Impact of serum uric acid on the aggravation of renal function; current knowledge and new concepts

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Abstract: After a prolonged time of inertia, in the last decade, much interest has been directed toward the uric acid due to the results from experimental investigations that reveal detrimental effects of uric acid on blood pressure and renal function. This review aimed to discuss the impact of serum uric acid on the aggravation of renal function.

Keywords: Chemotherapy; Cisplatin; renal toxicity

1. Introduction

After a prolonged time of inertia, in the last decade, much interest has been directed toward the uric acid due to the results from experimental investigations that reveal detrimental effects of uric acid on blood pressure and renal function (1-4). Until current years, uric acid was defined in the background of an end-product of purine degradation and encountered only in gout arthropathy and, to a lesser extent, in renal function disturbance in individuals with longstanding gout. Uric acid is now more recognized as the end-product of an enzyme system which is a main source of vascular oxygen radicals, namely the xanthine oxidoreductase system (3-7). An elevated serum uric acid value is frequently encountered in individuals who are found having chronic kidney disease. Epidemiological investigations have identified a relationship between hyperuricemia and cardiovascular risk in the general population and in chronic kidney disease patients (4-10). In hemodialysis individuals, investigations have shown a relationship between uric acid levels and mortality too (11-17). The relationship of uric acid and decline in kidney function has been investigated in various investigations which included healthy individuals, patients with chronic kidney disease stages I-II, patients with diabetes, and individuals on peritoneal dialysis (1-4,18-22). Nevertheless evidence about this association in patients with advanced chronic kidney disease (stages IV-V) is insufficient, and the effect on time until start of dialysis has not been evaluated properly(1-4,18-22). Various experimental studies have detected unequivocal results in which elevated serum uric acid levels have led to increased oxidative stress and inflammation, renal function deterioration, propagation of atherosclerosis and higher blood pressure. Improvement in these risk factors subsequent administration of allopurinol, a xanthine oxidase inhibitor which lowers serum uric acid levels, enforces the hypothesis that hyperuricemia is related to harmful impacts (1-8). Chronic renal failure is accompanied by significant morbidity and mortality (23-33). Besides to well-known risk factors such as hypertension and diabetes(34-40), several “non-traditional” risk factors could contribute to the higher risk of morbidity and mortality in patients with chronic renal failure compared to the general population (41-54). One of them is hyperuricemia. Previous studies have revealed that uric acid can result to glomerular hypertension, activation of renin-angiotensinsystem, arteriosclerosis, glomerular hypertrophy, elevated renal vascular resistance, reduced renal blood flow, glomerulosclerosis, and interstitial fibrosis by inducing endothelial dysfunction and oxidative stress addressing that uric acid could be a factor to kidney injury (1-8). Recently, it was detected that, uric acid is capable to activate NFkB in proximal tubular cells, and observation that lowering serum uric acid via a uricosuric agent increases 1,25(OH)₂D levels in humans with gout propose that uric acid inhibits 1-α hydroxylase activity. Subsequently, inhibition of 1-α hydroxylase by uric acid may induce the secretion of parathormone, a condition that aggravate renal
function in patients with chronic renal failure (1-8). In a study on 60 patients with type II diabetes without a history of gout, we found a significant positive association between body mass index (BMI) and serum uric acid levels (r = 0.428, P = 0.001). After adjustment for weight, a significant positive association of serum uric acid with proportion of proteinuria was detected (r = 0.47, P < 0.001) too (4). Furthermore, the correlation of serum uric acid with level of blood pressure was significantly positive (8). Subsequently, Jalalzadehet al., conducted a single-blind, randomized cross-over clinical study consisting 55 hemodialysis patients with serum uric acid level >6.5 (men) and >5.5 mg/dl (women) (55). They detected the a reduction of blood pressure by allopurinol treatment in hemodialysis patients (55). Moreover, Chen et al, in an in-vivo study on rats, found uric acid suppresses 1 alpha hydroxylase in vitro and in vivo(56). In fact, a reduction in 1,25(OH)2D secondary to reduced 1-α hydroxylase enzyme activity contributes to the development of secondary hyperparathyroidism in patients with chronic kidney disease as mentioned above too(57-60). Indeed, the direct association of hyperuricemia and vitamin D metabolism has two results. Firstly it is well understand that hyperuricemia by itself is an independent risk factor for kidney damage in various renal disease, like IgA nephritis or diabetic nephropathy(57-65). Many studies, support the hypothesis that elevated serum uric acid levels have an injurious effect, resulting to inflammation, endothelial dysfunction and vascular disease (1).Secondly, regardless of the deleterious effect of hyperuricemia on hypertension and aggravation of some type of nephropathies, its harmful effect on vitamin D production is of significant importance (57-67). Various studies had shown, supports vitamin D as a negative regulator of the circulating and local tissue renin-angiotensin system, while renin-angiotensin system has a critical implication in the physiology of sodium and volume homeostasis. Thus, excess activity of renin-angiotensin system is associated with high blood pressure, aggravation of renal disease and diabetic kidney disease (57-68).

