Ministry of Higher Education

and Scientific Research

University of Diyala

College of Medicine

Uric acid importance in chronic kidney disease and the patients on Dialysis

Submitted to the Council of the College of Medicine, Diyala University, In Partial Fulfillment of Requirements for the Bachelor Degree in medicine and general surgery.

Submitted by

Zainab Ahmed Kadhum

Supervised by

Dr. Adel Hassan

2022-2023

Abstract

Uric acid, the end-product of purine metabolism in humans, is excreted largely by the kidneys. In chronic kidney disease (CKD), plasma uric acid levels rise due to reductions in glomerular filtration rate (GFR). Hyperuricemia is a hallmark of gout and is also a suspected risk factor for conditions accompanying the metabolic syndrome such as hypertension, diabetes mellitus, and cardiovascular diseases. Uric acid can cause acute kidney injury, most notably in tumor lysis syndrome through precipitation and obstruction in tubules. Removal of uric acid in dialysate has a linear relationship with urea. Immediately after dialysis, uric acid levels will be markedly low compared to pre-dialysis levels. Therefore, timings of sample collection is important to explain the effect of dialysis on uric acid levels. Mean uric acid levels will be high between two dialysis sessions. In this review we demonstrated the association between the uric acid and CKD and the levels and importance of lowering Uric acid levels in patients on regular hemodialysis.

Introduction

Uric acid is synthesized mainly in the liver, intestines and other tissues such as muscles, kidneys and the vascular endothelium as the end product of an exogenous pool of purines, derived largely from animal proteins. In addition, live and dying cells degrade their nucleic acids, adenine and guanine into uric acid. Deamination and dephosphorylation convert adenine and guanine to inosine and guanosine, respectively. The enzyme purine nucleoside phosphorylase converts inosine and guanosine to the purine bases, respectively hypoxanthine and guanine, which are both converted to xanthine via xanthine oxidase-oxidation of hypoxanthine and deamination of guanine by guanine deaminase. Xanthine is further oxidized by xanthine oxidase to uric acid [1].

Normally, most daily uric acid disposal occurs via the kidneys. Humans cannot oxidize uric acid to the more soluble compound allantoin due to the lack of uricase enzyme. The enzyme uricase (urate oxidase) can metabolize uric acid to highly soluble 5-hydroxyisourate that is further degraded to allantoic acid and ammonia, easily excreted by the kidneys. However, several primates, including man have lost the functional activity of the enzyme uricase, as uricase mRNA may be detected in human livers but it displays two premature stop codons, and the encoding gene is, thus, a pseudogene [2].

Most serum uric acid is freely filtered in kidney glomeruli, and approximately 90% of filtered uric acid is reabsorbed, implying that it has a considerable physiological role [3]. In humans, over half the antioxidant capacity of blood plasma comes from uric acid. Uric acid is a strong reactive oxygen species (ROS) and peroxynitrite scavenger and antioxidant. High levels of uric acid are readily detected in the cytosol of normal human and mammalian cells, especially in the liver, vascular

endothelial cells, and in human nasal secretions, where it serves as an antioxidant [4].

The level of uric acid in humans (~6.0 mg/dL) is much higher than that in other mammals (<2.0 mg/dL) because of the absence of uricase. Loss of the uricase gene in humans could be a result of evolution since uric acid is a powerful antioxidant that accounts for up to 60% of the antioxidant capacity of human plasma. Uric acid exerts antioxidant effects by scavenging a free radical and chelating a metal ion. Indeed, uric acid is known to exert a protective effect against neurodegenerative diseases such as Parkinson's and Alzheimer's disease [5].

This advantageous feature of uric acid is limited by the fact that it acts as an antioxidant only in the hydrophilic environment of biological fluids, particularly in the presence of ascorbic acid. In modern society, an elevated uric acid level seems to be a disadvantageous inheritance. Since Garrod discovered that hyperuricemia is the cause of gout in the 19th century, the deleterious effects of uric acid on cardiovascular and kidney disease have been continuously documented [6].

Hyperuricemia is defined when the serum uric acid level is >6.8 mg/dL, at which point uric acid reaches saturation at physiological temperature and pH. Although an elevated uric acid level is a key factor for monosodium urate (MSU) crystal formation, urate solubility is also influenced by temperature, pH, and various ion concentrations as well as serum, synovial fluid, and cartilage contents. This variety of factors involved in MSU crystallization explains why only a minority (~0.5–4.9% annually) of individuals with hyperuricemia develop gout [7].

