Introduction

Many studies have documented that serum uric acid (UA) is a risk factor for cardiovascular disease (CVD) [1–10], but there has been very little clarification on how UA would alter the vasculature. This may be in part because uric acid has both antioxidant and pro-oxidant properties. However, the power of high UA levels to predict CVD in subjects with conditions such as diabetes, hypertension, hyperlipidemia, obesity, insulin resistance syndrome, renal disease, and preeclampsia is retained even in healthy adults. These findings point to a role for UA in the metabolic syndrome [11–17], but despite the strength of this association, it remains unknown whether elevated uric acid concentration has an independent pathogenic role in CVD or if it simply represents a marker for other risk factors [18]. Therefore, it is important to determine the main mechanisms by which hyperuricemia contributes to CVD.

Uric Acid and Hypertension

Hyperuricemia is commonly associated with hypertension. Approximately 25% of hypertensive patients have increased levels of uric acid [19]. In healthy adults, asymptomatic hyperuricemia predicts future development of hypertension, irrespective of renal function [20]. Serum uric acid has been also shown to correlate with blood pressure in children with new-onset, untreated, primary hypertension [21••]. Several mechanisms could explain the association of hypertension with hyperuricemia, including decreased renal blood flow, with subsequent stimulation of urate reabsorption [22], and inhibition of renal urate secretion, due to local tissue ischemia mediated by lactate [23], alcoholism [24], diuretic consumption, lead intoxication [25], and insulin resistance [26,27].

Uric Acid and Insulin Resistance

Hyperuricemia is a consistent feature of the insulin resistance syndrome, which is characterized by hyperinsulinemia, hyperglycemia, hypertriglyceridemia, raised body mass index, and high waist-hip ratio [28,29]. In the fasting state, accumulation of triglycerides highly correlates with increases in serum uric acid levels [30]. Insulin has a physiologic action on renal proximal tubules, causing increased sodium and urate reabsorption [31]. Moreover, elevated serum uric acid levels predict subsequent development of diabetes [32], even in the presence of normal plasma glucose levels and normal creatinine clearance, and, therefore, may be an early marker of the insulin-resistance syndrome.

Uric Acid, Impaired Nitric Oxide Production, and Endothelial Dysfunction

The endothelium has a significant role in maintaining vascular tone and releasing nitric oxide (NO), a potent vasodilator [33]. The endothelial dysfunction associated with impaired vasodilation results from excessive free-radical activity, which disrupts NO synthesis and accelerates its degradation. NO reacts with superoxide anion radicals and forms peroxynitrite, a potentially toxic compound, which quickly oxidizes uric acid [34]. Xanthine oxidase generates oxidants and uric acid in the presence of tissue ischemia. Uric acid is present in reactions leading to
endothelial dysfunction and, therefore, may represent more than a marker in conditions such as heart failure and diabetes mellitus. Allopurinol, a xanthine oxidase inhibitor, prevents uric acid and oxidant production and reverses the impaired NO generation in both heart failure and diabetes [35, 36, 37]. In addition, hyperuricemia is associated with an increase in platelet reactivity, pointing toward another potential mechanism in CVD [38]. There is also a reciprocal relationship between serum levels of uric acid and NO [39] that may explain the involvement of uric acid in impaired NO production.

Uric Acid, Vascular Smooth Muscle Cell Proliferation, and Atherosclerosis

Uric acid promotes low-density lipoprotein (LDL) oxidation in vitro that is an important factor in the progression of atherosclerosis [40,41]. There is no receptor for uric acid in vascular smooth muscle cells (VSMCs), but these cells have organic anion transporters for urate uptake [42]. After uptake, uric acid stimulates VSMC proliferation by increasing platelet-derived growth factor A-chain expression [43], local thromboxane production, and cyclooxygenase-2 (COX-2) stimulation that induce specific mitogen activated protein kinases [44]. Uric acid also has an adverse effect on the endothelium through leukocyte activation, and a consistent relationship has been noted between elevated serum uric acid and circulating inflammatory markers such as monocyte chemoattractant protein-1 (MCP-1), a chemokine whose production is stimulated by uric acid and that has an important role in atherosclerosis [44]. Uric acid traverses dysfunctional endothelial cells and accumulates as crystal within atherosclerotic plaques [45]. These crystals contribute to local inflammation and plaque progression.

Uric Acid and the Renin–Angiotensin System

Previous clinical studies reported that the renin–angiotensin system (RAS) is strongly related to elevated serum uric acid levels in hypertensive patients [46]. This close correlation may be only reflecting changes in extracellular fluid volume; however, both uric acid and angiotensin II stimulate VSMC proliferation and hypertrophy, essentially contributing to the atherosclerosis process [47]. The autocrine mechanisms that are responsible for the mitogenic effects of uric acid and angiotensin II on VSMC use platelet-derived growth factor (PDGF) A-chain as a mediator [43]. PDGF A-chain by itself is only a weak mitogen for VSMC, whereas uric acid stimulates VSMC proliferation significantly, so that other intracellular signals stimulated by uric acid may act in synergy with PDGF A-chain. It is possible that the renin–angiotensin system is implicated in the proliferation induced by uric acid in VSMC [48].

Perspective on Uric Acid as a Pathogen

A growing body of evidence, based on both animal and human studies, is beginning to offer strong support for an active role of uric acid in the pathogenesis of CVD. Recently, uric acid has been shown to cause vascular injury in various animal models. In a rat model of hyperuricemia, Sanchez-Lozada et al. [49] demonstrated that small increments in uric acid induced systemic hypotension but also a vasculopathy that reduced the vasoconstriction of the afferent arteries interfering with the autoregulation process, causing subsequent increases in intraglomerular pressure. In the same model, Kang et al. [50] showed that functional changes at the level of the preglomerular arterioles correlated with increases in renal renin and COX-2 expression, providing further evidence that uric acid has an active role in vascular disease. The mechanism by which hyperuricemia causes intrarenal vascular disease appears to be multifactorial and at the level of both the VSMC and the endothelial cells [43,50]. Hyperuricemia, also, has been found recently in animal and human studies to be associated with the presence of markers of systemic inflammation. In vitro, uric acid at physiologic concentrations has been shown to induce C-reactive protein expression and to decrease NO release from human vascular cells [51].

Baker et al. [52] reviewed 21 studies evaluating serum UA levels and their relationship to multiple cardiovascular outcomes. Among these studies, 10 were prospective cohorts involving healthy subjects. An independent link was found between serum UA and adverse cardiovascular events in six of these studies. Waring et al. [53], in a series of randomized controlled studies, investigated the effect of acute increases in UA on systemic vascular resistance, large artery compliance, and baroreflex sensitivity in healthy adults. Uric acid was given locally or systemically to cause a twofold increase in serum UA concentration, and basal blood flow was measured in the forearm vasculature using venous plethysmography before and after administration of acetylcholine, sodium nitroprusside, and L-N-monomethyl arginine. No effects on endothelium-dependent or endothelium-independent vasodilator response were documented in these experiments. However, the fact that transient hyperuricemia did not affect the endothelial function does not eliminate a pathologic interaction of UA with the vessel wall in states of chronic burden. Erdogan et al. [54] investigated 124 healthy adults between the ages of 18 and 55 years whose serum UA levels were in a physiologic range to determine a possible correlation between UA and predictors of atherosclerosis. They found that people with increased serum UA, even in the physiologic range, were at risk for increased carotid-intimal-media thickness, impaired brachial artery flow-mediated dilatation, and increased carotid stiffness, independent of other cardiovascular or metabolic risk factors.