Review

Hyperuricaemia—where nephrology meets rheumatology

Z. Avram and E. Krishnan

Rheumatologists care for patients with gouty arthritis, a condition caused by chronic and uncontrolled hyperuricaemia. Hyperuricaemia, gout and renal dysfunction are often bedfellows, raising the possibility of the former causing the latter. We sought the answer to the question ‘Among patients with normal measures of glomerular filtration, does hyperuricaemia predict future renal disease’? We identified prospective cohort studies evaluating the relationship between serum uric acid and chronic kidney function from the past 20 yrs, through MEDLINE, Cochrane Library and EMBASE searches and bibliography cross-referencing. Nine cohort studies that met the selection criteria were found. Because of the extreme heterogeneity, a statistical meta-analysis was not performed. Most (eight out of nine) studies found an independent risk factor for deterioration of kidney function. Nearly all published prospective studies support the role of hyperuricaemia as an independent risk factor for renal dysfunction. In the absence of large randomized controlled trials of uric acid reduction, it remains uncertain if this relation is causal or merely an epiphenomenon. Regardless, our review suggests that hyperuricaemia is a useful, inexpensively measured, widely available and useful early marker for chronic kidney disease.

KEY WORDS: Uric acid, Creatinine, Renal failure, Kidney disease.

Introduction

Elevated serum concentrations of uric acid—hyperuricaemia (often defined as a serum concentration ≥7 mg/dl)—is well known to be associated with renal disease [1]. Uric acid is freely filtered, reabsorbed and actively secreted in renal tubules and renal pathology that interferes with this process can lead to hyperuricaemia. On the other hand, chronic hyperuricaemia, as in gouty arthritis, can lead to deposition of urate crystals in the tubular system leading to renal failure. The true role of serum uric acid in the development and progression of chronic renal disease has been unclear. The question whether elevated serum uric acid can independently increase the risk for chronic renal dysfunction is clinically important, yet not well addressed in the literature.

As early as in 1928, Gudzant described the association between gouty arthritis and renal disease. The histological lesion, ‘gouty nephropathy’, was found in autopsies of 79–99% of patients with gout [2]. This lesion consists of interstitial fibrosis, glomerulosclerosis and renal arteriolar sclerosis and arterial wall thickening caused by intimal fibrosis. In 1975, Klinenberg et al. [3] studied a group of asymptomatic hyperuricaemic patients and found that they had a disproportionately high prevalence of renal dysfunction compared with healthy individuals with no hyperuricaemia [3]. Given the multiple risk factors involved in renal disease and their close relationship with serum uric acid, it has been difficult to prove a causal effect of uric acid in the pathogenesis of renal disease. In this review, we will examine the recent evidence trying to address the causal role of serum uric acid in renal dysfunction.

Methods

Literature search strategy

Our goal was to identify all articles evaluating the likelihood of an independent association of serum uric acid and chronic renal disease published until June 2006. All published literature on this subject was identified by means of multiple EMBASE, MEDLINE and Cochrane library searches, bibliography cross-referencing of all articles and previous review articles. We used in various combinations keywords including ‘uric acid’, ‘urate’ and ‘hyperuricemia’ combined with ‘renal disease’, ‘renal failure’, ‘renal insufficiency’, ‘risk factor’ and ‘mortality’. The studies identified in the searches were cross-referenced thoroughly to ensure that relevant studies were not missed. Articles were not included if they were non-clinical, did not focus on at least one of the specified outcomes or did not address whether serum uric acid was an independent risk factor.

Literature summarization

Our original intention was to perform a formal meta-analysis of the studies. In order to determine the suitability of these studies to such statistical summation we examined the characteristics (clinical characteristics, gender, follow-up duration, risk factor measurements, etc.) of subjects included in these studies and found too much heterogeneity. One of the main sources of heterogeneity was the clinical population studied. There were four broad patient populations: (i) healthy subjects, (ii) subjects with IgA nephropathy, (iii) subjects post-transplant and (iv) subjects with contrast-induced nephropathy. These groups vary widely in the putative causes of hyperuricaemia, renal disease, comorbidity and medication use. Further, within each patient population, there was significant heterogeneity in terms of study design, risk factor measurements and end-point definitions. We therefore decided to perform a qualitative review of the available studies within each subject/patient population.