This viewpoint has been challenged since the 2000s, when studies demonstrated that an elevated serum uric acid level is an independent risk factor for kidney function decline in the general population. Moreover, in subjects with

diabetes mellitus (DM) or established chronic kidney disease (CKD), hyperuricemia was significantly associated with new-onset microalbuminuria or progression of kidney disease [8]. Experimentally, oxonic acid-induced hyperuricemia in normal and remnant kidney rats exacerbated the decline in glomerular filtration rate (GFR) and albuminuria in association with various renal damages, such as glomerular hypertrophy, arteriolopathy, and tubulointerstitial nephritis. These findings led to a reappraisal of the role of uric acid from an innocent bystander toward a potentially modifiable risk factor for kidney disease [9].

Studying the role of uric acid in chronic kidney disease (CKD) is very difficult since uric acid is excreted primarily by the kidney, and hence a decrease in the glomerular filtration rate (GFR) is inevitably accompanied by a rise in the serum uric acid level. As such, studies in experimental animals in which serum uric acid can be modulated are critical to understanding if there is a role for uric acid in the causation or progression of kidney disease. In this regard, humans and great apes metabolize uric acid differently from most other mammals. All animals generate uric acid normally from the turnover of ATP and nucleic acids, and uric acid can also be generated *de novo* from amino acid precursors. However, in most animals uric acid levels are relatively low as there is an enzyme in the liver (uricase) that degrades uric acid to 5-hydroxyisourate, and eventually to allantoin [10].

Uric acid and chronic kidney disease

Uric acid, the end-product of purine metabolism in humans, is excreted largely by the kidneys. In chronic kidney disease (CKD), plasma uric acid levels rise due to reductions in glomerular filtration rate (GFR). Hyperuricemia is a hallmark of gout and is also a suspected risk factor for conditions accompanying the metabolic syndrome such as hypertension, diabetes mellitus, and cardiovascular diseases. Uric acid can cause acute kidney injury, most notably in tumor lysis syndrome through precipitation and obstruction in tubules. Uric acid may also lead to CKD and its progression by causing endothelial dysfunction, activation of the renin-angiotensin-aldosterone system (RAAS), inflammation, and oxidative stress [11].

Gout was considered a cause of CKD in the mid-nineteenth century [1], and, prior to the availability of therapies to lower the uric acid level, the development of end-stage renal disease was common in gouty patients. In their large series of gouty subjects. Talbott and Terplan found that nearly 100% had variable degrees of CKD at autopsy (arteriolosclerosis, glomerulosclerosis and interstitial fibrosis). Additional studies showed that during life impaired renal function occurred in half of these subjects. As many of these subjects had urate [12].

Renewed interest in uric acid as a cause of CKD occurred when it was realized that invalid assumptions had been made in the arguments to dismiss uric acid as a risk factor for CKD. The greatest assumption was that the mechanism by which uric acid would cause kidney disease would be via the precipitation as crystals in the kidney, similar to the way it causes gout. However, when laboratory animals with CKD were made hyperuricemic, the renal disease progressed rapidly despite an absence of crystals in the kidney [13].

The specific mechanism(s) by which uric acid may be causing these effects has been studied primarily in cell culture systems. One of the more striking findings is that uric acid, while being a potent antioxidant in the extracellular environment, is a pro-oxidant inside the cell where it can induce stimulation of NADPH oxidases with the induction of mitochondrial dysfunction [14]. Uric acid can also induce endothelial dysfunction via a variety of mechanisms and can also stimulate the release of alarmins (such as high mobility group box-1 protein) from endothelial cells that activate Toll-like receptor pathways [15]. Uric acid also stimulates vascular smooth muscle cell proliferation with the production of chemotactic factors and oxidants and the activation of the RAS. Uric acid can also induce phenotypic alterations and chemokines in tubular cells and can induce intrarenal inflammation following its infusion in mice [16].

In contrast, in subjects with normal renal function, an elevated serum uric acid has almost uniformly been found to independently predict the development of CKD, including end-stage renal disease. An elevated serum uric acid has also been found to independently predict the development of CKD in subjects with IgA nephropathy and of graft failure in transplant patients with chronic allograft nephropathy [17].

