Editorial

Asymptomatic Hyperuricemia: Perhaps Not So Benign?

Hyperuricemia was first discovered by Alfred Baring Garrod, who showed that subjects with gout had such high concentrations of uric acid in their blood that their serum could crystallize on a thread previously dipped in acetic acid[1]. With the development of biochemical tests, it became apparent that, while gouty subjects frequently are hyperuricemic, the majority of hyperuricemic subjects do not develop gout[2]. Further, there has been a dramatic rise in the prevalence of both hyperuricemia and gout in the United States and elsewhere over the last 80 years, with mean uric acid levels rising from less than 3.5 mg/dl to 4.2 mg/dl between the 1920s and 1940s (using the Folin reagent) and from 5.0 to > 6.0 mg/dl between the 1950s and 1980s (using the uricase method)[3]. A variety of factors have been suggested to account for this rise, including Western diet (including fructose intake), obesity, increasing diuretic use, and increasing aging in the population. As more and more patients become hyperuricemic, it seems relevant to reexamine the clinical associations of hyperuricemia outside of gout and nephrolithiasis, and to reconsider the old adage that asymptomatic hyperuricemia is a benign condition and does not require treatment.

Some investigators have argued that hyperuricemia is a good condition to have. For example, Orowan noted the similarity in chemical structure of uric acid with the trimethylated xanthine caffeine, and suggested that hyperuricemia may have a role in intelligence and human performance[4]. Following that article, numerous studies in the 1960s and 1970s documented that subjects with higher uric acid levels tended to have greater intelligence, achievement-oriented behavior, school performance, and reaction time. However, in most of the studies the biological effect appeared relatively small[5-7] and may be confounded by socioeconomic status. Nevertheless, there is some evidence to support a role for uric acid as a mild neurostimulant.

A second major area of investigation has related to the key observation that uric acid can function as an antioxidant that can block superoxide, peroxynitrite, and iron-catalyzed oxidation reactions[8]. Ames, *et al* have suggested that an elevated uric acid concentration may be one of the key antioxidants in plasma that may help prolong longevity by preventing aging-associated oxidative stress[8]. The infusion of uric acid into humans can immediately increase antioxidant activity and improve endothelial function[9]. The ability of hyperuricemia to reduce peroxynitrite-mediated nitrotyrosine formation has been suggested to have a key role in neuroprotection in diseases such as multiple sclerosis, Parkinson's disease, stroke, and others. Epidemiological studies suggest that subjects with elevated uric acid levels have a lower frequency of multiple sclerosis, Parkinson's disease, and Alzheimer's disease, and uric acid infusions can reduce the neurological sequelae observed in experimental models (such as experimental allergic encephalomyelitis)[10]. More recent studies suggest that the benefit of uric acid in these conditions may relate, not to its nitrotyrosine-blocking antioxidant effects, but rather to its ability to block the blood-brain barrier, or by its effects on astroglial cells[11,12]. Further, one must be careful in interpretation of cross-sectional studies, because patients with impaired neurological function may tend to have lower uric acid levels due simply to poor nutrition. Nevertheless, these studies raise the interesting possibility that use of uric acid or its precursors may have benefit in some neurological diseases[13].

While the studies above suggest advantage to having higher uric acid levels, most studies have linked hyperuricemia to poor clinical outcomes due to marked association with cardiovascular disease (CVD) and renal disease[14]. The associations are numerous: uric acid levels correlate with prehypertension, hypertension, increased proximal sodium reabsorption, microalbuminuria, proteinuria, kidney disease, obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol, hyperinsulinemia, hyperleptinemia, hypoadiponectinemia, peripheral, carotid and coronary artery disease, endothelial dysfunction, oxidative stress, renin levels, endothelin levels, and C-reactive protein levels. Uric acid levels are also higher in postmenopausal versus premenopausal women, in African Americans, in subjects living in urban versus rural areas, and in subjects on Western diets; again, all are factors associated with increased cardiovascular and renal risk[3,15,16]. The association of uric acid with almost all risk factors for CVD (with

smoking the only real exception) has made it very difficult to determine whether uric acid has a causal role in these conditions or whether it is simply a marker for individuals at increased risk.

In one approach to sort out the role of uric acid in CVD, data from observational clinical studies were used to determine whether uric acid is a risk factor for CVD, "independent" of other known risk factors. The underlying concept is that to be a true causal risk factor, uric acid needs to be independent of other established risk factors[17-19]. Accordingly, some have argued that studies showing uric acid to be an independent risk factor have simply not controlled for all the potential confounding risk factors shown above, and that even if uric acid is a risk factor, its biological effect is small and clinically insignificant[17-19]. On the other hand, studies in which uric acid was not determined to be independently associated with cardiovascular outcomes may have been related to insufficient power to detect low event rates[17,20,21].

