Hyperuricemia, Cardiovascular Disease, and the Metabolic Syndrome

To the Editor:

We read with great interest Dr. Neogi's recent editorial on asymptomatic hyperuricemia[1], as well as the correspondence from Drs. Marasini and Massarotti[2].

There are strong associations among hyperuricemia, cardiovascular disease, and the metabolic syndrome[3,4]. Still, the role of uric acid (UA) in the latter 2 conditions is lacking. Marasini and Massarotti state that "abdominal obesity has been found to be significantly related to serum uric acid levels probably because obesity interferes with urate synthesis and excretion." We provide a hypothesis that might explain how obesity interferes with UA excretion. This putative mechanism involves consideration of the renin-angiotensin system (RAS). Obesity, a component of the metabolic syndrome, may result in dysregulation of the RAS[5]; plasma renin and angiotensinogen concentrations are often elevated in obese individuals[6], and this leads to elevated angiotensin II activity. Angiotensinogen is synthesized within and secreted from adipose tissue[6], which may contribute to increased angiotensin II activity.

As well as increasing blood pressure, infusion of angiotensin II was found to reduce the fractional renal clearance of UA (i.e., the ratio of UA clearance to creatinine clearance)[7]. Additionally, water loading (the provision of large volumes of water prior to study participation) is associated with an increase in fractional clearance of UA[8], and in this situation, the RAS is less active. Further, autoimmune stimulation of angiotensin II receptors (AT1 receptors) is implicated in the pathophysiology of preeclampsia, a condition that also presents with elevated serum UA concentrations[9].

Therefore, we hypothesize that in obese individuals, excess angiotensin II activity causes a sustained reduction in the fractional clearance of UA, which leads to chronic retention of UA and thus hyperuricemia. Hyperuricemia may also contribute to atherosclerotic processes[4].

While there is no definitive explanation why angiotensin II may reduce the fractional clearance of UA, it was proposed by Enomoto, *et al* that UA transport is coupled with sodium transport in the proximal tubule[10]. If this is true, increased sodium reabsorption due to elevated angiotensin II activity will lead to increased UA reabsorption. Figure 1 summarizes how UA may be connected with cardiovascular disease and obesity.

Whether UA has a pathogenic role in cardiovascular disease remains uncertain; however, the hyperuricemia frequently observed in those with the metabolic syndrome may simply be a consequence of obesity and dysregulation of the RAS.

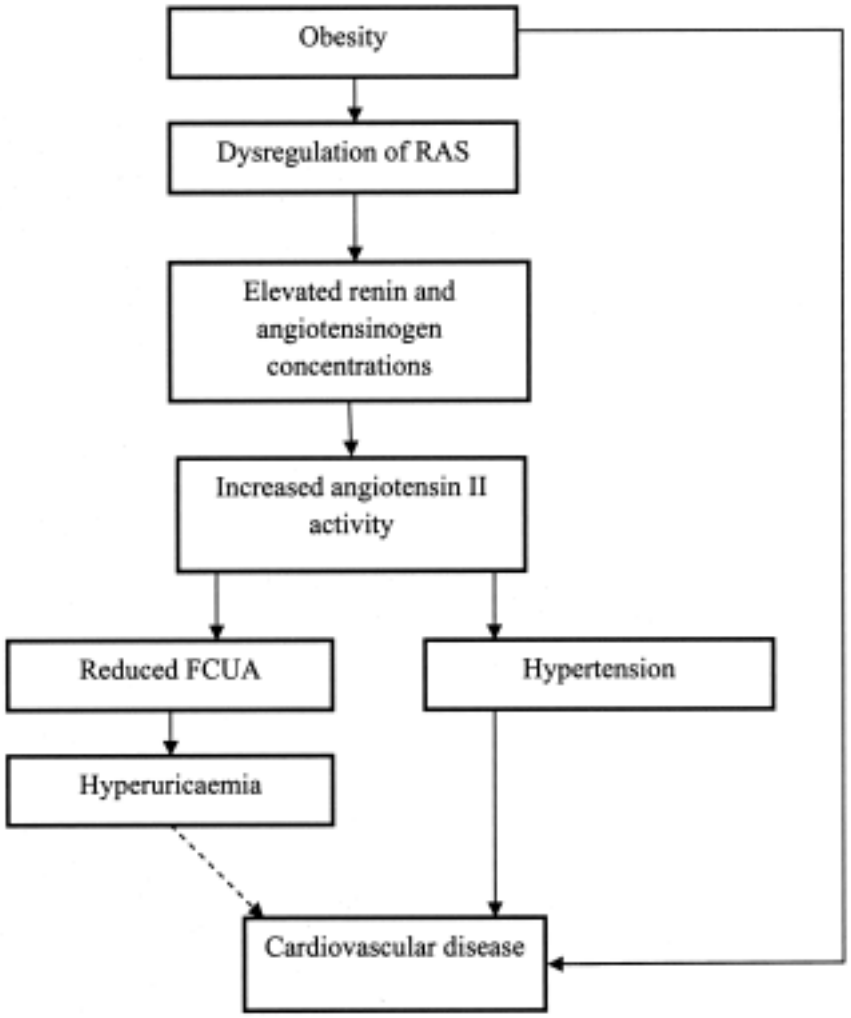

Figure 1. Hypothesized relationships between hyperuricemia and risk factors for cardiovascular disease. RAS: renin-angiotensin system; FCUA: fractional clearance of uric acid.

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