Definition of chronic renal failure

In an ideal world, renal function should be assessed by inulin clearance or similar studies of glomerular filtration. In real life, serum clearance of creatinine either measured directly or estimated using appropriate formulae would be a useful metric of renal function. In our review, increasing/increased serum level of creatinine was the most common metric of renal function although some studies used organ failure [end-stage renal disease (ESRD) or transplant failure], histopathological lesions and estimated glomerular filtration as the end-points.

All the studies reported serum creatinine and uric acid measurements in milligrams per decilitre. The conversion formulae are: serum uric acid to SI unit (micromoles/litre), multiply by 59.48; serum creatinine to SI unit (micromoles/litre), multiply by 88.4.
Results

Overall, we found nine studies that met our inclusion criteria. Three of them were performed in a healthy population, three in a post-transplant setting and two among subjects with underlying IgA nephropathy. One study was performed on patients with chronic renal disease that were undergoing imaging studies with intravenous contrast. Table 1 shows a summary of the cohort studies analysed in this review. As shown in the table, several studies used serum creatinine as a maker of the kidney dysfunction, while it is well known that creatinine level is not the best marker of renal failure [4]. We did not find any prospective study examining the relationship between gout (a consequence of severe hyperuricaemia) and renal dysfunction.

Studies performed in healthy subjects

Normative ageing study. Campion et al. [5], in a cross-sectional analysis of a prospective longitudinal study done on a sample of subjects (n = 2046) recruited from the Boston, MA, area found no deterioration of renal function secondary to asymptomatic hyperuricaemia. This study had 30,147 person-years of observation and defined renal failure as a serum creatinine level ≥2 mg/dl at the 15th yr of follow-up. However, the uric acid and creatinine data were analysed cross-sectionally using the final visit only. Overall, there were only 11 cases of renal failure. On cross-sectional analyses of data from the last visit, mean serum creatinine increased from 1.20 mg/dl among individuals with serum uric acid <6.0 to 1.43 mg/dl among those with serum uric acid levels ≥10 mg/dl. This difference was not statistically significant. Further, this analysis did not take into account confounders such as use of diuretics. Lack of information on baseline serum uric acid and creatinine and analyses not adjusted for important confounders such as diuretic use remain the major limitations of this landmark study.

Okinawa General Health Maintenance Association studies. Two other studies involving healthy subjects were reported by Iseki et al. [6, 7] from Japan. The first study [6] was based on 6403 subjects who participated in the Okinawa General Health Maintenance Association screening at 1997 and 1999. Renal dysfunction was defined as a serum creatinine >1.4 mg/dl for men and 1.2 mg/dl for women. Among those with normal renal function in 1997 screening (n = 6210), 241 subjects (3.8% overall, 5.5% among men and 0.8% in women) developed renal dysfunction at the 1999 visit. Baseline hyperuricaemia (serum uric acid ≥8 mg/dl) was associated with 2.9-fold increase of renal dysfunction among men and 2.2-fold among women, when compared with those with baseline serum uric acid <5.0 mg/dl and after adjustment for age, smoking, alcohol use, exercise habits, serum albumin, fasting glucose, baseline proteinuria and haematuria, obesity and systolic blood pressure. After additional adjustment for gender effects, the relative risk was 1.34 (95% CI 1.2, 1.5).

The second study by Iseki et al. [7] reported results from the same data source but with some significant differences. This study involved 48,177 screenees followed up from 1993 to December 2000 for onset of ESRD. The risk for developing ESRD with increasing levels of serum uric acid was calculated by means of Cox proportional hazards regression models that adjusted for the effects of baseline values of age, smoking, alcohol use, fasting glucose, proteinuria and haematocrit, total cholesterol, serum triglycerides, creatinine, obesity and systolic and diastolic blood pressure. Among men, hyperuricaemia (defined as baseline serum uric acid ≥7.0 mg/dl) was associated with a relative risk of 2.0 (95% CI 0.9, 4.4) while that among women was associated with a relative risk of 5.7 (2.3, 14.4). The large number of subjects and the excellent outcome assessment makes this study one of the most powerful ones published. The limitations include lack of

