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Potential Role of Uric Acid in Metabolic Syndrome, Hypertension, Kidney Injury, and Cardiovascular Diseases: Is It Time for Reappraisal?

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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, renal disease, and cardiovascular disorder; and the potential pathophysiology mechanisms involved.

Keywords

Uric acid; Hyperuricemia; Fructose; Metabolic syndrome; Obesity; Hypertension; Kidney disease; Cardiovascular disorder

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

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product of purine metabolism in humans.[1,2] As a consequence, humans have higher uric acid levels than most other mammals having the enzyme uricase.

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]

Since uric acid has the ability to act as an antioxidant, elevated plasma uric acid concentration has been considered as a beneficial phenomenon,[4] which has a compensatory role in response to increased oxidative stress in conditions such as cardiovascular disease.[5] 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.[6,7] Injurious impacts of uric acid include an inhibitory effect on nitric oxide (NO) production[8]; induction of platelet aggregation[9], and pro-inflammatory activity.[10]

Extending these observations, it has been proposed that hyperuricemia may predict the development of metabolic syndrome[11], diabetes[12], hypertension[13], kidney disease[14] and cardiovascular disorders[15]. These findings support the notion that elevated serum uric acid levels cannot just be viewed as a secondary phenomenon in these pathologies. However, it is still unclear whether uric acid plays a pathogenic role in the development and progression of these syndrome and diseases.

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.

Uric Acid and Metabolic Syndrome

Hyperuricemia is commonly observed in metabolic syndrome[16] and numerous epidemiological investigations have confirmed the association of hyperuricemia with metabolic syndrome.[17,18,19] 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[18,20,21], there is growing data that uric acid may predict the development of metabolic syndrome, obesity and diabetes.[22,23,24,25]

In a study by Chen et al, hyperuricemic subjects had an odd ratio of 1.6-fold higher for developing metabolic syndrome.[26] 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.[22] 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.[27] A recent human study also supports the premise that insulin resistance has an important role in the causal relationship between metabolic syndrome, and hyperuricemia.[28] 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.[29••]

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.[30,31] These effects are not observed with glucose-rich diet.[32] 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.[33] Nakagawa et al. also found that uric acid impaired endothelial function.[33]

Apparently, fructose-induced insulin resistance occurs as a result of fructose-induced hyperuricemia.[33,34] 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.

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.[35] The recent data also support an association between hyperuricemia and endothelial dysfunction in human[36] and importantly, that this endothelial dysfunction can be reversed by administration of allopurinol in animal model[35] as well as in human subjects.[37–40] In addition to the above mechanism, hyperuricemia induces intracellular ROS production and decreases NO bioavailability in adipose cells.[41,42] 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.

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.[43,44] 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.[44]

Associations of high uric acid levels and the development of type 2 diabetes have beendocumented.[45] A meta-analysis of 11 studies has revealed that every mg/dl increase in uric acid level is associated with 17% increased risk of diabetes.[45]

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.

Uric Acid and Hypertension

Hyperuricemia is commonly associated with arterial hypertension.[46] In an early study, hyperuricemia was repoted in 25–40% of untreated hypertensive and 75% of malignant hypertensive subjects.[47] In more recent investigations, it has been suggested that the serum uric acid level is an independent risk factor for the development of hypertension.[12,13,48] Uric acid has also been shown to be an independent risk factor for a non-dipper circadian pattern of hypertension.[49] Interestingly, serum uric acid levels of 5.5 mg/dL or higher indicated an increased likelihood of preeclampsia in hypertensive pregnant patients.[50]

Mazzali et al. reported that rats with elevated serum uric acid concentration developed hypertension with a direct relationship between the level of blood pressure and uric acid.[51] 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.[51] Importantly, each of these effects was ameliorated by uric acid lowering drugs.[51] 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.[52] 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.[53••]

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.[54] Furthermore, reduction of uric acid normalized blood pressure in 66% of hyperuricemic adolescents with hypertension as compared to 3% in the control individuals.[55] 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.

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.[56] As most diuretics elevate serum uric acid, developing uricosuric diuretics might be an exciting area of research.

