The Impacts of Serum Uric Acid on arterial hemodynamics and Cardiovascular Risks

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Hyperuricemia, and its clinical manifestation gout, is a metabolic disease process that has been recognized since the dawn of medical inquiry. Uric acid was hypothesized to be a mediator of cardiovascular disease for period of time. Epidemiological correlations of hyperuricemia with hypertension and cardiovascular events were evident for two centuries’ studies. With recent animal studies shedding light on the causal mechanisms of hypertension, and clinical trials suggesting that urate-lowering therapy can lower blood pressure, there appears to be growing evidence of a connection between hyperuricemia and cardiovascular disease. To help bring this recent uric acid research into context, we have undertaken this narrative review of hyperuricemia, hypertension, its hemodynamics and its outcomes, and the risk for cardiovascular diseases.

Key Words: Cardiovascular risk • Hemodynamics • Uric acid

PREVALENCE OF HYPERURICEMIA

According to statistics from the Nutrition and Health Survey in Taiwan, the prevalences of hyperuricemia in men (serum uric acid level > 7.0 mg/dl) and women (serum uric acid level > 6.0 mg/dl) were as high as 42.1% and 27.4%, respectively. The mean serum uric acid levels [6.63 mg/dl for men and 5.62 mg/dl for women (all Taiwanese participants, > 45 years of age)], and the prevalence of hyperuricemia was higher in the Taiwanese population as compared to other ethnic groups and other regions throughout the world. Using the same data collection from the Nutrition and Health Surveys in Taiwan (NAHSIT) conducted in 1993-1996 and 2005-2008, mean uric acid levels decreased between 1993-1996 and 2005-2008 in both genders (6.77 vs. 6.59 mg/dL in men and 5.33 vs 4.97 mg/dL in women), and the prevalence of hyperuricemia declined from 25.3% to 22.0% in men (p < 0.0001) and from 16.7% to 9.7% in women (p < 0.0001) for the general population. However, the prevalence of gout (self-reported) increased (4.74% vs. 8.21% in men and 2.19% vs 2.33% in women, p < 0.0001). Changes in dietary patterns may in part explain the decrease in uric acid levels between the two national surveys. According to reports by NHANES-III in the US and the Nutrition and Health Survey in Taiwan Elementary School Children from 2001 to 2002, the prevalence of metabolic syndrome increases substantially with increasing levels of serum uric acid, and vice versa.

URIC ACID, METABOLIC SYNDROME AND DIABETES

Uric acid is generated from purines which arise from metabolism of dietary and endogenous nucleic acids through the action of the enzyme xanthine oxidase. In
the human body, uric acid is distributed throughout the extracellular fluid compartment as sodium urate, which is cleared from the blood by the kidney. In the kidney, around 90% of filtered uric acid is reabsorbed from the proximal renal tubule, and further actively secreted into the distal tubule by an ATPase-dependent mechanism. So the urate concentration in humans is determined by a combination of the rate of purine metabolism (both endogenous and exogenous) and the efficiency of renal clearance. The serum uric acid concentration within the population has a Gaussian distribution. On the other hand, in animals, all species apart from man and higher apes express urate oxidase, an enzyme responsible for further metabolism of uric acid to allantoin (a more soluble waste product) prior to excretion.

Clinically, an association of gout with hypertension, diabetes, kidney disease, and cardiovascular disease has been observed since the late 19th century. Early investigators had hypothesized that uric acid might be a cause of hypertension, renal and even cardiovascular disease. Increasing evidence suggests that uric acid may play a role in metabolic syndrome. Previously, the elevated level of uric acid observed in metabolic syndrome has been attributed to hyperinsulinemia, and it was assumed that insulin reduces renal excretion of uric acid. Hyperuricemia, however, often precedes the development of hyperinsulinemia, obesity, and diabetes. Hyperuricemia may also be present in metabolic syndrome in people who are not overweight or obese. The role of uric acid in the development of metabolic syndrome has been suggested from studies in animal models which showed that decreasing uric acid levels can prevent or reverse features of metabolic syndrome. From those authors’ suppositions, two mechanisms were suggested to explain how hyperuricemia might induce metabolic syndrome. The first mechanism is related to the fact that glucose uptake in skeletal muscle depends in part on increases in blood flow mediated by the insulin-stimulated release of nitric oxide from endothelial cells. Features of metabolic syndrome develop in mice lacking endothelial nitric oxide synthase. The observations that hyperuricemia can induce endothelial dysfunction in rats and that treatment with allopurinol can improve endothelial function in patients with hyperuricemia may partly explain this association. The second mechanism concerns the inflammatory and oxidative changes uric acid induces in adipocytes, a process that is key in causing metabolic syndrome in obese mice.

