Serum Uric Acid is A Marker of Inflammation and A Marker Predicting The Risk of Developing CVD, Stroke, Renal Failure and Cancer

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Uric acid (UA) is converted from xanthine, the degradation product of purine nucleotides (adenine and guanine), by the enzyme xanthine oxidase (XO). As shown in Scheme 1A that a small elevation of serum uric acid, or mild hyperuricemia can be derived either from diet (such as proteins) rich in purine or from the impaired renal excretion of uric acid. As pointed out by Hayden [1] that an increase of urate reabsorption can be induced from a decreased renal blood flow due to a decreased glomerular filtration rate or taking diuretic medication and results in a slight increase of serum UA. Because XO enzyme is not involved in this type of elevation of serum uric acid, no superoxide is produced.

On the other hand, any local tissue ischemia (hypoxia) derived from any microvascular disease may also lead to an increased UA synthesis due to an increased RNA-DNA breakdown, resulting in an increased uric acid concentration and an increased substrate concentration for enzyme XO (xanthine)[1]. Under this condition, superoxide is also produced by XO enzyme (Scheme 1B). Like ischemia, hypoxia can also induce hyperuricemia. Braghiroli et al. have reported that hyperuricemia could be generated from hypoxia-induced ATP degradation and an increased xanthine from patients with chronic obstructive pulmonary disease and obstructive sleep apnea [2]. Hyperuricemia can also be derived from increased cell apoptosis and necrosis due to inflammation. Consequently increased XO activity is derived from increased concentration of breakdown products of RNA and DNA associated with cell apoptosis and necrosis (Scheme 1B).
Because elevated level of serum uric acid can be effectively reduced by allopurinol, an inhibitor of XO activity, therefore, the activity of XO enzyme is conceivably playing a critical role in the induction of hyperuricemia. It is important to note that it is the superoxide, not UA, which is most likely the causal factor initiating the inflammatory pathway leading eventually to the development of oxidative and nitrosative stress and all the subsequent development of inflammatory diseases [1].

**As Marker of Inflammation**

Listed below are reports from literature describing the fact that UA is closely associated with inflammation and explaining why UA is considered as an inflammation marker.

**Hyperuricemia Induced by Inflammatory Risk Factors**

Because inflammation will lead to increased cell apoptosis and necrosis it is not surprising that there have been reports suggesting that inflammation enhances XO activity and leads to an increased concentration of serum UA. Page et al. have shown that proinflammatory cytokines, produced by many inflammatory risk factors [3], would activate XO activity in human mammary epithelial cells [4] resulting in elevated serum UA. Regardless whether it is the cytokine or increased cell apoptosis and necrosis that activate XO activity, it is certain that many risk factors known to induce acute and chronic inflammation have been shown to link to hyperuricemia. For example, hyperuricemia has frequently been reported in individuals with bacterial infection, with hypertriglyceridemia and with obesity [5,6]. Viral infection, another risk factor, has also been shown to induce not only the activity of XO but also the activity of induced nitric oxide synthase (iNOS) [7]. As a result, there is always an increased concentration of superoxide associated with viral infection. There is also an increased level of 3-nitrotyrosine derived from both elevated concentration of nitric oxide and superoxide [8]. In addition, higher serum uric acid has been reported in individuals who smoke [9], another inflammatory risk factor.

**Generation of New Inflammation**

As we have described above that uric acid and superoxide are the two products produced simultaneously from xanthine by the enzymatic activity of XO. Superoxide has been known to promote the synthesis of many proinflammatory cytokines via its interaction with the transcription factor, NF-κB [10]. In fact, Jacobi et al. have
shown that a proinflammatory state could be promoted by superoxide generated from the human umbilical vein endothelial cells [11]. Therefore, it is not surprising to find a frequent association between hyperuricemia and the appearance of inflammation markers of especially the newly induced acute inflammation. For example, both hyperuricemia and elevated interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), and adhesion molecules have been detected simultaneously in many inflammatory diseases [12-15].

**Reduction by Anti-inflammatory Medication**

UA may be considered as a marker of inflammation is further supported by the fact that several anti-inflammatory drugs have been found to reduce the circulating level of UA. For example, atorvastatin (an anti-inflammatory drug) has been found to reduce UA levels significantly in patients with coronary heart disease [16], and with primary hyperlipidemia [17].

**Association of Hyperuricemia with Inflammatory Diseases**

It is realized now that hyperuricemia can be induced by most, if not all, inflammatory risk factors; and hyperuricemia can further induce acute and chronic inflammation because of its co-product of superoxide. Therefore, it is expected that elevated uric acid is detectable in all inflammatory disease including those life-threatening diseases such as CVD, stroke, renal failure, lung disease and cancer.

