

Uric Acid and Chronic Renal Disease: Possible Implication of Hyperuricemia on Progression of Renal Disease

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Although hyperuricemia has long been associated with renal disease, uric acid has not been considered as a true mediator of progression of renal disease. The observation that hyperuricemia commonly is associated with other risk factors of cardiovascular and renal disease, especially hypertension, has made it difficult to dissect the effect of uric acid itself. However, recent epidemiologic evidence suggests a significant and independent association between the level of serum uric acid and renal disease progression with beneficial effect of decreasing uric acid levels. Furthermore, our experimental data using hyperuricemic animals and cultured cells have provided robust evidence regarding the role of uric acid on progression of renal disease. Hyperuricemia increased systemic blood pressure, proteinuria, renal dysfunction, vascular disease, and progressive renal scarring in rats. Recent data also suggest hyperuricemia may be one of the key and previously unknown mechanisms for the activation of the renin-angiotensin and cyclooxygenase-2 (COX-2) systems in progressive renal disease. Although we must be cautious in the interpretation of animal models to human disease, these studies provide a mechanism to explain epidemiologic data that show uric acid is an independent risk factor for renal progression. Although there is no concrete evidence yet that uric acid bears a causal or reversible relationship to progressive renal disease in humans, it is time to reevaluate the implication of hyperuricemia as an important player for progression of renal disease and to try to find safe and reasonable therapeutic modalities in individual patients based on their clinical data, medication history, and the presence of cardiovascular complications. *Semin Nephrol* 25:43-49 © 2005 Elsevier Inc. All rights reserved.

Chronic renal disease often is associated with increased uric acid levels.¹ However, there remains controversy about the clinical implication of hyperuricemia in these patients. An increase in uric acid level may be a consequence of decreased clearance caused by the impairment in glomerular filtration rate (GFR), or it may reflect local tissue hypoxia or increased cell breakdown associated with renal disease.^{2,3} It remains possible, however, that hyperuricemia per se also may be involved in the induction or aggravation of some pathologic conditions of the host including renal disease. In this article, this bidirectional relationship between hyperuri-

emia and kidney disease is discussed together with recent evidence supporting an important role of uric acid on progression of chronic renal disease. The main objective of this article is to provide a balanced concept of the molecular and clinical implications of hyperuricemia in chronic kidney disease.

Metabolism and Excretion of Uric Acid

Uric acid is an end product of dietary or endogenous purines and is generated by xanthine oxidase/xanthine dehydrogenase, primarily in the liver and intestine. Exogenous purines also represent an important source of uric acid, and approximately 50% of RNA purines and 25% of DNA purines are absorbed in the intestine and subsequently excreted in urine. In most mammals, uric acid is degraded further by urate oxidase (uricase) to allantoin, which is excreted freely in the urine. However, a mutation occurred

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in uricase during early hominoid evolution, with the consequence that humans, the other great apes and some New World monkeys lack uricase activity and have 4- to 5-fold higher levels of uric acid.⁴ In adult humans, the uric acid pool is approximately 1.2 g and undergoes rapid turnover, with two thirds of the uric acid pool excreted in urine.⁵

The kidneys handle uric acid by multiple and complex processes, including glomerular filtration and reabsorption, secretion, and postsecretory reabsorption in the proximal convoluted tubule.^{5,6} However, ideas of the handling of uric acid by the kidney have changed greatly during the past decades with characterization and isolation of transporters and channels mainly or exclusively restricted to urate transport.⁷⁻⁹ URAT-1, a luminal anion exchanger for urate reabsorption, is present in the luminal brush border of human renal proximal tubules and has a high affinity for urate together with lactate, ketones, α -ketoglutarate, and related compounds. Pyrazinamide, probenecid, losartan, and benzbromarone all inhibit urate uptake in exchange for chloride at the luminal side of the cell by competition with the urate exchanger. Secretion of urate at the luminal brush border appears to be mediated principally by a voltage-sensitive uric acid transporter.^{9,10}

Urate binding to protein in vivo is low and, hence, urate is freely filterable. In adult humans, the renal tubule reabsorbs approximately 90% of filtered urea, so that the fractional excretion of urate is about 10%.¹¹ Urate handling by the kidneys can be influenced by multiple factors such as extracellular volume status, urine flow rate, urine pH level, urate load, and hormones. Several pharmacologic agents described earlier also modulate urate excretion including probenecid, salicylates, sulfipyrazone, and losartan. Serum uric acid levels are influenced acutely by exercise and diet, but persistent hyperuricemia typically occurs owing to defective renal urate clearance.¹¹