To date, only pilot studies have evaluated the benefit of lowering uric acid in CKD. Siu et al. reported that allopurinol therapy slowed renal disease progression in hyperuricemic subjects with modest (stage 3) CKD at 1 year compared with randomized controls [18].

There is some evidence that lowering the uric acid level may act in part by blocking the RAS. For one thing, uric acid stimulates the production of angiotensin II in vascular cells and also increases renin expression in laboratory animals Serum uric acid is also associated with elevated serum renin in humans and Perlstein et al. [19] found evidence that hyperuricemia was associated with activation of the

intrarenal RAS in humans. In a study by Shi et al. [20], subjects with IgA nephropathy were randomized to receive allopurinol therapy or no treatment for 1 year. None of these subjects were receiving angiotensin converting enzyme (ACE) inhibitors. In the first month, there was a fall in the GFR consistent with a hemodynamic effect similar to that observed with the initiation of ACE inhibitors, followed by a leveling of the slope in the change of GFR over the subsequent year

While these studies suggest that lowering the uric acid level may simply be another way to block the RAS, there is also some evidence that such a lowering may have other benefits in addition to RAS blockade. Indeed, one unique aspect of the angiotensin receptor blocker, losartan is that it also lowers the serum uric acid level. There are now a few reports that the lowering of uric acid by losartan may provide additional benefits for slowing renal disease and reducing cardiovascular events [21]. For example, in a post hoc analysis of the study, Miao et al. [22] found that renal events, i.e. doubling of serum creatinine or end-stage renal disease, were less frequent in individuals in whom—as a result of the known uricosuric effect of losartan—serum uric acid concentrations were lowered by >0.5 mg/dL compared with patients with lesser lowering or increase.

Uric acid and dialysis

Uric acid, xanthine, and hypoxanthine are some of porin metabolites, which accumulate in the plasma of patients with ESRD. Porin metabolites constitute an important group of uremic toxins. These toxins such as uric acid and hypoxanthine may cause damage to the structure of proteins and vitamin D. Also, these toxins have an important role in immune deficiency of hemodialysis patients. Furthermore, these metabolites may cause an escalation of anorexia and weight loss in hemodialysis patients [23].

high levels of SUA have been associated with several severe clinical conditions including hypertension, diabetes mellitus, insulin resistance and metabolic syndrome, CV disease, and chronic kidney disease. However, low SUA levels have been proposed as a surrogate of protein energy wasting in hemodialysis patients as a consequence of inadequate protein intake, given that SUA levels are strongly associated with the consumption of purine-rich meals. Serum uric acid has been shown to be associated with the nutritional status of patients on hemodialysis, as it correlates with laboratory nutritional markers, with parameters of anthropometry and with health-related quality of life scoring. Moreover, it was shown that the association between SUA levels and mortality was modified by nPCR [24].

There is no convincing data about when and how to treat hyperuricemia in CKD as well as dialysis and transplant recipients. Multiple observational studies have found a causative role of hyperuricemia in CKD progression. Srivastava, et al. recently established uric acid as an independent risk factor for renal failure in patients with early CKD but whether uric acid lowering strategies can help in retarding this progression remained inconclusive. Kidney Disease Improving Global Outcome (KDIGO) guidelines have no strong recommendation for treating hyperuricemia in CKD population due to lack of consensus. These guidelines do not even confirm the role of hyperuricemia treatment in slowing progression of kidney disease [25].

Uric acid levels are variably reported in studies to define hyperuricemia in dialysis population. Mean uric acid levels above 7.5mg/dl in hemodialysis and above 8.5mg/dl in peritoneal dialysis patients are considered abnormal. This variability is probably based on prescription of dialysis and timings of sample collection [26].

In patients with standard hemodialysis prescription, high flux dialyzer can remove almost 70% of uric acid and in PD, 15-20ml/min is removed based on peritoneal dialysate flow rate. In a review article by Murea, et al. 9 out of 14 studies showed an inverse relationship of uric acid levels with all-cause mortality. Rest of five studies found no association. This was a surprising finding because it was contrary to pre-dialysis CKD population. The same finding has also been reported by Latif, et al. Different theories have been suggested for this finding in HD patients. It was postulated that uric acid is a marker of better nutrition so a low uric acid level can lead to increased mortality. However this opinion was later rejected because mortality was not reduced even after correction of nutritional parameters [27].

