

# Potential Role of Uric Acid as a Risk Factor for Cardiovascular Disease

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## Cardiovascular epidemic and uric acid

The cardiovascular epidemic is a worldwide phenomenon that accounts for almost 50% of all deaths in industrialized nations, and coronary artery disease (CAD) is one of the most serious forms of cardiovascular disease (CVD). Despite the rapid progress made in modern medicine with regard to controlling the known risk factors for CAD, this worldwide epidemic still heads the list of national health concerns, which raises the possibility of the presence of unknown or underestimated risk factors. Therefore, we need to identify novel risk factors for CVD, including a potential therapeutic target. While there is no doubt that multiple factors play different roles in the development of CVD, recent studies have revealed the potential role of hyperuricemia as a novel risk factor. Uric acid is the final product of purine metabolism in humans, and its level is determined by dietary intake, rate of cell turn-over in the body, and renal excretion. Interestingly, primates are the only species with high uric acid levels, as there has been a uricase mutation to degrade uric acid into allantoin during hominoid evolution in contrast to most mammals in which serum uric acid levels range between 0.5 to 1.5 mg/dL [1].

Interestingly, uric acid levels have been increasing in human populations over the last 100 years and, thus, correlate with the CVD epidemic [2]. Most importantly, there is strong evidence from clinical studies and experimental animal models that uric acid is associated with hypertension and other CVDs. Elevated uric acid is observed in 89% of new onset essential hypertension in adolescents and in 25 to 50% of untreated hypertension in adults [3]. These effects are independent of renal function

or body weight. However, despite solid experimental data supporting the causative role of uric acid in CVD, most authorities have viewed hyperuricemia as a secondary and not causal effect, because hyperuricemia is associated with other CVD risk factors such as male gender, obesity, hypertension, renal dysfunction, and diuretic use.

## Uric acid and CAD: lessons from previous studies

In this issue of the Korean Journal of Internal Medicine, Lim et al. demonstrated an association between elevated uric acid and CAD in 687 patients without a history of taking diuretics. Although the CAD odds ratio was comparable to the uric acid quartile after adjusting for age, gender, diabetes, hypertension, and metabolic syndrome, there was a significant association between serum uric acid and CAD severity. The authors concluded that uric acid was not an independent risk factor for CAD, but rather a marker of metabolic syndrome based on multiple regression analysis results. Recent studies regarding the role of serum uric acid on CAD risk stratification have revealed inconsistent results. Hyperuricemia per se was a significant risk factor for determining the development or severity of CAD in some studies [4-8], but uric acid was not an independent factor for CAD and related cardiovascular mortality. The Japanese Coronary Artery Disease Study group demonstrated that elevated serum uric acid was an independent predictor for cardiovascular events in patients with severe coronary artery stenosis in their 3 year follow-up [4]. Interestingly, not only high levels of uric acid, but an increase in uric acid level 6 months after a coronary event was also associated with high cardiovascular and all-cause mortality. Another study in 2,796 patients with non-diabetic CAD also showed an association between serum uric acid and increased cardiovascular events,

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independent of renal function [9]. In contrast, the Genetic Epidemiology Network of Arteriopathy (GENOA) study showed that uric acid was associated with the presence and severity of CAD after adjusting for age and gender, but not after further adjustment for CVD risk factors [6]. Disparate conclusions regarding the clinical significance of hyperuricemia in CAD may be related to subject characteristics, study design, or statistical methodologies. Interestingly, Lim et al. found that hyperuricemia was more closely associated with CAD in women than men. Premenopausal women have a lower uric acid level due to the uricosuric effect of estrogen; therefore, increased uric acid levels in women may reflect the presence of other risk factors resulting in hyperuricemia. The differential effect of hyperuricemia on CVD according to gender has already been demonstrated in previous studies but in a different pattern. A cross-sectional evaluation of the Atherosclerosis Risk in Communities study population, in white and black US individuals, showed that serum uric acid levels were associated with carotid intima-media thickness in both genders [10]. However, this association lost its significance in women and was reduced in men after adjusting for other risk factors. A recent study by Ishizaka et al. [11] in a large Japanese cohort revealed that increased uric acid levels were associated with increased carotid atherosclerosis in men without metabolic syndrome, but no association was found in either men with metabolic syndrome or in women. The differential association between uric acid and CVD in men and women has been well reviewed in a study by Gagliardi et al. [12]. Further studies are necessary to investigate the differential impact of hyperuricemia on the development or aggravation of CVD in different populations.

### **Mechanism of uric acid-induced CVD or metabolic syndrome**

The mechanism by which uric acid may cause CVD has been explored using cell culture and animal models. It appears that uric acid must enter the endothelial and vascular smooth muscle cells via a specific organic anion exchanger, where it activates a variety of intracellular signaling molecules involved in inflammation and proliferation. In the endothelial cells there is a decrease in nitric oxide levels and an inhibition of endothelial proliferation, whereas in vascular smooth muscle cells there is activation of proliferative and inflammatory pathways [13,14]. Local activation of the renin-angiotensin system has also been shown [14]. Low nitric oxide may

also have a central role in the induction of insulin resistance, as insulin requires nitric oxide for its action (by stimulating blood flow to the skeletal muscle) [15].

New studies have also suggested that hyperuricemia may have a pathogenetic role in obesity-related metabolic syndrome. Thus, an elevated uric acid level predicted the development of both obesity and hyperinsulinemia in normal subjects [15,16], and an elevated uric acid level is universally present in patients with metabolic syndrome [17], which was also demonstrated in the study by Lim et al. Furthermore, recent studies in which rats were fed fructose to induce metabolic syndrome found that lowering uric acid levels with allopurinol could significantly prevent hypertension, hyperinsulinemia, hypertriglyceridemia, and obesity [16].

### **Perspectives**

Despite the consensus that hyperuricemia is a significant CVD marker, there are controversies regarding a causative role for uric acid in CVD and/or metabolic syndrome. Prospective clinical studies are necessary to investigate whether a reduction in uric acid levels prevents CVD or metabolic syndrome. Considering the wealth of basic and clinical data suggesting a role for uric acid as a vascular risk factor, and the ease and cost-effectiveness of uric acid-lowering therapy, the potential causality of hyperuricemia in CVD and its possible mechanism needs to be further explored to reduce the cardiovascular epidemic in modern society. **(Korean J Intern Med 2010;25:18-20)**

### **Conflict of interest**

No potential conflict of interest relevant to this article was reported.

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