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Mean Years of Follow-up</th>
<th>Metric of Renal Function</th>
<th>Highest Division Serum Uric Acid (mg/dl)</th>
<th>Adjusted relative risk (male/female)</th>
<th>Factors adjusted for</th>
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<tbody>
<tr>
<td>Iseki et al. [7]</td>
<td>Healthy subjects</td>
<td>52</td>
<td>Presence of end-stage renal disease</td>
<td>Serum creatinine &lt;6.0</td>
<td>5.59/4.57</td>
<td>Age, blood pressure, BMI, cholesterol, triglycerides, FBG, haematocrit</td>
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<td>Iseki et al. [6]</td>
<td>Healthy subjects</td>
<td>52</td>
<td>Presence of end-stage renal disease</td>
<td>Serum creatinine ≥8.0</td>
<td>2.29/1.39</td>
<td>Age, blood pressure, BMI, cholesterol, triglycerides, FBG, haematocrit</td>
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<tr>
<td>Campion et al. [5]</td>
<td>Healthy subjects</td>
<td>48</td>
<td>Ages 24-65</td>
<td>Serum creatinine &lt;7.0</td>
<td>1.87/1.50</td>
<td>Age, blood pressure, BMI, cholesterol, triglycerides, FBG, haematocrit</td>
</tr>
<tr>
<td>Gores et al. [15]</td>
<td>Healthy subjects</td>
<td>56</td>
<td>Ages 24-65</td>
<td>Serum creatinine &gt;8.0</td>
<td>1.67/1.76</td>
<td>Age, blood pressure, BMI, cholesterol, triglycerides, FBG, haematocrit</td>
</tr>
<tr>
<td>Syrjanen et al. [12]</td>
<td>Patients with IgA nephropathy</td>
<td>41</td>
<td>Serum creatinine ≥8.0</td>
<td>Serum creatinine &lt;5.0</td>
<td>6.39/5.39</td>
<td>Proteinuria, hypertension, diabetes, hyperlipidaemia, smoking, age, gender, BMI</td>
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<tr>
<td>Myllymaki et al. [10]</td>
<td>Patients with IgA nephropathy</td>
<td>41</td>
<td>Serum creatinine ≥8.0</td>
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<td>6.09/5.39</td>
<td>Proteinuria, hypertension, diabetes, hyperlipidaemia, smoking, age, gender, BMI</td>
</tr>
<tr>
<td>Armstrong et al. [13]</td>
<td>Renal transplant recipients</td>
<td>51</td>
<td>eGFR ≥70</td>
<td>eGFR &lt;60</td>
<td>2.2/2.5</td>
<td>Age, blood pressure, BMI, smoking, diabetes, hypertension, hyperlipidaemia</td>
</tr>
<tr>
<td>Gerhardt et al. [14]</td>
<td>Renal transplant recipients</td>
<td>41</td>
<td>Transplant failure</td>
<td>Transplant failure</td>
<td>5.1/4.2</td>
<td>Age, blood pressure, BMI, smoking, diabetes, hypertension, hyperlipidaemia</td>
</tr>
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To convert serum creatinine to SI unit (micromoles/litre) multiply by 88.4; to convert serum uric acid to SI unit (micromoles/litre) multiply by 59.48. FBG, fasting blood glucose; ACEI, angiotensin-converting enzyme inhibitor; eGFR, estimated glomerular filtration rate.
information on medication use (such as diuretics). Further, the list of covariates could include those in the pathophysiological pathways such as hypertension and haematuria as well as those that are potentially a consequence of renal dysfunction such as low haematocrit.

Studies performed in subjects with IgA nephropathy

IgA nephropathy is an immune complex glomerulonephritis of undetermined aetiology characterized by intense deposition of IgA1 within the mesangium of the glomerulus [8]. This is one of the most common forms of glomerulonephritis in the world [8]. Approximately 25–30% of people with this disease reach ESRD after 10 yrs [9]. Two studies were done to determine the effect of hyperuricaemia in the progression of IgA nephropathy. In one of the studies, the histopathological changes and risk factors associated with these parameters were the end-points, while in the second study the serum creatinine was the outcome measured.

