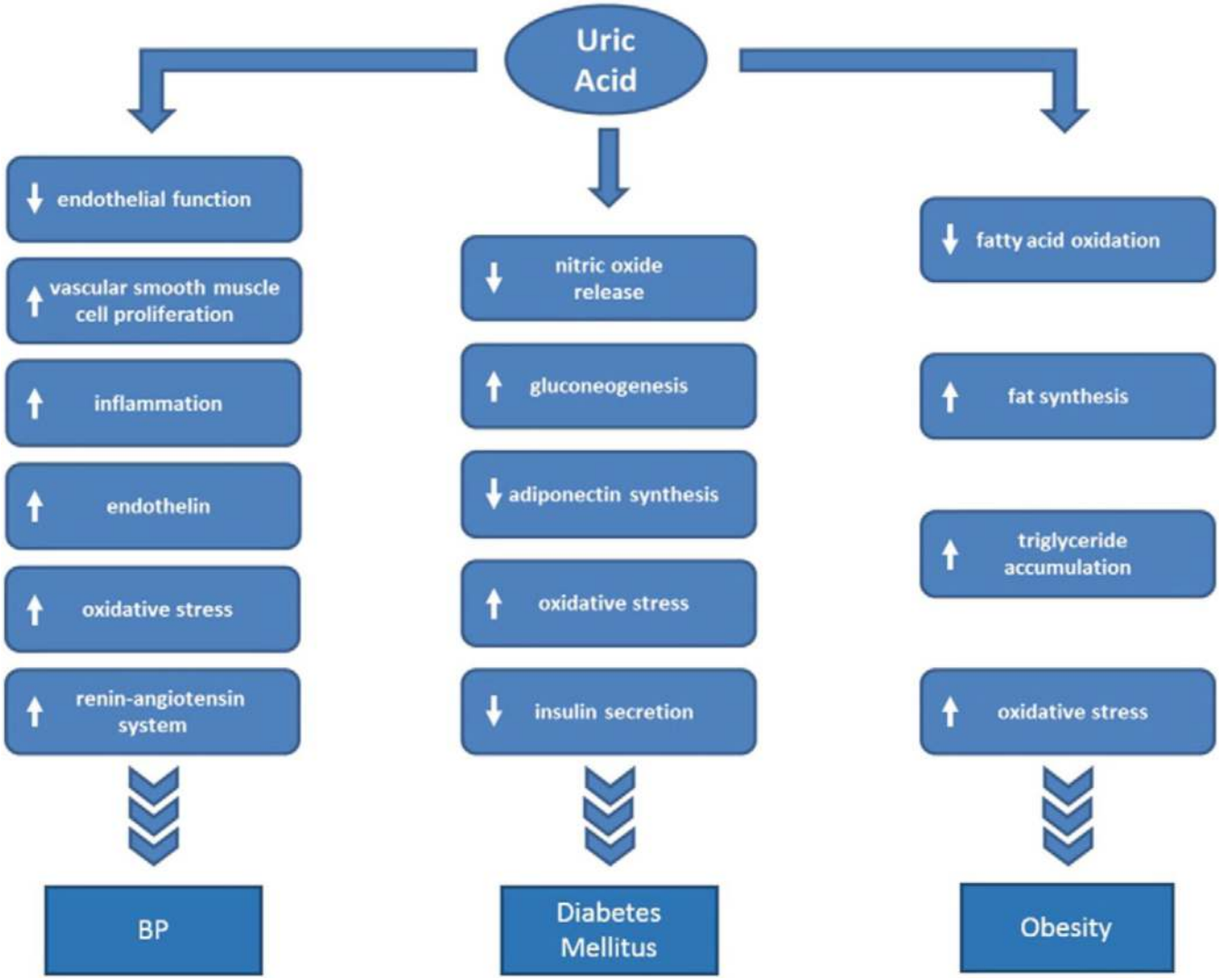

Fig. 1.

Uric acid induced effects that may play a role in the pathogenesis of hypertension, diabetes, and obesity.

