

A Little Citrus Might Go a Long Way!



The scourge of gout remains highly prevalent¹. Its incidence is on the rise², and the predominant clinical manifestations are as challenging as ever to safely manage. When a gout attack strikes, often at the least convenient of times, the affected host is overcome by misery, if not incapacitated, as was the case during antiquity. Although an estimated 3 million Americans experienced a gout attack in 2005¹, the range of available treatment options — for both acute intervention and prophylaxis — is virtually unchanged from 40 years ago. While nonsteroidal antiinflammatory drugs, corticosteroids (oral, intravenous, and intraarticular), colchicine and allopurinol have established therapeutic benefit, they each possess a considerable side-effect profile^{3,4}.

Older age and underlying renal insufficiency are 2 important risk factors for iatrogenicity arising from gout medication^{3,4}. These are, nonetheless, key demographic and clinical features of the population segment at risk to develop incident gout and to experience recurrent gout flares. Novel therapeutic strategies, particularly those that might offer incremental clinical benefit without the counterbalancing peril of treatment-related toxicity, are sorely needed. A recent development was the arrival of febuxostat, a novel xanthine oxidase inhibitor, that would potentially offer greater safety over traditional allopurinol, with its primary hepatic (febuxostat) rather than renal (allopurinol) metabolism⁵. Although its therapeutic upside was demonstrated in a randomized clinical trial⁵, approval from the US Food and Drug Administration has seemingly been elusive. Caution in the drug approval process may be influenced by lingering concern about safety, coming on the coattails of the contemporary experience with selective inhibitors. These arthritis agents were ultimately recognized to engender an increase in cardiovascular morbidity and mortality. It is only with postmarketing surveillance in an expanded population that quantitatively richer pharmacoepidemiologic data may come forward⁶.

Interestingly, the lay public has maintained a longstanding interest in complementary and alternative therapies,

including the use of vitamins, to manage or prevent a broad range of disorders⁷. Such an option might be especially germane to gout (and hyperuricemia) if a therapeutic agent is found to offer clinical benefit with a concomitant diminution (rather than an escalation) in iatrogenic risk! In such a scenario, not only might the attention of the public be galvanized, but the medical community might simultaneously generate enthusiasm. The key is to strive for clear and compelling scientific evidence culled from well designed and rigorously analyzed clinical studies. In this vein, vitamin C or ascorbic acid, might fit the billing.

Ascorbic acid is an essential micronutrient that has antioxidant properties protective against free radicals and reactive oxygen species⁸. Exogenous administration of ascorbic acid, at high doses, megadoses, exerts a uricosuric effect. Relevant studies have shown that uric acid excretion is enhanced by consumption of ascorbic acid. Current molecular endeavors have improved the understanding of the cellular sites that mediate renal tubular absorption and secretion of urate. Such a molecular target includes the urate anion-exchange transporter, URAT1, situated at the apical brush border of the nephron⁹.

Recently, 184 adults in Baltimore, MD, USA, participated in a randomized double-blind placebo-controlled trial in which the impact of vitamin C supplementation upon the serum concentration of uric acid was examined¹⁰. As is commonly appreciated, men had higher levels of serum uric acid than women [mean (SD) = 5.9 (1.2) vs 4.6 (1.4), $p < 0.0001$]. In addition, a positive history of elevated cholesterol, hypertension, or diabetes was also related to higher serum uric acid ($p = 0.003$). Importantly, at the end of the 2 month trial, serum uric acid was significantly reduced in the active vitamin C group but not in the placebo group ($p < 0.0001$). On average, urate levels fell 0.5 mg/dl [95% confidence interval -0.6, -0.3] in univariate analysis and following adjustment for age, sex, and baseline serum concentrations of ascorbic acid and uric acid. Alternatively stated, an inverse relationship was identified between the observed

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changes in serum uric acid and serum ascorbic acid; as the former value fell, the latter measure rose. The benefit of vitamin C supplementation persisted in subgroup analyses according to age, sex, chronic illness, baseline diuretic use, and quartiles of baseline uric acid level. The therapeutic benefit of vitamin C was similarly evident in the hyperuricemic participants (serum uric acid > 7 mg/dl) at baseline. In this stratum, assignment to vitamin C resulted in an adjusted mean diminution of serum uric acid by 1.5 mg/dl ($p = 0.0008$).