In the setting of decreased renal function, the fractional excretion of urate increases but is inadequate to compensate fully for the decrease in GFR, and, as a consequence, serum uric acid levels increase.¹² On the other hand, uric acid excretion via the gastrointestinal tract is also enhanced,^{13,14} and therefore serum uric acid levels tend to be increased only mildly in patients with chronic renal disease, and gout is relatively rare.

Kidney Disease in Gout: Chronic Urate Nephropathy

In patients who have had gout for many years, renal disease frequently is present. Before the availability of uric acid-decreasing drugs, as many as 10% to 25% of patients with gout developed end-stage renal disease (called *gouty nephropathy*).¹⁵ Histologic changes have been observed in autopsy studies of 75% to 99% of patients with gout, and consist of tubulointerstitial fibrosis, arteriosclerosis, and occasional glomerulosclerosis.¹⁵ Renal functional changes such as a decrease in GFR occur in 30% to 60% of cases with gout.¹⁶ In recent years, the nature of gouty nephropathy or even its

existence as such has been the subject of much debate. It may relate to the fact that the presence of hyperuricemia and renal disease may have other causes. These include familial hyperuricemic nephropathy, patients with lead intoxication, and patients with a partial deficiency of hypoxanthine-guanine phosphoribosyltransferase; all of these represent different entities other than classic gout. However, whatever the cause and the mechanism of hyperuricemia, gout is associated with renal pathology. Small foci of urate crystals often are found in the interstitium of the medulla.¹⁷ Experimental studies suggest that in some cases these crystals may have originated in the tubular lumen, but then ruptured into the interstitium.^{18,19} Renal functional abnormalities also are common in patients with asymptomatic hyperuricemia.²⁰

Typically, the patient with chronic hyperuricemia and renal disease presents with hypertension with mild azotemia, mild proteinuria, an unremarkable urinary sediment, and minimal tubular dysfunction. A history of gouty attacks may or may not be present.

Although there is controversy over whether decreasing the uric acid level is helpful in this disease (see later), it seems prudent to decrease the serum uric acid level with a xanthine oxidase inhibitor (allopurinol) with a target serum uric acid level of 5.5 mg/dL or less. Because allopurinol is excreted by the kidneys, one should initiate treatment at 100 mg/d, increasing the dose to 200-300 mg/d if tolerated. Monitoring for toxicity from allopurinol (such as a rash or increased liver function tests) is important because toxicity is more likely in patients with renal dysfunction. Alternative agents (uricosurics) generally are regarded as less effective in the setting of decreased renal function. However, benzbromarone completely inhibits urate uptake by URAT-1, and is the most potent uricosuric agent available today, being able to decrease plasma uric acid even in severe renal disease.

It should also be noted that the entity of chronic gouty nephropathy is distinct from an acute renal insufficiency associated with a marked increase in serum uric acid level. This latter entity, termed *acute urate nephropathy*, often occurs in association with chemotherapy with the tumor lysis syndrome and results from marked increases in urinary urate excretion with intratubular crystal deposition. In this condition, serum uric acid levels frequently are more than 15 mg/dL, and the urinary urate (mg)/creatinine(mg) ratio typically is more than 1.²¹ This entity is observed less commonly now that prophylaxis with aggressive fluid hydration, allopurinol, and/or recombinant uricase²² is administered to high-risk patients.

Etiology of Gouty Nephropathy: Does Uric Acid Really Matter?