For diabetes and hyperuricemia, the Finnish Diabetes Prevention Study based on 475 overweight or obese individuals with impaired glucose tolerance found that having a serum uric acid level within the top tertile (≥ 6.4 mg/dL) was associated with a twofold increase in the risk of type 2 diabetes compared with the lowest tertile (< 5.2 mg/dL). The Rancho Bernardo Study with 566 participants (mean age 68 years) found a 65% increase in the risk of incidence of type 2 diabetes per mg/dL increase in uric acid level. The Rotterdam Study, a prospective cohort of individuals aged 55 years and older, showed that the risk of developing type 2 diabetes in the top quartile of uric acid (> 6.2 mg/dL) was 1.68 times that in the lowest quartile (uric acid ≤ 4.5 mg/dL). Recently, prospective data from two generations of the Framingham Heart Study provided evidence that individuals with higher serum uric acid, including younger adults, are at a higher future risk of type 2 diabetes independent of other known risk factors. Multivariable relative risks per mg/dL increase in serum uric acid levels were 1.20 (95% confidence interval (CI), 1.11 to 1.28) for the original cohort and 1.15 (95% CI, 1.06 to 1.23) for the offspring cohort.

Although epidemiological evidence and basic research of hyperuricemia may lead to a better understanding of endothelial dysfunction and nitric oxide inhibition, which in turn contribute to insulin resistance and thus diabetes, any causal inference remains to be clarified by future studies.

**HYPERURICEMIC HYPERTENSION**

Studies of uric acid levels and the development of hypertension have generally been consistent, continuous, and of similar magnitude. This concept that hyperuricemia may lead to hypertension is not a novel one. In 1870, Frederick Mahomed proposed uric acid as an important mediator for hypertension, and published the first sphygmograph tracings showing a patient with gout who had increased systemic systemic blood pressure (BP). Until recently, the studies of Feig and Johnson and colleagues in many animal studies had revealed that acute elevation of serum urate induces a prompt eleva-

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tion of blood pressure, and that chronic elevation sustains the abnormal pressure and induces irreversible vascular and glomerular changes that lead to a form of salt-sensitive hypertension.21,22

Besides, hyperuricemia is also common among adults with prehypertension.23 The observation that hyperuricemia precedes the development of hypertension indicates that it is not simply a result of hypertension per se.

Abundant recent clinical evidence supports the possibility that an elevated uric acid level may lead to hypertension. Numerous studies have reported that hyperuricemia carries an increased relative risk for developing hypertension, independent of other risk factors.24-39 Furthermore, the strength of the relationship between uric acid level and hypertension decreases with increasing patient age and duration of hypertension,40 suggesting that uric acid may be more important in younger subjects with early-onset hypertension.

In animal models, where hyperuricemic rats were treated with a uricase inhibitor, hypertension developed several weeks after the uric acid level was increased. In such animals, BP correlated directly with serum levels of uric acid and decreased when uric acid was reduced with either a xanthine oxidase inhibitor or a uricosuric agent.21 Moreover, the hypertension was shown to result from uric acid-mediated renal vasoconstriction due to a reduction in endothelial levels of nitric oxide, with activation of the renin-angiotensin system.22,41,42 Consistent with these observations, elevated uric acid levels in humans also correlate with endothelial dysfunction and increases in plasma renin activity.43-47

