Posing the Question Again: Does Chronic Uric Acid Nephropathy Exist?

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ABSTRACT

The question of whether hyperuricemia can induce chronic direct renal injury has been argued for many decades. Despite continued efforts and strong motivations to seek an answer, the current evidence still cannot definitively prove or refute the hypothesis. Recent data in rodents do favor causality between hyperuricemia and renal disease. Human epidemiologic data are quite varied, but positive studies do exist. Pathophysiologic models of biology for this entity are sparse in animals and nonexistent in humans.


Some practitioners will recall dutifully treating asymptomatic hyperuricemia some decades ago for the sole purpose of forestalling or preventing impending cardiovascular morbidity.\textsuperscript{1} In addition to the proposed cardiovascular ill effects, hyperuricemia has also been considered by some as a pathogenic factor in chronic kidney disease now for half a century. Gouty nephropathy or chronic uric acid nephropathy is supposedly a condition where uric acid or urate crystals deposited in parenchyma and tubule lumens independently and directly confer injury to the kidney over time, eventuating in renal failure. Foley and Weinman\textsuperscript{2} presented a compelling argument against the existence of this entity in 1984. In 1986, a seminal article by Beck\textsuperscript{3} in an authoritative renal journal bearing the word “requiem” in its title proposed to usher the entombment of this entity. If this was truly terminal as all elegies are, why do controversies about its existence still linger and why is this current commentary even necessary? Truth in biomedicine, as is truth in any discipline, should be perpetual. Has the database changed or simply our interpretation of the evidence that is evolving? The answer is both.

The association between hyperuricemia and chronic kidney disease is not in doubt. It is the nature of the association that is under debate. Figure 1 provides a theoretical consideration of the possible nature of this association. Of the three pathogenically significant relationships (top panel), the third one (asterisk) is the most important and is the source of the never-ending quest. This possibility is of significant interest and importance to many parties. For the biomedical researcher, this entity represents important and novel mechanisms of chronic kidney injury. For clinicians, this condition calls for a dramatic change in practice because we are expected and committed to controlling plasma uric acid to discreet levels in the general population. The medico-legal profession will view allowance of patients to live with an elevated serum uric acid level to be negligence worthy of litigation. The industry covets a colossal increment in prescription of hypouricemic agents (impairing enzymatic production, promoting excretion or degradation) from the current modest pool of gouty arthritis sufferers and hyperuricosuric stone formers to virtually a generous fraction of the Western world. If such is the magnitude of the driving force on multiple fronts, why is the answer still so ethereal?

By stating that \textit{Mycobacteria} should be isolated from the disease tissue and inoculation of this organism should reproduce the disease, Robert Koch\textsuperscript{4} set the criteria for causality in infectious disease. To guide the distinction of association from causation based primarily on epidemiologic data, the distinguished statistician, Sir Austin Bradford Hill,\textsuperscript{5} proposed to examine strength of association, dose-response, consistency, specificity, temporal relation, and, most importantly (in this author’s opinion), biologic basis of causality, to provide guidance (not criteria) to assess the probability of cause-and-effect when confronted with a given association. We will exercise a combination and modification of the Koch and Hill measures, when appropriate, to analyze the uric acid–kidney disease relationship.
Of foremost importance is whether there is a biologic basis for this entity. Human histopathologic data shows interstitial inflammation and fibrosis coexisting with crystalline uric acid deposits, which are interpreted by some as “smoking guns.” A scatter of physiology studies also showed abnormal indices of renal and endothelial function in the backdrop of asymptomatic hyperuricemia. None of these provide proof and most of them are challenged by studies showing contrary results. The most convincing data to date are derived from rodent models. Heinig and Johnson eloquently summarized this body of literature recently. Induction of hyperuricemia elevates BP and produces renal microvascular, glomerular, and tubulointerstitial lesions that are without doubt detrimental to the organism. The mechanisms by which these lesions transpire are not yet known even with these models in hand. Based on the rodent database, one will have to agree with the compelling view espoused by Henin and Johnson that the data are very close to satisfying Koch’s criteria for uric acid nephropathy.

