EDITORIAL

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Hyperuricemia and gout: A reign of complacency

IS THERE REALLY ANYTHING NEW to say about hyperuricemia? And does this topic warrant a review?

The answers are yes and yes, and for that reason, in this issue of the *Journal*, H. Erhan Dincer, MD, and colleagues review the topic of hyperuricemia.[1]

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There are indeed new findings that may prompt some reflection about the pathogenesis and systemic impact of hyperuricemia. And yes, the topic warrants review because, in my opinion, we have become complacent in our approach to patients with gouty arthritis, with a false sense of confidence that we actually know the correct way to manage this common disease and the associated biochemical abnormality of hyperuricemia.

IS INTRACELLULAR URATE AS IMPORTANT AS SERUM URATE?

As to what is new, genetic findings are providing new insight into how urate is transported from inside cells. Lipkowitz et al[2] have cloned a human voltage-sensitive urate transporter protein (hUAT). This protein can be inserted into artificial membranes, where it mimics its own biologic action as a specific unidirectional urate transporter.

For years we have conceptually focused on the proximal renal tubule as a site of urate transport, recognizing that inhibition of the tubular secretory transporter sites, or a genetic inefficiency of tubular secretion, can cause hyperuricemia. Indeed, decreased renal clearance is far and away the most common mechanism causing hyperuricemia in patients with gouty arthritis. The familial and apparently sporadic occurrence of hyperuricemia may well be explained by genetic heterogeneity of the structure or expression of the renal tubule hUAT protein.

But all nucleated cells generate uric acid and must dispose of it by secreting it from their cytoplasm. If heterogeneity in hUAT is responsible for decreased renal excretion with resultant hyperuricemia, perhaps it may also cause decreased secretion from other cells, with a resultant increase in intracellular urate concentration. The effect, if any, of elevated intracellular uric acid is currently unclear. However, we do know that patients with severe metabolic disturbances of the uric acid pathway (eg, Lesch-Nyhan syndrome) suffer multiple medical problems in addition to gout and nephrolithiasis, although not necessarily premature coronary artery disease.

New findings should make us reconsider old complacencies

DOES HYPERURICEMIA CAUSE OR EXACERBATE HYPERTENSION, CORONARY DISEASE, AND RENAL FAILURE?

For years, circular arguments have been offered regarding the association (or lack thereof) between hyperuricemia and coronary artery disease, hypertension, and progression of renal failure.

Johnson et al[3] recently reopened this debate with a provocative reinterpretation of older data pointing out that, in some conditions, hyperuricemia precedes the development of hypertension. They reemphasized that several of the older studies repeatedly cited as demonstrating that hyperuricemia is not a risk factor for the development or progression of renal disease may have been flawed in their methods of patient selection, ie,

patients with hyperuricemia-induced progression of renal failure may have been (inadvertently) systematically excluded.

Interventional studies that focused on lowering the serum uric acid level to slow progression of coronary artery disease or renal failure have offered mixed results but certainly did not yield dramatically altered outcomes. These disappointing results have been interpreted as implying a lack of a pathogenic association between uric acid and progression of coronary artery disease or renal failure.

But what if the pathogenic culprit is elevated *intracellular* uric acid, not elevated *serum* uric acid? A defect in hUAT could cause both, and therapy to lower serum uric acid might not be adequate to lower the intracellular urate concentration sufficiently to elicit a clinically meaningful response.

The general belief among internists is that hyperuricemia per se is more likely an associated finding than a pathogenic factor in hypertension, coronary artery disease, progressive renal insufficiency, and metabolic syndrome X. This belief is founded on the lack of compelling epidemiologic data noted above, and the lack of any known mechanism or convincing animal data to support a pathogenic role for uric acid. Recent work from Johnson and colleagues[4] may change our perspective. In a rat model of hyperuricemia, they utilize oxonic acid dietary supplementation to inhibit uricase and cause mild hyperuricemia, without causing uric acid crystallization in the kidney. The treated animals developed high renin hypertension by 3 weeks, with mild renal tubulointerstitial injury characterized by interstitial collagen deposition and some macrophage infiltration. The hypertension and renal injury were both prevented by use of a xanthine oxidase inhibitor that blocked the development of hyperuricemia.

In gout, a uric acid level of 7.0 mg/dL may not be low enough

The observations of Lipkowitz et al[2] and the critique and data of Johnson et al[3,4] should prompt us to reconsider our current understanding of "asymptomatic" hyperuricemia.

THE TWO PARADIGMS OF TREATING HYPERURICEMIA AND GOUT

Even greater unwarranted complacency exists in our management of patients with gouty arthritis and coincident hyperuricemia. There are two distinct paradigms of therapy, the pathophysiologic paradigm and the pragmatic "treat-the-attack" paradigm.

The pathophysiologic paradigm

Pathophysiology-based therapists argue that chronic hyperuricemia and tissue saturation with urate are prerequisites to the development of gouty arthritis. The tissue deposition, whether or not the deposits are physically or radiographically visible as tophi, represents the true disease, and the arthritis cannot be completely and effectively addressed without removing the primary problem—the hyperuricemia. These tissue deposits can be removed with long-term, daily, effective uric acid-lowering therapy.[5] Reducing the body's uric acid load will result in fewer attacks of gout, thus necessitating fewer treatment courses with anti-inflammatory drugs and, conceivably, fewer missed work days and less accumulated joint damage.

As with LDL cholesterol, there is likely a continuum of risk associated with the serum uric acid level. However, uric acid and urate have the additional issue of solubility of the compound in biologic tissues: uric acid is relatively insoluble and tends to precipitate as urate when it is present in higher concentrations. Hence, it has been accepted that the serum level of uric acid should be conservatively maintained below 6 mg/dL in order to solubilize urate tissue stores (via a mass action effect).