Removal of uric acid in dialysate has a linear relationship with urea. Immediately after dialysis, uric acid levels will be markedly low compared to pre-dialysis levels. Therefore, timings of sample collection is important to explain the effect of dialysis on uric acid levels. Mean uric acid levels will be high between two dialysis sessions. Patients with high pre-dialysis uric acid levels may have normal levels after dialysis which are sufficient to carry out anti-oxidant activity. This is another explanation of protective effect of hyperuricemia in HD patients [28].

Contrary to our hypothesis, a study found that uric acid–lowering therapy (which was predominantly achieved with the administration of allopurinol in our cohort) was associated with a higher incidence of new-onset CKD and showed no association with incident ESKD. In subgroup analysis, the association of uric acid–lowering therapy with unfavorable kidney outcomes was limited to patients with baseline serum uric acid levels of 8 mg/dL or less, while the same associations were not significant in patients with serum uric acid levels greater than 8 mg/dL. These results do not support a direct benefit of urate lowering on the development of new-

onset CKD, and support the results of recent large randomized clinical trials29,30 that found no benefit of allopurinol in delaying progression of established CKD [29].

Conclusion

There is a strong evidence of the association of hyperuricemia and the development of CKD and lowering the uric acid level was proven to slow the progression and decrease mortality in patients on hemodialysis.

References

1. Chaudhary K, Malhotra K, Sowers J, Aroor A. Uric acid-key ingredient in the recipe for cardiorenal metabolic syndrome. Cardiorenal medicine. 2013;3(3):208-20.
2. Chang BS. Ancient insights into uric acid metabolism in primates. Proceedings of the National Academy of Sciences. 2014 Mar 11;111(10):3657-8.
3. Maiuolo J, Oppedisano F, Gratteri S, Muscoli C, Mollace V. Regulation of uric acid metabolism and excretion. International journal of cardiology. 2016 Jun 15;213:8-14.
4. Peden DB, Swiersz M, Ohkubo K, Hahn B, Emery B, Kaliner MA. Nasal secretion of the ozone scavenger uric acid. American Review of Respiratory Disease. 1993 Aug 1;148:455-.
5. Yeum KJ, Russell RM, Krinsky NI, Aldini G. Biomarkers of antioxidant capacity in the hydrophilic and lipophilic compartments of human plasma. Archives of biochemistry and biophysics. 2004 Oct 1;430(1):97-103.
6. Tuttle KR, Short RA, Johnson RJ. Sex differences in uric acid and risk factors for coronary artery disease. American Journal of Cardiology. 2001 Jun 15;87(12):1411-4.
7. Campion EW, Glynn RJ, Delabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. The American journal of medicine. 1987 Mar 1;82(3):421-6.
8. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS. Uric acid and incident kidney disease in the community. Journal of the American Society of Nephrology. 2008 Jun 1;19(6):1204-11.

9. Sanchez-Lozada LG, Tapia E, Santamaria J, Avila-Casado C, Soto V, Nepomuceno T, Rodriguez-Iturbe B, Johnson RJ, Herrera-Acosta J. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. Kidney international. 2005 Jan 1;67(1):237-47.
10. Sánchez-Lozada LG, Soto V, Tapia E, Avila-Casado C, Sautin YY, Nakagawa T, Franco M, Rodríguez-Iturbe B, Johnson RJ. Role of oxidative stress in the renal abnormalities induced by experimental hyperuricemia. American Journal of Physiology-Renal Physiology. 2008 Oct;295(4):F1134-41.
11. Yu MA, Sánchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an activation of the renin–angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. Journal of hypertension. 2010 Jun 1;28(6):1234-42.
12. Star VL, Hochberg MC. Prevention and management of gout. Drugs. 1993 Feb;45:212-22.
13. Johnson RJ, Kivlighn SD, Kim YG, Suga S, Fogo AB. Reappraisal of the pathogenesis and consequences of hyperuricemia in hypertension, cardiovascular disease, and renal disease. American journal of kidney diseases. 1999 Feb 1;33(2):225-34.
14. Sánchez-Lozada LG, Lanaspa MA, Cristóbal-García M, García-Arroyo F, Soto V, Cruz-Robles D, Nakagawa T, Min AY, Kang DH, Johnson RJ. Uric acid-induced endothelial dysfunction is associated with mitochondrial alterations and decreased intracellular ATP concentrations. Nephron Experimental Nephrology. 2012;121(3-4):e71-8.
15. Rabadi MM, Kuo MC, Ghaly T, Rabadi SM, Weber M, Goligorsky MS, Ratliff BB. Interaction between uric acid and HMGB1 translocation and

release from endothelial cells. American Journal of Physiology-Renal Physiology. 2012 Mar 15;302(6):F730-41.

16. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid–induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. Journal of the American Society of Nephrology. 2005 Dec 1;16(12):3553-62.
17. Akalin E, Ganeshan SV, Winston J, Muntner P. Hyperuricemia is associated with the development of the composite outcomes of new cardiovascular events and chronic allograft nephropathy. Transplantation. 2008 Sep 15;86(5):652-8.
18. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. American Journal of Kidney Diseases. 2006 Jan 1;47(1):51-9.
19. Perlstein TS, Gumieniak O, Hopkins PN, Murphey LJ, Brown NJ, Williams GH, Hollenberg NK, Fisher ND. Uric acid and the state of the intrarenal renin-angiotensin system in humans. Kidney international. 2004 Oct 1;66(4):1465-70.
20. Shi Y, Chen W, Jalal D, Li Z, Chen W, Mao H, Yang Q, Johnson RJ, Yu X. Clinical outcome of hyperuricemia in IgA nephropathy: a retrospective cohort study and randomized controlled trial. Kidney and Blood Pressure Research. 2012;35(3):153-60.
21. Smink PA, Bakker SJ, Laverman GD, Berl T, Cooper ME, De Zeeuw D, Heerspink HJ. An initial reduction in serum uric acid during angiotensin receptor blocker treatment is associated with cardiovascular protection: a post-hoc analysis of the RENAAL and IDNT trials. Journal of hypertension. 2012 May 1;30(5):1022-8.

22. Miao Y, Ottenbros SA, Laverman GD, Brenner BM, Cooper ME, Parving HH, Grobbee DE, Shahinfar S, De Zeeuw D, Lambers Heerspink HJ. Effect of a reduction in uric acid on renal outcomes during losartan treatment: a post hoc analysis of the reduction of endpoints in non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan Trial. Hypertension. 2011 Jul;58(1):2-7.
23. Owen Jr WF, Lew NL, Liu Y, Lowrie EG, Lazarus JM. The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. New England Journal of Medicine. 1993 Sep 30;329(14):1001-6.
24. Zawada AM, Carrero JJ, Wolf M, Feuersenger A, Stuard S, Gauly A, Winter AC, Ramos R, Fouque D, Canaud B. Serum uric acid and mortality risk among hemodialysis patients. Kidney international reports. 2020 Aug 1;5(8):1196-206.
25. Oluwo O, Scialla JJ. Uric acid and CKD progression matures with lessons for CKD risk factor discovery. Clinical Journal of the American Society of Nephrology. 2021 Mar 8;16(3):476-8.
26. Hsu SP, Pai MF, Peng YS, Chiang CK, Ho TI, Hung KY. Serum uric acid levels show a ‘J-shaped’association with all-cause mortality in haemodialysis patients. Nephrology dialysis transplantation. 2004 Feb 1;19(2):457-62.
27. Beberashvili I, Sinuani I, Azar A, Shapiro G, Feldman L, Stav K, Sandbank J, Averbukh Z. Serum uric acid as a clinically useful nutritional marker and predictor of outcome in maintenance hemodialysis patients. Nutrition. 2015 Jan 1;31(1):138-47.

28. Barata R, Cardoso F, Pereira T. Hyperuricemia in Chronic Kidney Disease: a role yet to be explained. Port J Nephrol Hypertens. 2020 Mar;34(1):30-5.
29. Hassan W, Shrestha P, Sumida K, Thomas F, Sweeney PL, Potukuchi PK, Rhee CM, Streja E, Kalantar-Zadeh K, Kovesdy CP. Association of Uric Acid–Lowering Therapy With Incident Chronic Kidney Disease. JAMA network open. 2022 Jun 1;5(6):e2215878-.