Although these types of analyses aim to elucidate the direct effect of uric acid on CVD independent of other factors, a problem with this type of analysis is that it does not consider the possibility that uric acid may cause heart disease indirectly by causing hypertension or kidney disease. For example, let us assume that elevated uric acid leads to hypertension, which in turn leads to CVD, and that uric acid has no other direct effects on CVD. In this example, hypertension is an intermediate in the causal pathway between uric acid and CVD. By adjusting for hypertension, no effect of uric acid would be seen if uric acid has no other effects on CVD except through hypertension. One would therefore correctly conclude that uric acid has no association with heart disease independent of hypertension, but will have missed identifying uric acid as a strong risk factor for hypertension, which in turn is a strong risk factor for heart disease. If the question is whether uric acid has causal effects on a particular risk factor (e.g., hypertension), which can in turn lead to heart disease, one must evaluate uric acid's relation to that risk factor rather than to CVD as the outcome. If the question is about the sum total effect of uric acid on heart disease, both direct and indirect, then one should not adjust for risk factors that are intermediates along the pathway from uric acid to heart disease; indeed special analytic methods may be needed[22]. Because biological pathways are often complex (in some cases even unknown), clinical researchers must carefully consider the implications in their choices for adjustment of various risk factors, the methods of analysis (particularly when a factor can be both confounder and intermediate), and the outcomes assessed, so as not to miss potentially important upstream effects. Well conducted, randomized clinical trials are best suited to demonstrating any clinical effects of uric acid on adverse cardiovascular effects or on intermediate risk factors such as hypertension or renal disease.

Ideally, one should assess the risk of asymptomatic hyperuricemia and determine pertinent biological pathways: that is how Robert Koch proved tuberculosis was caused by a mycobacterium; that is, by reproducing effects of hyperuricemia in animals. In this regard, rats have lower uric acid levels compared to humans because rats have the enzyme, urate oxidase (uricase), that degrades uric acid into allantoin. Interestingly, the inhibition of uricase in the rat results in development of hypertension that is mediated by endothelial dysfunction (reduction in nitric oxide) and by activation of the renin-angiotensin system[23]. Over time, the rats develop renal microvascular disease (with arteriolosclerotic-type lesions) and hypertension switches from uric acid- and renin-dependence to salt-sensitive and kidney-dependence[24]. In keeping with these observations, hyperuricemia was found to precede the development of hypertension[25,26] and to be present in nearly 90% of newly diagnosed hypertensive adolescents[27], and lowering uric acid with allopurinol has been found to reduce blood pressure in pilot studies[28]. Results of a US National Institutes of Health-sponsored, double-blind placebo-controlled study to determine if allopurinol lowers blood pressure in this latter population are forthcoming.

Other studies suggest uric acid may have numerous other deleterious roles: inhibiting endothelial function, stimulating vascular smooth muscle cell proliferation, inducing inflammatory pathways, stimulating innate immunity, activating the renin-angiotensin system, and activating adipocytes[23,29-33]. Experimental studies have also shown a role for uric acid in mediating both metabolic syndrome[34] and kidney disease[35], suggesting complex but substantial roles for uric acid in the cardiorenal epidemic. Indeed, several recent clinical trials suggest a benefit of lowering uric acid for blood pressure, renal function, and systemic inflammation[36-38]. Clinical trials being conducted for evaluation of new gout treatments may provide further information about such benefits.

Numerous questions remain regarding the role of uric acid and CVD. First, how can uric acid function as an antioxidant with benefits for endothelial function acutely, yet chronically be associated with prooxidative effects associated with endothelial dysfunction? However, uric acid can also generate radicals on reaction with oxidants[39] and can stimulate NADPH oxidase in some cell types[40]. Thus, this effect may relate to the effects of chronic hyperuricemia on intracellular signaling, as opposed to the effects of acutely raising uric acid on intravascular function.

Second, most of the clinical studies suggesting benefit of lowering uric acid have been performed with allopurinol, which is a xanthine oxidase inhibitor; indeed, some studies suggest that other uric acid-lowering agents are less effective, for example, at improving endothelial function[41,42]. This raises the possibility that the effects are mediated by xanthine oxidase-associated oxidants as opposed to uric acid itself. Alternatively, xanthine oxidase inhibitors may be

more effective at lowering intracellular uric acid, since it appears to be the intracellular uric acid that is driving most of the cardiorenal effects[29].

If asymptomatic hyperuricemia does affect clinical outcomes, then either dietary or pharmaceutical interventions to lower uric acid may become a new therapeutic approach for preventing cardiovascular and renal disease. While lowering purine intake has been shown to have relatively mild effects on serum uric acid, the possibility that low-fructose diets may provide benefit deserves study, especially since studies suggest that those subjects with the highest uric acid levels also have the highest fructose intake[43]. Allopurinol also becomes an attractive option, but not a completely benign one, since 2% develop rash that can rarely progress to a full-blown hypersensitivity syndrome with potential mortality[44]. Finally, allopurinol can accumulate in renal disease and has been found to be nephrotoxic in animals[45]; hence, some care may be indicated in allopurinol treatment in humans with renal dysfunction. Uricosuric agents are also problematic in persons with renal insufficiency. New agents being evaluated for the management of gout may provide additional opportunities for lowering uric acid.

In summary, uric acid can no longer be considered biologically inert, but rather has numerous biologic functions. Emerging studies suggest a role for asymptomatic hyperuricemia in both neurological and cardiorenal diseases. Clearly, additional experimental and clinical studies are needed before any intervention is recommended. However, the next decade will likely provide illuminating new information on the role of uric acid in diseases other than gout.

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