A central question is the role of uric acid itself in the pathogenesis of gouty nephropathy. Just as with the debate of uric acid with cardiovascular disease, many authorities do not consider hyperuricemia as a causative factor for renal disease for several reasons. First, the interstitial disease and arteriosclerosis observed in renal biopsy specimens and autopsies of hyperuricemic individuals are similar to what one can

observe in hypertensive renal disease, and because most of the patients are hypertensive it is difficult to ascribe the lesion to hyperuricemia.²¹ Indeed, several studies performed in the 1970s and 1980s suggested that hyperuricemia in the absence of hypertension or being elderly was not associated with any risk for progression unless the serum uric acid level was markedly increased (>10 mg/dL in women or >13 mg/dL in men).²⁴⁻²⁷ Second, hyperuricemia often is associated with many other risk factors, including old age, male sex, obesity, and hyperinsulinemia.²⁸ Therefore, it is difficult to dissect the effect of uric acid itself from possible complex interactions between uric acid and other risk factors. Third, the uric acid crystal deposition also often is minor and focal, and cannot explain the frequently diffuse disease present.²⁹ Finally, although some studies have reported an improvement in renal function with uric acid-decreasing agents in patients with gout, it is unclear if this is owing to the fact that better uric acid control would lead to less use of nonsteroidal agents.^{30,31} Other studies have found no benefit, although most were either nonrandomized or short-term studies.³² Thus, many authorities considered the term gouty nephropathy a misnomer, and concluded that uric acid level had relatively little to do with the renal disease present in these patients.²³

Uric Acid as a Risk Factor for Progression of Renal Disease, Revisited

As a consequence of the earlier-mentioned studies, most authorities have not considered uric acid level a true risk factor for renal disease.^{33,34} However, 2 recent studies have found that hyperuricemia is an independent risk factor for progression in immunoglobulin A nephropathy.^{35,36} Furthermore, in a recent study of 6,400 patients with normal renal function, a serum uric acid level of more than 8.0 mg/dL, when compared with a serum uric acid level of less than 5.0 mg/dL, was associated with a 2.9-fold increased risk for developing renal insufficiency within 2 years in men and a 10.0-fold increased risk in women.³⁷ This increased relative risk was independent of age, body mass index, systolic blood pressure, total cholesterol level, serum albumin level, glucose level, smoking, alcohol use, exercise habits, proteinuria level, and hematuria level. Indeed, an increased uric acid level was more predictive for the development of renal insufficiency than proteinuria level. Finally, an increased uric acid level was associated independently with a marked increase risk for renal failure in another study of over 49,000 male railroad workers.³⁸ Thus, these studies re-raise the possibility that high uric acid levels may cause renal injury.

Animal Models

To investigate the role of uric acid level in renal disease, we recently developed a model of hyperuricemia in rats by providing low doses of oxonic acid, which is a uricase inhibitor.³⁹ Unlike previous models of uricase inhibition, which

result in massive uricosuria with intrarenal crystal deposition and obstructive renal disease, this model resulted in mild hyperuricemia without intrarenal crystal deposition.³⁹ Nevertheless, subtle interstitial renal injury developed, and this was associated with activation of the renin-angiotensin system (RAS) and the development of hypertension. The hyperuricemic animals also developed an afferent arteriopathy that occurred independently of changes in blood pressure.⁴⁰ The vascular injury was mediated in part by direct effects of uric acid to induce vascular smooth muscle cell proliferation, and also by activation of the RAS. In addition, micropuncture studies performed on the hyperuricemic rats showed that the rats developed glomerular hypertension and a decrease in renal plasma flow, both mechanisms that could lead to renal injury.⁴¹ Consistent with this observation, Nakagawa et al⁴² found that hyperuricemic rats developed glomerular hypertrophy by 7 weeks, and this was followed by the development of albuminuria with increased glomerulosclerosis and tubulointerstitial fibrosis at 6 months. Most importantly, the renal injury induced by the chronic hyperuricemia was not associated with intrarenal crystal deposition, so it was occurring via a novel crystal-independent mechanism.

We further showed that hyperuricemia could accelerate renal damage in 2 models of renal disease. In the first study we examined the effect of hyperuricemia (induced by oxonic acid) on cyclosporine (CSA) nephropathy in rats.⁴³ Oxonic acid-treated CSA nephropathy rats had higher uric acid levels in association with more severe arteriolar hyalinosis, macrophage infiltration, and tubulointerstitial damage compared with rats with CSA nephropathy. Intrarenal urate crystal deposition was absent in all groups. Both CSA and hyperuricemic CSA-treated rats had increased renin and decreased nitric oxide synthase-1 and nitric oxide synthase-3 in their kidneys, and these changes were more evident in hyperuricemic CSA-treated rats. These findings suggest that an increase in uric acid level exacerbates CSA nephropathy in the rat. The mechanism does not involve intrarenal uric acid crystal deposition and appears to involve activation of the RAS and inhibition of intrarenal nitric oxide production. Consistent with our study, Kobelt et al⁴⁴ reported that allopurinol decreases blood pressure and improves renal blood flow in rats administered cyclosporine, and Assis et al⁴⁵ also reported that allopurinol improved GFR (inulin clearances) in cyclosporine-treated rats. Most notably, Neal et al⁴⁶ recently reported that allopurinol therapy resulted in improved renal function in liver transplant patients receiving CSA in association with a decrease in uric acid levels.