Uric Acid and Cardiovascular Disease

An association between high uric acid and cardiovascular disease has been reported since the19th century.[57] Since this time, a number of studies have not only supported this relationship but also have considered uric acid as an independent risk factor for cardiovascular events, including coronary vascular disease, cerebrovascular disease, and congestive heart failure in high risk population (subjects with diabetes mellitus, hypertension, hyperlipidemia).[58–64] However, the importance of a link between high uric acid and cardiovascular events in the general population still remains to be clarified.

In a study involving a large group of patients with hypertension and/or diabetes, a serum uric acid level higher than 7 mg/dl was correlated with increased cardiovascular mortality.[64] Likewise, an elevation in serum uric acid concentration to a level of 7.5 mg/dl or higher has been demonstrated to increase the risk of mortality in patients with acute coronary syndrome who underwent percutaneous coronary intervention (PCI).[65] However, other studies have not agreed to consider uric acid as an independent risk factor for coronary vascular disease.[66,67]

Hyperuricemia is also significantly correlated with an increased mortality rate in patients with congestive heart failure.[64,68–70]

In a study of 9 patients with dilated cardiomyopathy, intracoronary administration of allopurinol in combination with standard therapy (ACE inhibitor, diuretics, digoxin, β-blocker, and spironolactone) decreased oxygen consumption and improved left ventricular function.[71] Since this effect was not observed with uricosuric agent (probenecid), George et al. postulated that this favorable effect of allopurinal in patients with heart failure likely relates to the inhibition of xanthine oxidase-induced oxidative stress not a reduction in serum uric acid level.[72]

Interestingly, a Cox regression analysis of data from patients with hypertension and left ventricular hypertrophy who participated in the Losartan Intervention For Endpoint Reduction (LIFE) Study showed that 29% of cardioprotective effect of losartan was attributed to this drug's hypouricemic properties.[73,74]

Furthermore, in a meta-analysis of 16 prospective cohort studies, Kim et al have suggested that there is a possible role of uric acid in the development of stroke.[75] Additionally, hyperuricemia appears to deteriorate the long-term clinical outcomes in diabetic patients presenting with stroke.[76] Contrary to these data, there is evidence in favor of an association between elevated uric acid and better clinical outcome in stroke patients.[77] Future research should focus on confirming the above conflicting data and pathogenetic mechanisms of hyperuricemia in stroke.

The exact mechanisms by which uric acid contribute to cardiovascular events is still unclear but may be due to inhibition of nitric oxide (NO) production[8]; induction of oxidative metabolism[78] and platelet aggregation[9], and pro-inflammatory activity.[10]

In summary, uric acid appears to be a possible mediator for cardiovascular events. Recent data provide more evidence to show uric acid may be involved in the development and progression of cardiovascular disease. The precise role of uric acid in cardiovascular disease remains an interesting area for further investigation.

Uric Acid and Kidney Disease

Since the 1890s, hyperuricemia has been considered to be associated with chronic kidney disease (CKD).[79] This link first emerged in the context of the gouty nephropathy. In a study conducted prior to availability of uric acid lowering drugs, 20–60% of 524 patients with gout were reported to have mild or moderate renal injury.[80]

While some experts consider asymptomatic hyperuricemia as an independent predictive factor in renal disease, others argue against it.[81,82,83,84] These variable results may be due to methodological and patient population differences. The largest impact of hyperuricemia on CKD risk was shown by Iseki and colleagues. They found that a serum uric acid >8mg/dL was associated with a 3-fold increased risk in developing CKD in men and more than a 10-fold increased risk in women.[83•] This increased risk was independent of age, systolic blood pressure, body mass index, glucose, smoking, alcohol use, and proteinuria.

In a recent study, 788 patients with normal kidney function who underwent PCI were enrolled to hyperuricemic and normouricemic groups. The hyperuricemic group had a significant risk to develop contrast-induced acute kidney injury and need for renal replacement therapy after the intervention.[85] In addition, in 680 patients with autosomal-dominant polycystic kidney disease (ADPKD), elevated serum uric acid concentration was found to be correlated with earlier development of hypertension, larger kidney volume, and increased risk for developing end stage renal disease. This link was independent of body mass index and renal function.[86•]

Although a relationship between uric acid and kidney injury has been reported in various populations through epidemiological studies,[87] the potential pathophysiological mechanisms remain to be clarified. In animal studies, hyperuricemic rats show more renal hypertrophy, proteinuria, interstitial fibrosis, preglomerular arteriolopathy and glomerulosclerosis.[88,89] It appears that uric acid may exacerbate renal injury via multiple mechanisms, including activation of the RAAS[51], inhibition of neuronal nitric oxide synthase[51], stimulation of VSMC proliferation[7], and expression of COX-2 in the vascular wall.[88]