Lower is likely better. Clinical studies show that low serum levels seem to be associated with a decreased chance of finding urate crystals in synovial fluid obtained from asymptomatic joints of patients with prior episodes of gouty arthritis, supporting the argument that the serum uric acid level can influence the dynamics of urate in the joint space.[6] In patients with gouty arthritis and continued hyperuricemia, urate crystals can almost invariably be found in the synovial fluid—even from apparently normal, uninflamed joints.

Unfortunately, many patients do not achieve goal levels of uric acid with medications, even in the ideal setting of a clinical trial.[6,7] In actual practice, I suspect that many primary care physicians simply give the 300-

mg dose of allopurinol and are not vigilant about monitoring the serum uric acid level. If hypouricemic therapy is to be used, the target should be a sufficiently lowered uric acid level, not a set dosage of medication. If this paradigm is to be used, physicians must be compulsive about monitoring and achieving the targeted degree of hypouricemia

Arguments against the pathophysiologic approach. As scientifically cohesive as this approach is, no data exist to document that treating *all* patients with gout in this manner results in improved outcomes. In addition, when patients who have received successful hypouricemic therapy stop therapy, the tophi return fairly quickly and the gouty attacks recur.[5]

The pragmatic paradigm

Pragmatic therapists argue that although the joint tissues are indeed supersaturated with urate, not everyone with a single attack of gout will suffer another one (although likely 90% will, if they live long enough). And because not everyone with gouty arthritis suffers from tophi or joint damage, why should patients be routinely subjected to a lifetime of daily hypouricemic therapy when only some—and we do not know how many—may actually need this therapy?

Even in the great toe, not all arthritis is gout

Patients with normal renal function can receive long-term, effective anti-inflammatory therapy with daily low doses of colchicine, which is cheaper and more benign than allopurinol. Occasional attacks can be promptly and effectively treated with corticosteroids, nonsteroidal anti-inflammatory drugs, analgesics, or colchicine.

Arguments against the pragmatic approach. The pragmatic therapists suggest that the number of attacks per year can help guide when to start hypouricemic therapy. But should the threshold number be 3, 4, or 16? At what point does the frequency of attacks become enough of a burden to the patient to warrant specific suppressive therapy, as opposed to treating the individual attacks?

This question must be answered in the context of how much risk and inconvenience each acute treatment and attack poses to the individual patient. The risk is different for a 45-year-old otherwise-healthy man compared with a 60-year-old patient with diabetes, peptic ulcer disease, and a renal transplant in whom any acute therapeutic option is fraught with risks.

Moreover, does this pragmatic, treat-the-attack approach permit an undue burden of hyperuricemia-mediated tissue damage to occur in joints and perhaps other tissues? There are clearly insufficient data on this question. But we must consider that gouty arthritis (an indication of urate deposits in intra-articular tissues) may not be the same as true asymptomatic hyperuricemia, in which urate may or may not be deposited in tissues.

TOWARD AN INDIVIDUALIZED APPROACH

In the absence of appropriate outcome data, we need to thoughtfully individualize the treatment of patients with gouty arthritis and hyperuricemia, and we should not complacently adhere to any single treatment philosophy.

If the uric acid level needs to be lowered, it should be lowered aggressively to approximately 5.5 mg/dL. I advocate this admittedly arbitrary level instead of the generally recommended value of 6 mg/dL because I believe that our intermittent laboratory measurements miss the fluctuations in uric acid levels that accompany food intake, periodic fasting, alcohol ingestion, and exercise, and the lower value provides a greater buffer to permit reabsorption of tissue urate deposits on a more continuous basis.

I do not recommend major dietary changes to most patients, with the exception of education about the effects of intermittent binge alcohol consumption and ingestion of large quantities of organ meats on the uric acid levels.

Young patients with documented gouty arthritis and transplant patients with a single attack of gout should, I believe, undergo aggressive hypouricemic therapy because they are at high risk of developing large burdens of urate deposition disease. Additionally, transplant patients face many unique pharmacologic problems in the treatment of their acute attacks.

New drugs for hyperuricemia are currently in development. These include non-allopurinol inhibitors of xanthine oxidase and

preparations of uricase. Some of our European colleagues have access to benzbromarone,[7] a uricosuric with apparently better efficacy than the uricosurics currently available in the United States. Patients generally respond to adequate doses of allopurinol whether they are "overproducers" or "underexcretors." Thus, xanthine oxidase inhibition therapy does not require a pretreatment 24-hour urine collection for uric acid excretion.

A set dosage of allopurinol 300 mg daily may be insufficient in almost 50% of patients; the dose must be individualized.

At present, patients who need their uric acid level lowered but who cannot tolerate allopurinol and who do not respond to uricosurics or cannot take uricosurics owing to a history of nephrolithiasis, renal insufficiency, or hyperexcretion of uric acid have limited options, including a trial of oxypurinol or allopurinol desensitization.[8]

COMPLACENCY IN DIAGNOSIS

As a rheumatologist, I feel compelled to comment on the complacency frequently exhibited in the clinical diagnosis of gouty arthritis. Not all acute or intermittent arthritis is gout, even if it involves the great toe, and even if the patient has hyperuricemia. Before considering lifelong hypouricemic therapy for the treatment of gouty arthritis, the diagnosis should be confirmed by demonstration of uric acid crystals in the synovial fluid. Although questions remain regarding treatment algorithms, the diagnosis of gouty arthritis in the individual patient should rarely, if ever, be open to question.

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