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Hyperuricemia and deterioration of kidney function; a mini-review to the pathophysiological mechanisms

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ABSTRACT

Uric acid, as the end-product of purine metabolism, is excreted principally by the renal proximal tubules. Abnormal serum level of uric acid are owing to modifications in excretion or production. Uric acid may be a principal factor in the pathogenesis of acute renal failure, aggravation of diabetic kidney disease, aggravation of chronic renal failure and hypertension. Uric acid may not only be a sign but also a potential therapeutic target in various renal disease. Elevated serum uric acid levels initiate an endothelial cell dysfunction through activating the renin–angiotensin system, and inhibiting nitric oxide synthase and then producing a pro-inflammation state resulted to change the morphology of endothelial and vascular smooth muscle cells, and finally contributing to atherosclerosis.

Mini-Review

Core tip: Elevated serum uric acid levels initiate an endothelial cell dysfunction through activating the renin–angiotensin system, and inhibiting nitric oxide synthase and then producing a pro-inflammation state resulted to change the morphology of endothelial and vascular smooth muscle cells, and finally contributing to atherosclerosis.

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Introduction

Uric acid, as the end-product of purine metabolism, is excreted principally by the renal proximal tubules. Abnormal serum level of uric acid are owing to modifications in excretion or production (1,2).

After a long-lasting time of inertia, in the last decade, much interest has been directed concerning impact of hyperuricemia on level of blood pressure and kidney function. Until recent years, the importance of hyperuricemia, was assessed in the setting of an end-product of purine degradation and confronted only in gout arthropathy and, to a slighter extent, in kidney function disturbance in patients with established gout. In fact, uric acid is currently more identified as the end-product of an enzyme system which is a main source of vascular oxygen radicals, entitled as the xanthine oxidoreductase system (1-5).

Materials and Methods

This mini-review article discusses the pathophysiological mechanisms encountered the impact of hyperuricemia on renal function in acute kidney injury, chronic renal failure and particularly in diabetic kidney disease. For this review, we used a variety of sources by searching through Web of Science, PubMed, EMBASE, Scopus and directory of open access journals (DOAJ). The search was performed using combinations of the following key words and or their equivalents such as diabetic kidney disease, chronic kidney disease, hemodialysis, renal failure and hyperuricemia.

Hyperuricemia and chronic kidney disease

Hyperuricemia is frequently found in patients who are found having chronic renal failure. Epidemiological studies have detected an association of hyperuricemia and risk of heart and vascular disease in the general population and in chronic renal insufficiency patients (1,2). In hemodialysis patients, recent studies have demonstrated a relationship of uric acid levels and mortality rate too (1-3). Accordingly, the relationship of uric acid and decline in renal function has been considered in various investigations which included healthy individuals, patients with chronic renal failure of stages I and II, patients with diabetes mellitus, and patients on peritoneal dialysis (2,3). Moreover data regarding the association of hyperuricemia and renal function declining, in patients with advanced chronic renal failure (stages IV-V) and the impact of hyperuricemia on start of dialysis has not been evaluated

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properly (1-5). Recent experimental studies have noticed unequivocal results in which elevated serum uric acid levels have directed toward increased oxidative stress and inflammation, renal function deterioration, acceleration of atherosclerosis and hypertension. Correction in these risk factors following application of allopurinol, a xanthine oxidase inhibitor which reduces serum uric acid levels, inflicts the hypothesis that hyperuricemia is directed to harmful influences. Chronic kidney disease is associated with noteworthy morbidity and mortality. In addition to well-documented risk factors such as diabetes and hypertension, various "non-traditional" risk factors could attribute to the higher risk of morbidity and mortality in individuals with chronic kidney disease compared to the general population (1-6). One of them is hyperuricemia. Previous investigations have detected that hyperuricemia may lead to activation of renin-angiotensin system, glomerular hypertrophy, elevated kidney vascular resistance, glomerular hypertension, arteriolosclerosis, reduced kidney blood flow, glomerulosclerosis, and renal interstitial fibrosis by inducing oxidative stress and endothelial dysfunction , which imply that hyperuricemia could be a factor to renal damage (2-8). Currently, it was identified that, high serum uric acid is able to activate NFκB in renal proximal tubular cells. Likewise, it was observed that lowering serum uric acid by a uricosuric drug will increase serum 1,25(OH)2D levels in individuals with gout imply that high serum uric acid is able to inhibit, 1-α hydroxylase activity. Consequently, inhibition of 1-α hydroxylase by hyperuricemia may improve the secretion of parathyroid hormone, a situation that worsen kidney function in individuals with chronic kidney disease (3-9). In an investigation on 60 type II diabetes patients without a history of gout, we detect, a significant positive association between body mass index (BMI) and serum uric acid values ($r = 0.428$, $P = 0.001$). After adjustment for weight, a meaningful positive correlation of serum uric acid with quantity of proteinuria was detected ($r = 0.47$, $P < 0.001$) too (10). Additionally, the association of serum uric acid with level of blood pressure was appreciably positive (11). Previously, Jalalzadeh et al, in a single-blind, randomized cross-over clinical investigation consisting 55 hemodialysis participants with serum uric acid level >6.5 (men) and >5.5 mg/dl (women), detected the reduction of blood pressure by allopurinol treatment in these patients (12). Similarly, Chen et al, in an in-vivo investigation on rats, observed, uric acid capable to suppress 1 alpha hydroxylase in vitro and in vivo (13). Therefore, a diminution in 1,25(OH)2D secondary to decreased 1-α hydroxylase enzyme activity attributes to the development of secondary hyperparathyroidism in individuals with chronic renal failure (13). Hence, the direct relationship of hyperuricemia and vitamin D metabolism has two consequences. Initially it is well recognize that hyperuricemia by itself is an independent risk factor for renal injury in various kidney disease, such as immunoglobulin A nephropathy or diabetic kidney disease (12,13).

