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Review Article

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.

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.

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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.

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 4 weeks 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].

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].

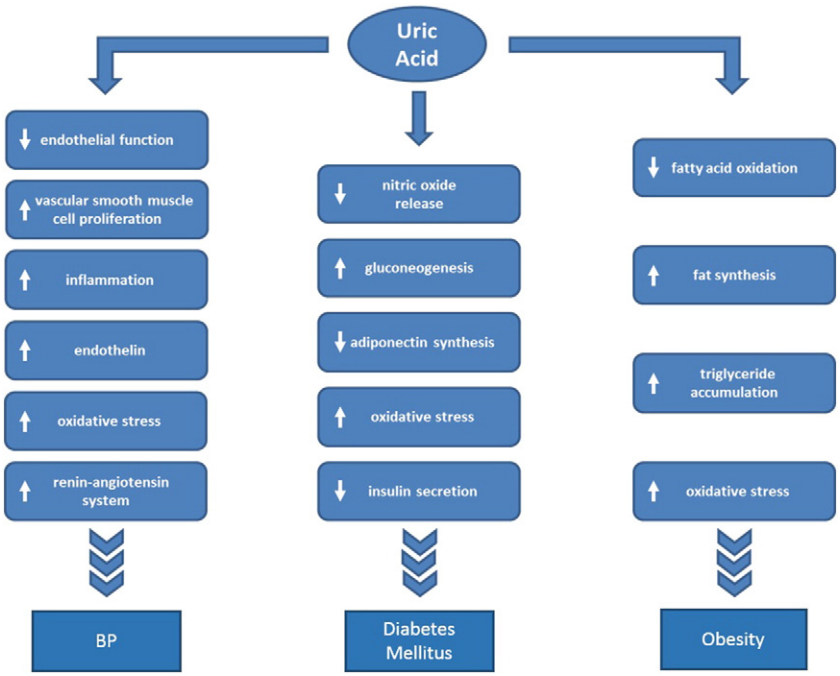

Fig. 1. Uric acid induced effects that may play a role in the pathogenesis of hypertension, diabetes, and obesity.