Some clinical trial data also support a role for uric acid in early-onset primary hypertension. A double-blind, placebo-controlled crossover trial was performed on 30 adolescents with hyperuricemia and hypertension.48 In this trial, treatment with allopurinol was associated with a significant reduction in both casual and ambulatory BP, and the reduction was similar in magnitude to that achieved with most antihypertensive agents [-6.9 ± 4.4 mmHg and -5.1 ± 2.4 mmHg as compared with -2.0 ± 0.4 and -2.4 ± 0.7 for placebo for casual systolic and diastolic BP, respectively (p = 0.007 and p = 0.03)]. This evidence was extended to obese prehypertensive adolescents. A randomized, double-blinded, placebo-controlled trial was conducted comparing 2 mechanisms of urate reduction with placebo in prehypertensive obese adolescents, aged 11 to 17 years. The subjects were randomized to the xanthine oxidase inhibitor, allopurinol, uricosuric, probenecid, or placebo. It was observed that prehypertensive adolescents treated with urate-lowering therapy experienced a highly significant reduction in BP. In clinic, the systolic BP fell 10.2 mmHg, and diastolic BP fell 9.0 mmHg in treated patients compared with a rise of 1.7 mmHg and 1.6 mmHg systolic and diastolic BP, respectively, in patients on placebo. Urate-lowering therapy also resulted in significant reduction in systemic vascular resistance. These data indicate again, in adolescents with prehypertension, uric acid causes increased BP that can be mitigated by urate-lowering therapy.49

HEMODYNAMIC EFFECT OF URIC ACID

Arterial stiffness, wave reflection and hypertension

Cardiovascular disease may be considered as a manifestation of premature, accelerated, or early vascular aging.50 Early vascular aging and the associated target organ damage represent a mediating step between risk factor exposure and cardiovascular events. Markers of early vascular aging and target organ damage reflect cumulative damaging effects from risk factors, and may become relevant targets for aggressive intervention for the prevention and treatment of cardiovascular disease.51 Increased arterial stiffness was observed to be a direct manifestation of early vascular aging. Carotid-femoral pulse wave velocity (PWV), an index of aortic stiffness, is considered the “gold standard” measurement of arterial stiffness.52 Increased carotid-femoral PWV has been proven to be an independent predictor of cardiovascular events in patients with hypertension, impaired glucose tolerance and diabetes mellitus, end-stage renal disease, and in the elderly and general populations.53-58

Systolic blood pressure (SBP) and pulse pressure (PP) levels rise progressively as the pressure wave travels in the continuously narrowing and branching system from the central aorta toward the peripheral arteries. This is the so-called phenomenon of PP amplification, mainly due to wave reflections detectable at any peripheral point.59 Early return of a large reflected wave augments central aortic SBP and PP, and the re-
reflected wave, independent of its timing, impacts adversely on the left ventricular afterload and coronary perfusion, and was supposed to be related to ischemic heart disease. However, whether increased wave reflection is an effective marker of early vascular aging remains controversial. Specifically, wave reflection intensity gauged by the augmentation index (AI) and augmented pressure (Pa) (Figure 1) has only been shown to be an independent predictor of cardiovascular events in relatively elderly patients with end-stage renal disease and patients after percutaneous coronary intervention. On the other hand, AI and Pa failed to predict cardiovascular events in elderly female hypertensives, patients with chronic kidney disease, and relatively young nondiabetic dialysis patients. To date, evidence supporting the role of wave reflection in the prediction of cardiovascular events in the hypertensive and general populations is still lacking. However, using the triangulation method, the carotid pressure waveform can be separated into its forward and reflected components to calculate transit time-independent parameters of wave reflection intensity termed as forward wave (Pf) and backward wave (Pb) (Figure 2). The Pb, a transit time-independent measure of reflected wave magnitude, has been proven to predict long-term cardiovascular mortality in men and women independent of arterial stiffness. To sum up, the arterial stiffness indexed by cf-PWV was well defined; however, the association of arterial wave reflection and other clinical parameters was still not fully elucidated.