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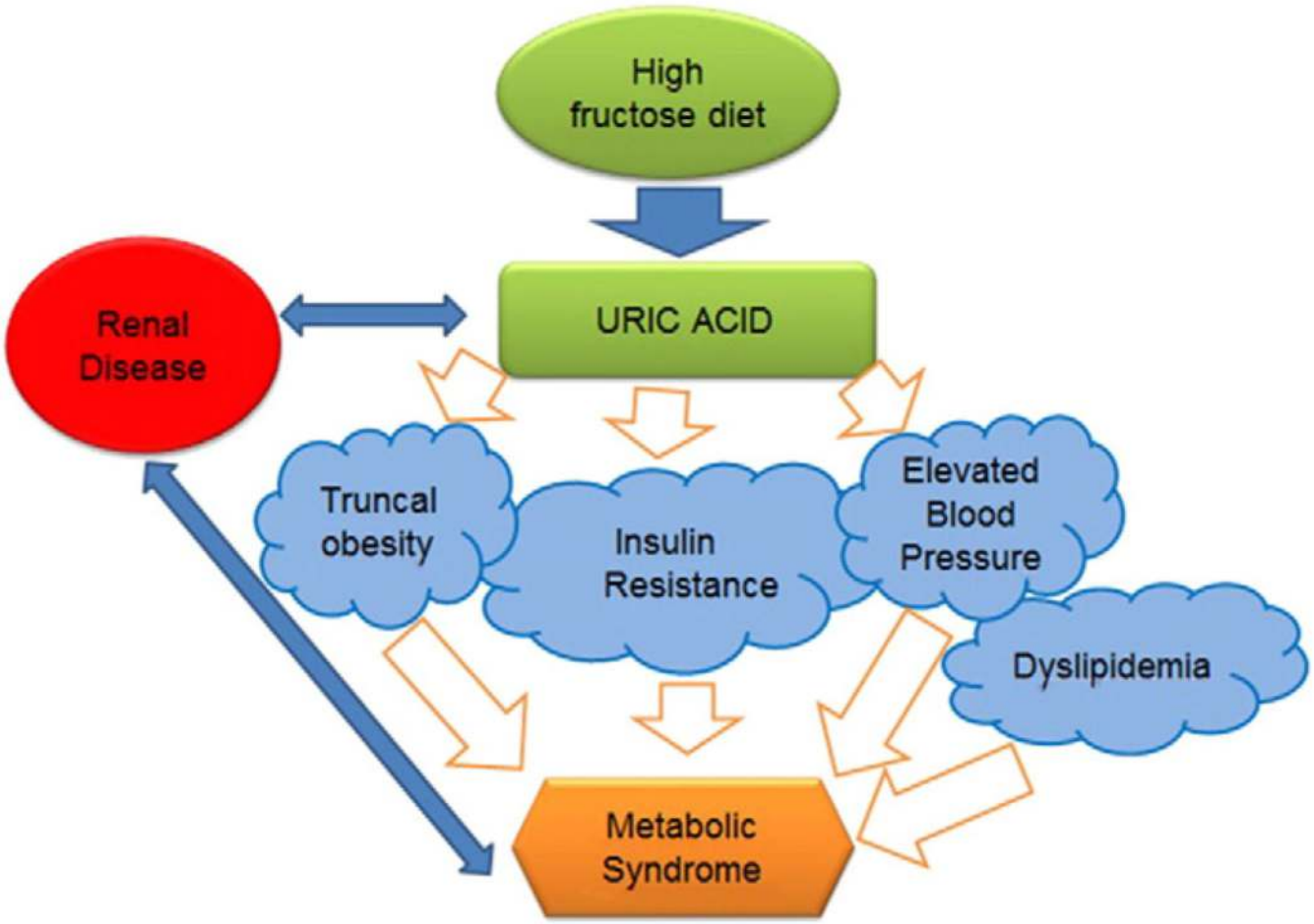

Fig. 2.

Relationship between high-fructose diet, generation of hyperuricemia and resulting metabolic syndrome. Renal disease is linked to both metabolic syndrome and hyperuricemia in a mutual way.