The role of uric acid level in an animal model of chronic renal failure, the so-called remnant kidney (RK) model, also was investigated.⁴⁷ Hyperuricemic RK rats showed higher blood pressure, greater proteinuria, and higher serum creatinine levels than RK rats. Hyperuricemic RK rats had more renal hypertrophy and greater glomerulosclerosis ($24.2\% \pm 2.5\%$ versus $17.5\% \pm 3.4\%$, $P < .05$) and interstitial fibrosis ($1.89\% \pm 0.45\%$ versus $1.52\% \pm 0.47\%$, $P < .05$). Hyperuricemic rats also developed vascular disease consisting of thickening of the preglomerular arteries with smooth muscle cell proliferation and de novo expression of cyclooxygen-

ase-2 (COX-2) in vessel walls. The xanthine oxidase inhibitor allopurinol significantly decreased uric acid levels and blocked the renal functional and histologic changes. Benzydaron decreased uric acid levels less effectively and only partially improved blood pressure and renal function, with minimal effect on the vascular changes.

What are the Potential Mechanisms by Which Uric Acid Could Aggravate Renal Disease?

The earlier-described experimental models provide direct evidence that uric acid may have a role in causing renal disease. However, it is critical to identify a pathogenic mechanism of action to verify the causative role of uric acid on progression of renal disease. According to the data from our group and others, uric acid induced preglomerular arterial disease, renal inflammation, and hypertension via an activation of RAS and COX-2.^{40,47,48} We still are exploring the potential mechanisms to explain how these vascular and inflammatory changes can be induced by uric acid.

Uric acid crystals are proinflammatory and can activate platelets, suggesting that hyperuricemia may increase cardiovascular disease or renal disease via a prothrombotic effect.⁴⁹ Although uric acid crystals often are found in the kidneys of patients with long-standing gout, even in this situation they are present only focally and cannot account for the diffuse interstitial disease. Therefore, it seems unlikely that urate crystals could provide a pathogenic mechanism.

Uric acid is a mitogen for vascular smooth muscle cells. Previously, we reported, as did Rao et al,⁵⁰ that uric acid directly stimulated vascular smooth muscle cell proliferation.⁴⁰ We recently found that rat aortic vascular smooth muscle cells showed de novo expression of COX-2 messenger RNA after incubation with uric acid.⁴⁷ Incubation of the smooth muscle cells with either a COX-2 inhibitor or with a thromboxane-A₂ receptor inhibitor could prevent the proliferation in response to uric acid. COX-2 also was shown to be expressed de novo in the preglomerular vessels of hyperuricemia RK rats, and its expression correlated both with the uric acid levels and with the degree of smooth muscle cell proliferation. These findings suggest a critical role for uric acid-mediated COX-2-generated thromboxane in vascular smooth muscle cell proliferation in animal models of chronic progressive renal disease. Interestingly, COX-2 also has been shown recently to be important in the mechanism by which angiotensin II stimulates vascular smooth muscle cell proliferation.⁵¹ In addition to COX-2, it is likely that angiotensin II is also contributing to uric acid-induced vasculopathy. Preglomerular vasculopathy in rats with oxonic acid-induced hyperuricemia can be largely prevented by blocking the RAS, and we also have found that uric acid-mediated vascular smooth muscle cell proliferation can be inhibited partially by blocking the angiotensin II type 1 receptor.⁴⁰ Thus, it is likely that both angiotensin II and COX-2 are involved in the vascular proliferation and inflammation observed in our model.

Further *in vivo* studies evaluating the effect of inhibition of the RAS or COX-2 in the model of progressive renal disease with hyperuricemia would provide a more direct proof of the importance of these systems.