Importantly, in a recent animal study by Kim et al, administration of allopurinol to diabetic mice has shown to attenuate transforming growth factor-β(1)-induced tubulointerstitial fibrosis in kidneys. This novel finding suggests that lowering serum uric acid may be an effective way to prevent the progression of diabetic nephropathy.[90]

If high uric acid level directly causes preglomerular arteriolopathy, and interstitial fibrosis, uric acid may be a modifiable mediator for CKD in the absence of other mechanisms. In this regard, allopurinol therapy on hyperuricemic individuals for 4 months has been shown to decrease systolic blood pressure, and proteinuria; increase estimated glomerular filtration rate; and improve enthothelial dysfunction as compared with pre-drug baseline values.[38] Also, Terawakhe et al. suggested that use of allopurinol in humans with hypertensive nephropathy appears to be beneficial for decreasing all-cause mortality, denoting that this xanthine oxidase inhibitor might have a protective role on the vascular system.[91•]

Despite these promising results, appropriate randomized controlled trials are needed before allopurinol can be implemented into daily clinical practice, since allopurinol therapy may be complicated by kidney toxicity.

It is worth noting that the hypouricemic effect of losartan appears to attenuate the risk of kidney disease as demonstrated in a recent post hoc analysis of data from patients with type II diabetes and nephropathy who participated in the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial. With each 0.5 mg/dl decrease in uric acid level, the risk of kidney event was declined by 6%. After adjustment, 25% of renoprotective effect of losartan was attributed to this drug's hypouricemic properties.[92•]

Fructose Diet and Epidemic of Obesity, Diabetes and Renal Disease

The prevalence of obesity has been grown rapidly since Japanese scientists introduced the high fructose corn syrup as a sweetener to the world in the 1970s. Initially, high fructose corn syrup represented 1% of all caloric sweeteners in the United States, but it now is a standard part of the American diet and represents 40% of caloric sweeteners.[93] Interestingly, the prevalence of obesity, diabetes, CKD and cardiovascular diseases has all followed these trends. In the last decade, investigators have revealed a link between consumption of fructose and metabolic syndrome, diabetes, hypertension, kidney injury and cardiovascular diseases.[94,95]

In addition, it has been demonstrated that rats (remnant kidney model) that receive a high fructose diet have a significant progression of kidney injury, increased proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis.[96] Similarly, Shoham et al speculated that high fructose corn syrup could contribute to kidney disease in human by finding a link between consumption of frucose-sweetened soft drinks and albuminuria.[97] In support of this possibility, Brymora et al. also showed that when placed on a low-fructose diet for 6 weeks, subjects with CKD had a reduction in inflammatory markers, a fall in blood pressure, and no worsening of kidney function.[98•] The mechanisms by which fructose may affect the disease processes noted above are complex and seem not to be limited to the obesity-related pathways.

The mean uric acid level has also increased over the past several decades[99] which could be secondary to increased consumption of a high fructose diet. Given that fructose is the only sugar raises uric acid levels, it is tempting to link the trends in each of these disease states to uric acid-related pathway. Related to this concept, in a study, an increase in blood pressure after administration of high fructose diet (200 g of oral fructose/day) for two weeks was normalized in 74 overweight individuals concomitantly received uric acid lowering drug.[100]

However, the hypothesis of uric acid-related pathway does not nullify the importance of other risk factors, such as increased salt intake, physical hypoactivity, increased caloric intake and other mechanisms, driving concurrent epidemic of obesity, diabetes, and kidney and cardiovascular disease states.

Conclusion

Available data suggests that hyperuricemia may not be benign and appears to be a potential contributor to the worldwide obesity pandemic, diabetes, and kidney and cardiovascular disease states. Despite the evidence for a possible causal role of elevated serum uric acid concentration, consensus on treatment of asymptomatic hyperuricemia is lacking. We believe that it is a time for appropriate randomized controlled trials to be performed to critically determine whether treatment of asymptomatic hyperuricemia slows the development and progression of metabolic syndrome, diabetes, and kidney disease, particularly, diabetic nephropathy which is the most common cause of CKD in the United States.

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