In this issue of *The Journal* we are further informed about the apparent benefits of vitamin C intake in relation to levels of serum uric acid¹¹. The present report was undertaken in a subset of the Health Professionals Followup Study (HPFS). In total 1387 male health professionals, without prevalent hypertension and aged 40–75 years at cohort entry, were studied. Comprising dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians, this prospective cohort was well suited to address the association of vitamin C (exposure) to serum uric acid (outcome) in that information regarding Vitamin C from both dietary sources and dietary supplements was ascertained. Similarly, quantitative data regarding the concentration of serum uric acid was systematically assessed.

First, there appears to be an inverse relationship between vitamin C intake and risk factors for hyperuricemia. As such, a pattern of higher mean levels of body mass index (BMI), a greater quantity of meat intake, higher mean systolic blood pressure, and higher mean coffee intake in association with lower levels of vitamin C intake seemed to emerge. Second, higher quantities of total vitamin C intake (and of supplement intake) were in fact related to lower mean levels of serum uric acid. This association was present in age and BMI-adjusted models and in multivariate analysis that took into account the gamut of additional known predictors of hyperuricemia and gout. Third, these associations were further evident in subgroup analyses according to categories of age (< 60 vs > 60 yrs), smoking (never vs ever), BMI (< 25 vs > 25 kg/m²), and alcohol consumption (none vs any). Finally, the authors point out that the risk of hyperuricemia, defined as a serum concentration > 360 $\mu\text{mol/l}$ (~6.1 mg/dl), was successively reduced by incrementally higher levels of total vitamin C intake. This last finding implies that vitamin C might be a viable therapeutic option in the primary prevention of gout and in prophylaxis against recurrent gout attacks, by preventing or reducing the hyperuricemic state. The above associations were most evident for supplemental use of vitamin C rather than when derived from food sources; the association with dietary intake of vitamin C seemed to follow the same pattern but was not statistically significant.

Although the HPFS participants were queried regarding their dietary patterns, what specific food items were used to derive vitamin C consumption levels is not explicated in

detailed fashion. Such quantification of relevant food groups would facilitate a direct translation of the paper's findings for the treating physician and the inquisitive patient alike. In addition, it would be clinically relevant, and of potential public health import, to examine the observed association in an obese population (BMI > 30 kg/m²); obesity was an exclusionary criterion in the present study. Further, the HPFS cohort is limited to a cohort of men and to health professionals. Therefore, it would be informative to examine the above associations in a nationally representative population of Americans and among women. Such an undertaking in those with prevalent gout would be particularly relevant, even more so among persons with concomitant renal insufficiency and of older age, in whom the arrival of an efficacious and safe alternate agent might have an impressive population-level impact.

The present findings ought to be viewed within the context of the prolific output of gout-related contributions from the investigative group. A unifying theme of their work has been an assessment of a range of dietary exposures to incident gout. Specifically, these investigators have demonstrated that compared to teetotalers, men who consume 15.0–29.9 g/day of alcohol have a 49% increase in risk of gout; a nearly 2-fold increase in risk was present for those consuming 30.0–49.9 g/day¹². Sugar sweetened, but not diet, soft drinks¹³, as well as high levels of meat and seafood consumption (but not dairy products) contribute to an increase in risk of developing gout¹⁴. Interestingly, coffee consumption, but not tea, was protective against incident gout¹⁵.

Above and beyond the direct musculoskeletal health benefit of ascorbic acid, additional therapeutic gains might also accrue to those who ingest vitamin C. Notably, the prevalence of the metabolic syndrome is known to rise at successively higher levels of hyperuricemia¹⁶. Hyperuricemia, in turn, and gout are reported to increase the risk of coronary heart disease and of cardiovascular mortality, although with inconsistent results across studies^{17–19}. Nevertheless, greater intake of vitamin C, if confirmed in future clinical trials, not only may diminish the burden of gout, but may also be advantageous and protective against comorbid metabolic syndrome and ischemic heart disease²⁰. At both the individual and population level, we may further learn that the health benefits of ascorbic acid may be substantial; a little vitamin C might go a long way!

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