Hyperuricemia and acute kidney injury

While, various clinical investigations of recent years have detected that hyperuricemia is linked to poor outcomes like cardiovascular mortality and dialysis inefficacy in hemodialysis patients, studies regarding the impact of hyperuricemia in acute kidney injury is of significant importance.

On the other hand some studies have established that pharmacological lowering of uric acid may slow the progression of chronic renal failure (6-9). In a similar manner, in the background of acute kidney injury, hyperuricemia, may be a risk factor for the development of acute renal failure. Regardless of established crystal precipitation with sever hyperuricemia, various non-crystal mechanisms have also been postulated in the pathogenesis of acute renal failure. It is important to highpoint that, uric acid can acutely activate several inflammatory transcription factors. Uric acid is able to induce acute inflammation of the renal tubular epithelial cells by uric acid crystals. Uric acid can also have an influence in the human body by its non-crystal effects (2-6). It may cause endothelial cell dysfunction and trigger an afferent kidney arteriolopathy and initiate the fibrosis in tubulointerstitial area by stimulating the renin-angiotensin-aldosterone system, activate several inflammatory transcription factors, and may induce systemic cytokine production like tumor necrosis factor alpha. These processes will lead to local expression of cyclooxygenase 2 (COX-2) in blood vessels and also some chemokines like monocyte chemotactic protein 1 in the kidney tissue (1-5). Importantly, hyperuricemia may also leads to reduce urinary nitrite level, decreasing in nitric oxide production which may lead to nitric oxide depletion and resultant glomerular hypertension and systemic hypertension (5-9).

While, acute kidney injury as a well-recognized problem in hospitalized patients, with accompanied mortality and morbidity, thus, more attention to the treatment if hyperuricemia in acute kidney injury is a reasonable modality.

Hyperuricemia and hypertension

More recent studies, reinforce the hypothesis that raised serum uric acid levels has a detrimental influence, ensuing to endothelial dysfunction, micro-inflammation, and vasculopathy. Furthermore, regardless of the deleterious effect of hyperuricemia on level of blood pressure and worsening of various types of nephropathies, its harmful influence on vitamin D production is of significant importance (14-18). Thus, it should interpreted that, vitamin D as a negative regulator of the circulating and local tissue renin-angiotensin system, and whilst renin-angiotensin system has a critical impact on the physiology of sodium and volume homeostasis, hence, excess activity of renin-angiotensin system is associated with high blood pressure, aggravation of kidney disease and diabetic kidney disease (14-18).

Some factors regulate the uric acid in the chronic kidney

failure. Dietary intake of purines and fructose is a primary source of uric acid. Therefore, its levels could vary with the nutritional station. While the kidney removes much of the generated uric acid, a decrease in kidney function is accompanying to an increase in blood uric acid levels. Upon reaction of uric acid with oxidants, it will undergo degradation to allantoin and other products. In chronic renal failure patients, this degradation pathway is amplified five-fold or more (4-7,14-18). Findings regarding uric acid and beginning of hemodialysis have detected that, high uric acid level at baseline was related to a shorter time until initiate of hemodialysis. Additionally, gout is caused by deposition of uric acid crystals in the joints, most particularly in the metatarsal-interphalangeal joint of the big toe. Painful and disabling symptoms of gout arthritis could have attributed to the decision of the physician and patient to start hemodialysis (4-7,14-18). Accordingly, a high level of uric acid lead to other symptoms or clinical circumstances like kidney stones or high blood pressure that, influence the decision to start hemodialysis (6-11,14-18). Indeed, higher uric acid level in incident pre-dialysis individuals is a risk factor for an early start of hemodialysis. In fact, more recent findings indicated that individuals with higher uric acid level should presented earlier to pre-dialysis care in order to certify an appropriate preparation for initiating of hemodialysis (3-9,15-18). Even, some investigators suggested that serum uric acid levels, may be a guide for nephrologists to assess the optimal moment to start hemodialysis, whilst recent investigations have detected that higher baseline uric acid level results to an earlier start of hemodialysis, regardless of other factors (1-6). Moreover some investigations have suggested whether allopurinol therapy could prevent or at least slow down the progression of kidney disease. It is imaginable that, early treatment of individuals with familial juvenile hyperuricemic nephropathy with allopurinol lessened the morbidity and mortality from kidney insufficiency as compared with their untreated siblings and previous generations of recruited families (7-13,14-18). Also in hyperuricemic patients with chronic renal disease, who administered allopurinol, at a dose of 100 to 300 mg/day, or usual therapy for 12 months, a tendency toward a lower serum creatinine level in the treatment group compared with control subjects at study completion, even though this difference did not reach statistical significance (7-13,14-18). Furthermore, various clinical investigations have identified that, lowering uric acid with allopurinol improved endothelial dysfunction in both hyperuricemic persons and hypertensive type II diabetes with normal serum uric acid level as well (14-18). To find the possible effect of hyperuricemia on blood pressure, Xu et al found, distal nephron epithelial sodium channels (ENaC), is an important element of sodium balance and blood pressure regulation (19).

Conclusion

The possible mechanism is that elevated serum uric acid levels initiates an endothelial cell dysfunction through activating the renin–angiotensin system, and inhibiting nitric oxide synthase and also producing a pro-inflammation state resulted to change the morphology of endothelial and vascular smooth muscle cells, and finally contributing to atherosclerosis (1-10). In the meantime, further clinical studies are warranted to elucidate the beneficial effect of allopurinol therapy in nephropathies.

Author's contribution

HN was the single author of the paper.

Conflicts of interest

The author declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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