Some factors regulate the uric acid in the chronic renal disease patient. Dietary intake of purines and fructose is a primary source of uric acid. Hence, its levels could vary with the nutritional status. While the kidney eliminates much of the generated uric acid, a decrease in renal function is associated with an increase in blood uric acid levels. Upon reaction of uric acid with oxidants, it will undergo degradation to allantoin and other products. In the chronic kidney disease patients, this degradation pathway is augmented five-fold or more (1-10). Studies regarding uric acid and start of dialysis have shown that, high uric acid levels at baseline were associated with a shorter time until initiate of dialysis. On the other hand, gout is caused by deposition of uric acid crystals in the joints, most notably in the metatarsal-interphalangeal joint of the big toe. Painful and disabling symptoms of gout arthritis could have contributed to the decision of the physician and patient to start dialysis (1-10). In addition, another explanation could be that high levels of uric acid might have resulted in other symptoms or clinical conditions such as renal stones or hypertension that affect the decision to start dialysis (1-10). In fact, higher uric acid levels in incident pre-dialysis patients are a risk factor for an early initiate of dialysis. Indeed, studies some studies indicated that patients with higher uric acid levels should be referred earlier to pre-dialysis care in order to guarantee appropriate preparation for beginning of dialysis (69-75). It is possible that serum uric acid levels, may be a guide for nephrologists to assess the optimal moment to start dialysis, while some studies have established that higher baseline uric acid levels lead to an earlier start of dialysis, independent of other factors (1-9). Since various investigations have assessed whether allopurinol could prevent or at least slow the progression of renal disease. It is possible that, early treatment of patients with familial juvenile hyperuricemic nephropathy with allopurinol diminished the morbidity and mortality from renal failure as compared with their untreated siblings and previous generations of recruited families (1-0,76-84). Additionally in hyperuricemic patients with chronic renal failure, who received allopurinol, dosed at 100-300 mg/day, or usual therapy for 12 months, a trend toward a lower serum creatinine level in the treatment group compared with controls at study completion, though this difference did not reach statistical significance (2-9). Additionally, various clinical studies have detected that, lowering uric acid with allopurinol ameliorated endothelial dysfunction in both hyperuricemic individuals and hypertensive type II diabetic patients with normal serum uric acid levels too (3-11,85-108). The suggested mechanism is that elevated serum uric acid levels causes endothelial dysfunction by activating the renin-angiotensin system, inhibiting nitric oxide synthetase and causing pro-inflammation and resultant endothelial dysfunction, and vascular smooth muscle cell, and finally contributing to atherothrombosis (1-10). In the meantime, further clinical studies are warranted to elucidate the beneficial effect of allopurinol therapy in nephropathies.
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