In contradistinction, the human evidence supporting a biologic mechanism of uric acid–induced injury in the kidney is rather weak in comparison to the rodent data. One needs to exercise heightened caution to extrapolate data gathered from species such as rodents endowed with uricase and evolved with extremely low plasma and tissue levels of uric acid, which are then rendered severely hyperuricemic experimentally. Similar findings in higher primates with relative high normal plasma uric acid levels would be substantially more persuasive. The current status of the bench data is convincing for the rodent model but still uncertain for humans. For humans, one needs to turn to clinical data that are more challenging to unravel.

Because one is equipped almost exclusively with epidemiologic data in humans, one can apply some of Hill’s guidelines to attempt to gain more insight into causality. The strength of association is variable from study to study ranging from none to weak⁶–¹⁰; space does not permit exhaustive citation of all studies. A recent article in this journal cites little debate. The study of Obermayr et al.¹¹ prospecitively followed more than 21,000 patients for a median of 7 yr with different serum uric acid levels but the same baseline estimated GFR. They found mild hyperuricemia (7.0 to 8.9 mg/dl) nearly doubled the risk for incident kidney disease, and more severe hyperuricemia (≥9.0 mg/dl) tripled the risk. The significant odds ratios survived albeit diminished with adjustments for baseline estimated GFR, gender, age, drugs potentially altering serum uric acid levels, and components of the metabolic syndrome. This is one of the strongest associations that survived multiple adjustments by robust statistical models and does support, although not prove, a pathogenic role for uric acid.

Dose-response in humans is difficult to establish, because one cannot possibly “dose” the uric acid level. However, in the study by Obermayr et al.,¹¹ a model was constructed with the prospective data that displayed a curvilinear relationship between risk and the serum uric acid as a continuous variable. Consistency of finding is one of the weakest links in our current database. As pointed out earlier, more than its weight of negative associations balances each positive study. For this discussion, specificity of the association as proposed by Hill is less relevant and need not be fulfilled because hyperuricemia can lead to multiple consequences, and chronic kidney disease can result from hyperuricemia alone or in conjunction with many other predispositions. Temporal relation can be powerful and revealing in population-based data. The occurrence of a risk factor before the disease of interest lends support to a causal relationship. This is particularly important because reduction of GFR begets hyperuricemia, a fact that incites little debate. The study of Obermayr et al. showed that hyperuricemia precedes reduction in glomerular filtration. The amelioration of disease after elimination or reduction of the risk factor also strongly supports causality. Unfortunately, we do not have the luxury of such data. Although the animal data that emerged in the last decade are compelling, definitive proof of uric acid assuming a causative role in chronic kidney disease is still not very satisfactory after all these years. With that background, a few general points are noteworthy.

For the reasons stated in the beginning of this commentary, the motivation driving one to pose this question will continue until a definitive affirmative or negative answer is secured. The effect of uric acid per se on progression of renal disease in humans is unlikely to be large. The impact, if it exists, is unlikely to be of the same magnitude as hypertensive or
diabetic nephropathy. From the view of a pragmatic practitioner, whether uric acid is a risk factor for cardiovascular disease, chronic kidney disease, or both does not make a lot of difference in terms of patient management because uric acid control will have to be instigated. A similar argument has been submitted against studying the effect of hyperlipidemia on renal disease because lipid-lowering therapy is mandatory for its cardiovascular benefits. Such view will undoubtedly be too nihilistic for the pathophysiologist and even for the practice-oriented realist; the relationship between hyperuricemia and cardiovascular disease is no firmer established than that of renal disease.\(^\text{12}\)
The quest should and will continue. One needs more experimental models, perhaps in uricase-null species, to provide pathophysiologic mechanisms to be eventually tested in well-controlled human physiologic studies and more vigorous population-based prospective observational and intervention studies. With wishful optimism, the question mark should be removed from the title of a paper bearing the term “uric acid nephropathy.”

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DISCLOSURES

None.

REFERENCES