Once thickening of the afferent arterioles and macrophage infiltration in vessel wall was induced, preglomerular vasculopathy could potentiate the renal injury by causing ischemia to the postglomerular circulation. The decrease in lumen also could provide a stimulus for the increase in renin expression we observed, and also might contribute to the development of the marked hypertension in these rats. Furthermore, there is evidence that the arteriopathy also leads to ineffective autoregulation and increased transmission of systemic pressures to the glomerulus,⁴¹ which also can potentiate renal damage.

Uric acid also induced the proinflammatory cytokine monocyte chemoattractant protein-1 in vascular smooth muscle cells, which was shown further to be caused by direct entry of uric acid into vascular smooth muscle cells with activation of mitogen-activated protein kinase and nuclear transcription factor (NF- κ B).⁴⁸ Recently, we have found that uric acid itself induced de novo expression of C-reactive protein in cultured human vascular cells.⁵²

In addition, uric acid can become pro-oxidative under certain circumstances.⁵³ Consistent with this possibility, there is evidence that increased serum uric acid levels promote oxidation of low-density lipoprotein cholesterol to then facilitate lipid peroxidation. On the other hand, some investigators have reported that uric acid may function as an antioxidant, particularly as a scavenger of peroxynitrite.⁵⁴ These investigators propose that an increase in uric acid level may be beneficial and represent a host response to combat the inflammatory processes associated with atherosclerosis and hypertensive vascular damage. However, these benefits may be overwhelmed by the detrimental effect of uric acid.

Uric Acid as a Risk Factor for Cardiovascular Morbidity and Mortality in Chronic Renal Failure Patients: Another Issue About the Relationship Between Hyperuricemia and Renal Failure

Recent epidemiologic studies showed that uric acid level is an independent risk factor for cardiovascular events and mortality in patients with hypertension, congestive heart failure, and end-stage renal disease, as well as in the general population.^{26,55,56} We observed that endothelial dysfunction in predialysis chronic renal failure patients with a mean serum creatinine level of 2.2 mg/dl was correlated significantly with serum uric acid levels.⁵⁷ Hsu et al⁵⁶ recently reported that a high serum uric acid level was a