Uric acid and arterial stiffness

The association between serum uric and arterial stiffness has been reported in scant few studies. In a study involving 1225 Caucasian patients, newly diagnosed, never-treated hypertensive subjects, uric acid positively correlated with cf-PWV in both men and women after adjusting for confounders. In 200 Taiwanese patients with essential hypertension (64 women), uric acid was independently associated with increased carotid-radial PWV after controlling for all possible confounding factors. In 982 Japanese who underwent health screening, hyperuricemia was associated with increased brachial-ankle PWV independent of other conventional risk factors for atherosclerosis and metabolic syndrome, in both men and women. In addition, in 9375 Taiwanese participating in a health-screening program, both male and female subjects with hyperuricemia had a significantly higher brachial-ankle PWV than those without it. In contrast, in a study with 940 Chinese workers and their family members, serum uric acid collected during cardiovascular health examinations was significantly and positively associated with cf-PWV in men but not in women, after full adjustment for covariates. In 1276 Koreans subjects who underwent a health checkup, uric acid was not significantly associated with heart-femoral or brachial-ankle PWV in men or women. Thus, the relationship between serum uric acid levels and arterial stiffness appears to be inconsistent and may depend on ethnicity, gender, and other confounders such as hypertension status and use of medications. In contrast, insulin resistance and/or metabolic syndrome have been consistently associated

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**Figure 1.** Augmentation index (Alx) and the augmented pressure illustration.

**Figure 2.** The forward (Pf) and backward wave (Pb) decomposed from carotid wave form by triangulation method.
with increased arterial stiffness in various ethnicities and in both genders.\textsuperscript{74-77}

**Uric acid and arterial wave reflections**

Studies showing any correlation between uric acid level and arterial wave reflections were also few and controversial. In the same studies performed by Vlachopoulos C et al., results showed weak but significant negative correlation between uric acid and augmentation index in the never-treated hypertensive women.\textsuperscript{68} It was speculated by the author that processes such as systemic inflammation that can cause peripheral vasodilation may reduce the magnitude of the reflected wave and lead to a final decrease of the augmentation index.\textsuperscript{68} However, chronic inflammation, such as in patients with rheumatoid arthritis or chronic fatigue syndrome, is usually associated with endothelial dysfunction and increased augmentation index.\textsuperscript{78,79} In fact, increased intensity of wave reflections with increased serum uric acid level as observed with the presence of endothelial dysfunction is frequently associated with hyperuricemia.\textsuperscript{80,81} For the peripheral vascular resistance, there is indirectly associated evidence that urate-lowering therapy can reduce peripheral vascular resistance in a randomized clinical trial for prehypertensive adolescents, with around 25.1% reduction in allopurinol and 18.3% of probenecid treatment group.\textsuperscript{49}

**THE ASSOCIATION OF HYPERURICEMIA AND CARDIOVASCULAR DISEASES**

The status of hyperuricemia as an independent risk factor for cardiovascular disease is still debated. However, recently in regional Taiwanese studies, an increasing volume of literature had suggested that hyperuricemia was an independent risk factor of mortality for all causes, total cardiovascular disease (CVD), ischemic stroke and ischemic heart disease in the general population, in high-risk groups, and potentially in low-risk groups.\textsuperscript{82-84}

For the role of uric acid in cardiovascular disease, epidemiologists have often used multivariate analyses to assess whether an elevated uric acid level is an independent cardiovascular risk factor. Using this usual statistical method, a number of studies have suggested that uric acid is not independent of other established risk factors, such as hypertension, for the development of cardiovascular disease.\textsuperscript{40} On the other hand, some experts have argued that studies indicating uric acid is an independent risk factor did not fully control for other known risk factors. Furthermore, if uric acid were a risk factor, then a mechanism by which uric acid could cause cardiovascular disease should be apparent. Others have also pointed out that one of the main functions of uric acid is its role as an antioxidant, which, if anything, would make it beneficial to people with cardiovascular disease.\textsuperscript{85,86} Finally, the elevation of uric acid levels in patients with cardiovascular disease could simply be a result of the common presence of factors such as reduced glomerular filtration rate, hyperinsulinemia, renal vasoconstriction, or diuretic use or of alcohol use, tissue ischemia, or oxidative stress.\textsuperscript{87} However, in our previous study, the significance of adding hyperuricemia to traditional cardiac risk prediction models did not significantly improve the ability to predict the risk of cardiac or all-cause death, regardless of whether we used receiver-operating-characteristic curve analysis or reclassification methods. It seemed that hyperuricemia per se, may not be designated as a treatment target at present for reducing cardiac or even all-cause death.\textsuperscript{88}