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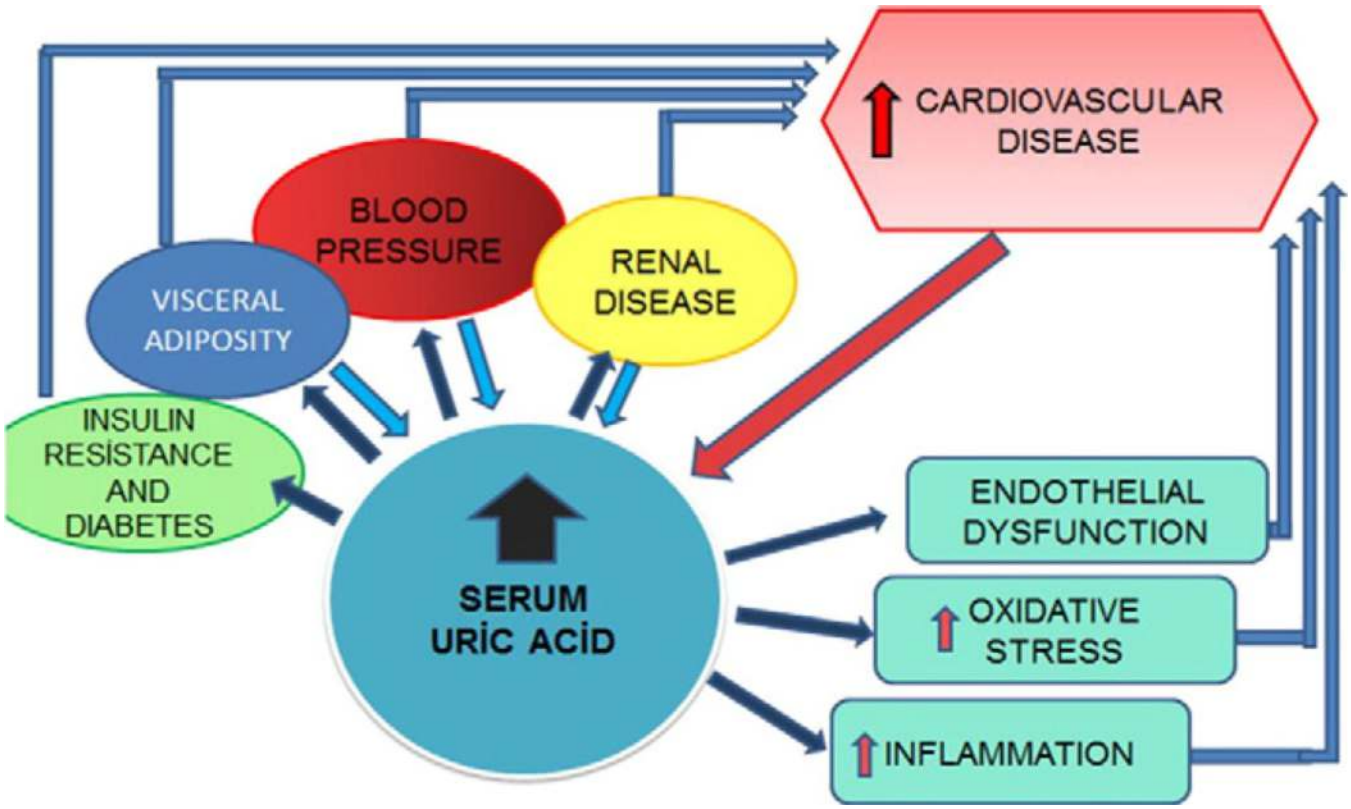

Fig. 3.

Schematic diagram showing complex interaction of uric acid, components of metabolic syndrome and cardiovascular disease. Note that elevated uric acid can lead to development of individual components and these components in turn can lead to elevations in serum uric acid. Elevated serum and intracellular uric acid may lead to increased incidence of cardiovascular disease both directly through inflammation, oxidative stress and endothelial dysfunction and indirectly through developing other established cardiovascular risk factors such as hypertension, diabetes and visceral obesity.