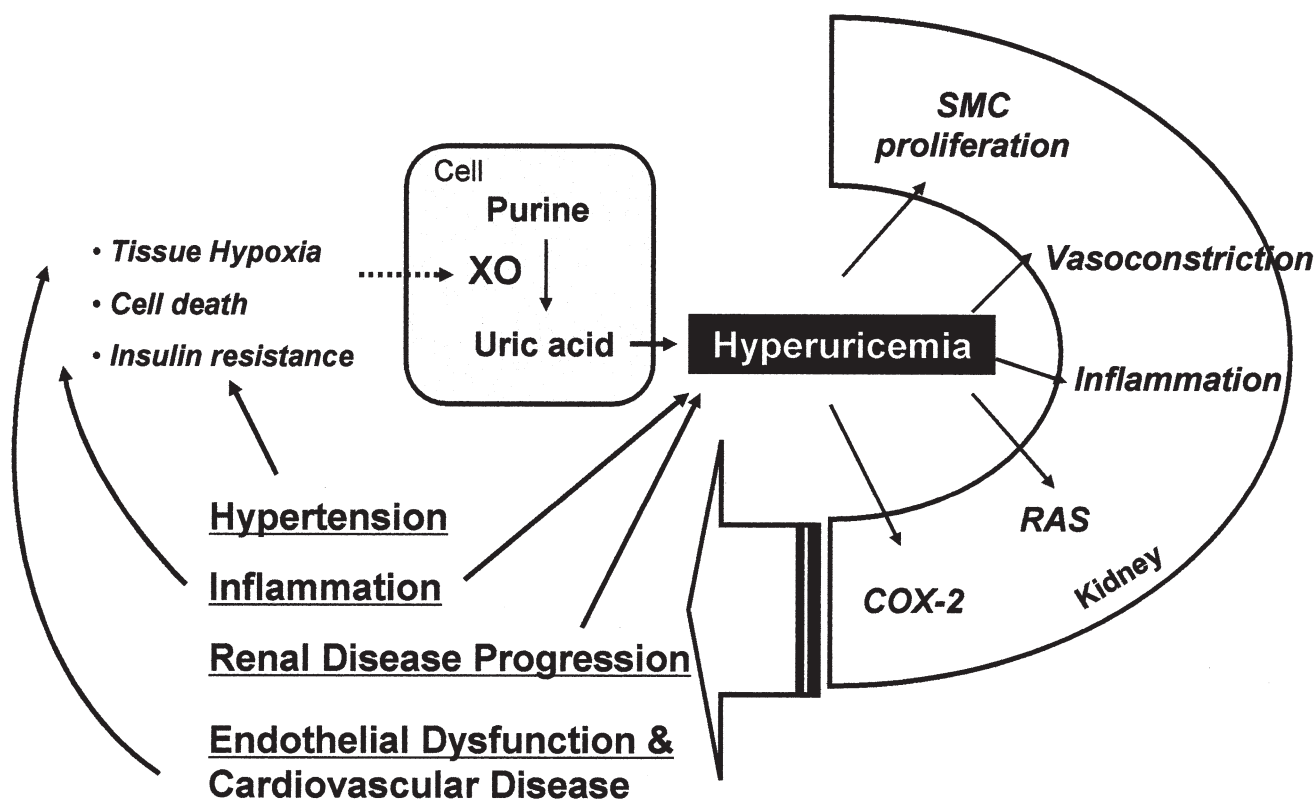


Figure 1 Interrelationship between hyperuricemia, hypertension, progression of renal disease, and cardiovascular disease. Hyperuricemia can be a marker of increased xanthine oxidase (XO) activity, renal dysfunction, or the presence of an inflammatory reaction. However, uric acid per se plays a key role in the development of renal microvascular disease, inflammation, and activation of RAS and COX-2, which in turn aggravates renal disease and hypertension and induces endothelial dysfunction and cardiovascular disease. Again, these events further increase the uric acid level by increased XO activity, decreased renal excretion, or inflammation, making a vicious cycle and complex interrelationship, which make the initiating event indistinct.

significant and independent predictor of cardiovascular mortality in 146 hemodialysis patients by the Cox proportional hazard regression model. They also showed the higher serum uric acid level in patients who died of cardiovascular disease compared with patients who died of sepsis (9.0 ± 1.0 versus 6.7 ± 1.8 mg/dl, $p < .05$). Therefore, uric acid level may be a risk factor for the development of functional and structural damage of blood vessels in renal failure patients, which links these patients to high cardiovascular mortality even after the commencement of renal replacement therapy. Therefore, hyperuricemia in chronic renal failure may not only be a risk factor for renal disease progression, but also may affect patients' survival by inducing or aggravating cardiovascular disease. Because uric acid is regarded as a general marker of tissue oxygenation, xanthine oxidase activity, and cell death, an increased uric acid level can be a reflection of tissue hypoxia or increased oxygen free radical formation, which is related closely to cardiovascular pathology; however, hyperuricemia may play a key role in causing cardiovascular disease in chronic renal failure via aforementioned mechanisms (Figure 1).

Conclusion

We have provided evidence that uric acid level is a new and potentially important mediator of renal disease. Hyperuricemia increased systemic blood pressure, proteinuria, renal dysfunction, and progressive renal scarring in RK rats. Hyperuricemia also induces vascular disease via a COX-2-dependent pathway. Furthermore, recent data from our group suggest hyperuricemia may be one of the key and previously unknown mechanisms for the activation of the RAS and COX-2 system in progressive renal disease. Uric acid level also is associated with endothelial dysfunction and cardiovascular mortality in chronic renal failure. Although we must be cautious in the interpretation of animal models to human disease, recent studies provide a mechanism to explain epidemiologic data that show uric acid is an independent risk factor for renal progression.

There is still no consensus on the treatment of individuals with chronic renal disease and asymptomatic hyperuricemia, although the animal experiments and epidemiologic data clearly show a detrimental effect of hyperuricemia on cardiovascular and renal disease in different groups of patients. Therefore, it is time to reevaluate the implication of hyper-

uricemia as an important player for progression of renal and cardiovascular disease and to try to find safe and reasonable therapeutic modalities in individual patients based on their clinical data, medication history, and the presence of cardiovascular complication.

With this purpose, we should consider whether we have to treat hyperuricemia itself, which modality is the best to decrease the uric acid level, and, finally, what level of uric acid should be targeted.

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