In fact, many reports can be found in the literature describing hyperuricemia in association with various inflammatory diseases [18]. Hyperuricemia has been detected in patients with chronic heart failure [19, 20], with type 2 diabetes [21], with end-stage renal disease (ESRD)[18] and in individuals who smoke [22]. Hyperuricemia is also common in elderly since they are often associated with chronic inflammation [23].

Hypoxia or ischemia can be detected in clinical disorders such as obstructive sleep apnea, lung disease and advance stage of atherosclerosis. An increased degradation of ATP (one source of purine nucleotide) has been found with all these inflammatory diseases, which result in the increased production of uric acid by XO. Therefore, in addition to the impact of inflammation on the XO activity, state of ischemia would increase the degradation of purine nucleotide (probably also has to do with an increase of apoptosis and necrosis of the cells involved) and the availability of the substrate for XO, all lead to an increased production of UA and superoxide. Consequently, hyperuricemia has been detected in patients with chronic obstructive pulmonary disease (COPD) associated with hypoxic state [24] and in patients with obstructive sleep apnea [25].

Exercise, especially the strenuous exercise, is known to generate acute inflammation. This explains why that hyperuricemia and an increased xanthine oxidase activity have been reported in human skeletal muscle following eccentric exercise [26].

**As A Risk Marker**

It should be noted that UA itself does not appear to be a risk factor as commonly believed [1]. Elevated serum uric acid, however, has been found to be a graded marker of risk for the development of coronary heart disease (CHD), cerebrovascular disease, stroke, and acute renal failure [1, 27]. As we know now that the association of hyperuricemia with these clinical disorders is actually due to the superoxide radical produced by the enzyme XO. The superoxide produced in parallel with uric acid by XO enzyme was the major causal factor for generating risk for the development of all inflammatory diseases. In the absence of intervention, superoxide would lead not only to the onset of acute and chronic inflammation but also oxidative and nitrosative stress, and gene mutation.

It is conceivable that although UA is not a risk factor, the detection of hyperuricemia can be used as a risk marker signaling the risk for the development of additional clinical complications such as coronary artery disease, renal failure and hypertension as has been pointed out by Madsen et al. [28]. The consideration of UA as a risk marker for inflammatory diseases is also supported by the result of many trials showing that treatments designed to lower UA (at the same time reduce the superoxide concentration) has effectively reduced the rate of cardiovascular complications in patients with coronary heart disease, congestive heart failure and dilated cardiomyopathy [1, 29]. These UA lowering treatments have also been shown to slow the progression of renal disease [30].

**Final Thought**

Measurement of uric acid is clinically useful because it provides many important prognostic information. As
noted by Strazzullo et al. [29] that in general population associated with minor risk of heart disease, serum UA appears to be a weak predictor of CVD. Mild asymptomatic hyperuricemia could be derived from impaired renal function, some local minor ischemia associated with small degradation of purine nucleotide, with slight obesity and with type 2 diabetes at early stage. On the contrary, UA becomes a significant independent predictor among subjects who are at high risk. It appears that only when hyperuricemia occurs in those who already are associated with increased inflammation, such as in hypertensive population and patients with type 2 diabetes and with pre-existing CVD that UA becomes a risk marker of severe consequence. In other words, during screening, detecting elevated serum UA does not predict poor prognosis if no other inflammation markers, especially markers of chronic inflammation, were detectable at the same time.

References


尿酸，是嘌呤核苷酸经黄嘌呤氧化酶作用后的黄嘌呤核苷酸，再代谢所得之产物。由于高尿酸血症不单由发炎危险因子所引发，它本身亦可能引起新的急性及慢性发炎反应，因此，血液中的尿酸升高被认作是可用作检测身体内部不明显发炎反应的灵敏指标。如同预期地，几乎在所有的发炎性的疾病中皆可测得血液尿酸过高的现象，若投入抗发炎的药物，便可有效降低血液中的尿酸浓度。但必须注意的是，高尿酸血症本身并不是一个危险因子，而是示意体内存在有会发展成严重并发症的危险指标。这是因为大部分伴随著高尿酸血症一起发生的损伤，并非直接由尿酸引起的，而是由黄嘌呤氧化酶催化尿酸代谢过程中的超氧化物自由基所引起的。对于一般无症状族群是否会发生心血管疾病，血清尿酸是一个预测效果较佳的指标，但对于已是有高危险族群的族群而言，血清尿酸异常便是一个有意义且独立的预测指标。

关键词：尿酸、超氧自由基、发炎指标、危险指标、发炎疾病