Although the association between hyperuricemia and CVD mortality has been studied to some extent, fewer studies have investigated the relationship between serum uric acid and CVD morbidity. Univariate analyses of the Framingham Heart Study data\textsuperscript{40} and the Atherosclerosis Risk in Communities Study\textsuperscript{89} data and a multivariate analysis of the British Regional Heart Study\textsuperscript{90} data had indicated that serum uric acid was not associated with coronary heart disease (CHD) events. Moreover, a meta-analysis involving 16 relevant prospective studies had shown only a weak association between serum uric acid and CHD events. Furthermore, in eight studies that more extensively adjusted for possible confounders, no association was found. According to this result of meta-analysis study by Wheeler JG et al., measurement of serum uric acid is unlikely to enhance the prediction of CHD and is unlikely to be a major determinant for the disease in the general population.\textsuperscript{91}

Nevertheless, with respect to the relationship between hyperuricemia and myocardial infarction, the
Rotterdam study\textsuperscript{92} and the Multiple Risk Factor Intervention Trial\textsuperscript{93} (MRFIT) recently reported, after analyzing the data using a multivariate model adjusted for other known CHD risk factors, that those patients with elevated serum uric acid or highest quintile had a significantly greater risk for acute myocardial infarction. In the MRFIT study, subjects were followed-up for a mean duration of 6.5 years. There were 118 events of acute myocardial infarction (MI) in the group with gout (10.5%) and 990 events in the group without gout (8.43%; \( p = 0.018 \)). Hyperuricemia was an independent risk factor for acute MI in the multivariable regression models, with an odds ratio (OR) of 1.11 [95% confidence interval (95% CI) 1.08-1.15, \( p < 0.001 \)]. In multivariable regressions after adjusting for covariates, gout was found to be associated with a higher risk of acute MI [OR 1.26 (95% CI 1.14-1.40), \( p < 0.001 \)]. In the Rotterdam study with average follow-up of 8.4 years, high serum uric acid levels were associated with risk of myocardial infarction. Adjusted hazard ratios (95% CIs) for highest versus lowest quintile of uric acid were 1.87 (1.12 to 3.13) for MI.

Besides, there were already studies which confirmed that hyperuricemia or gout, especially untreated gout, are poor prognostic markers with recent or post myocardial infarction event.\textsuperscript{94,95} Furthermore, a large cross-sectional study in Taiwan had also suggested that gout is associated with Q wave MI by both the severity of gouty arthritis and serum urate level, and there existed a gender difference in this association.\textsuperscript{96}

On the other hand, the association between hyperuricemia and cerebral vascular events was also controversial. A recent meta-analysis showed that hyperuricemia may modestly increase the risks of both stroke incidence and mortality. A total of 16 studies including 238,449 adults were eligible and abstracted in that analysis. Hyperuricemia was associated with a significantly higher risk of both stroke incidence [6 studies; RR 1.41, 95% confidence interval (95% CI) 1.05, 1.76] and mortality [6 studies; RR 1.36, 95% CI 1.03, 1.69] in meta-analyses of unadjusted study estimates. Subgroup analyses of studies adjusting for known risk factors such as age, hypertension, diabetes mellitus, and cholesterol still showed that hyperuricemia was significantly associated with both stroke incidence (4 studies; RR 1.47, 95% CI 1.19, 1.76) and mortality (6 studies; RR 1.26, 95% CI 1.12, 1.39).\textsuperscript{97,98}

**CONCLUSIONS**

With the increasing prevalence of obesity and diabetes worldwide, co-existing hyperuricemia is getting more focused attention than ever before. This kind of problem is more prominent in Taiwan than in other countries, and deserves to be designated as an emerging public health problem. Although many epidemiological and clinical studies suggested a strong correlation between hyperuricemia and cardiovascular risks and events, findings in these studies were controversial and ambiguous. Debates continue to this day, and the problem has remained, but it has been substantially clarified. In the future, in an effort to prevent future cardiovascular events, treatment modalities for hyperuricemia may begin to be practical and implemented for use by the general population.

**REFERENCES**