Myllymaki et al. [10] correlated clinical and metabolic risk factors with histopathological parameters in patients with IgA nephropathy [10]. It is a well-known fact that tubulointerstitial damage has a central role in progression of IgA nephropathy [11]. After adjustments were done with other clinical parameters such as mean arterial pressure, urine protein excretion, BMI, diabetes and age it was found that serum uric acid is independently associated with tubular atrophy ($P < 0.01$) and interstitial fibrosis ($P < 0.05$). This way it appears possible that uric acid may be an independent factor in progression of IgA nephropathy by tubulointerstitial damage.

Syrtanen et al. [12] studied risk factors associated with poor prognosis of IgA nephropathy. The population studied was subdivided into two subgroups: patients with increased serum creatinine and patients with normal serum creatinine (subgroup N) at the time of the diagnosis of the IgA nephropathy and the serum creatinine was followed as a marker of progression of kidney disease. It was observed that hyperuricaemia increased the risk of progression of IgA nephropathy 2.4- and 2.6-fold in all patients and in the subgroup N, respectively. Also hyperuricaemia was associated with progression of IgA nephropathy even in patients who were not using anti-hypertensive drugs. The Cox model was used and adjustments were done for proteinuria, hypertension, diabetes, hypertriglyceridaemia, hypercholesterolaemia, age, gender and BMI with hyperuricaemia remaining a significant risk factor only for a smaller subgroup. Although it was found that hyperuricaemia is associated with progression of renal disease it was not concluded that hyperuricaemia is per se pathogenic since it is possible that it is a marker of other factors not considered in the Cox model.

Studies performed in transplant patients

Three studies evaluated the prevalence of hyperuricaemia and the relationship of the serum uric acid to graft function in renal transplant recipients. Graft function was differently evaluated in each study, by estimated glomerular filtration rate measurement, serum creatinine or by terminal insufficiency secondary to rejection.

The prospective observational study done by Armstrong et al. [13] concluded that there is a significant inverse correlation between baseline uric acid and estimated glomerular filtration rate (eGFR) after 2 yrs of follow-up and this remained true even after the adjustment done for baseline renal function. Although serum uric acid was one of the variables associated independently with GFR at follow-up, there was no association between the serum uric acid level and the change in GFR over time. This most probably was due to the limitations of this study such as the poor power secondary to the small sample size, the short period of follow-up and possible bias introduced by exclusion of patients who did not complete the study (10%). Since calcineurin inhibitors, such as cyclosporin and tacrolimus, which are used after renal transplant, are known to cause nephrotoxicity leading to deterioration of renal allograft function, their levels were measured during this study. It was observed that although uric acid increased with immunosuppressant therapy there was no association between uric acid and immunosuppressant drug levels. We need to highlight that only the baseline uric acid was used during the analysis with eGFR, precluding such confounding.

Gerhardt et al. [14] followed the rate of graft survival in a population of renal transplant patients finding that serum uric acid is an independent predictor of renal graft survival. It was reported that the rate of transplant survival 2, 4 and 5 yrs post-transplantation in hyperuricaemic patients compared with normouricaemic recipients was significantly reduced (92.2, 70.6 and 68.8% vs 98.1, 85.6 and 83.3%). Cyclosporin contributed to the uric acid level but no statistical significance was reached. Although it was found that hyperuricaemia is a predictor of renal transplant survival it could not be concluded that hyperuricaemia is the cause of the transplant failure.

However, in a prospective study by Gores et al. [15] on 131 renal transplant recipients, it was found that serum uric acid does not adversely affect graft function. No difference in mean serum creatinine between severely hyperuricaemic patients (10% of patients) (serum uric acid $>14$ mg/dl) and normouricaemic patients (serum uric acid $<8$ mg/dl) (1.8 mg/dl versus 1.6 mg/dl) was reported. Both groups were under the same immunosuppressant treatment (cyclosporin and prednisolone), but no information on the correlation between uric acid and cyclosporin level was provided. The 4-yr graft survival rate in the severely hyperuricaemic patients was found to be 90%. Limitations of this study are the small group of patients and the short period of follow-up. Also the criterion of transplant function was serum creatinine level vs terminal insufficiency secondary to rejection in the study done by Gerhardt.

Studies performed in subjects with contrast-induced nephropathy

One of the studies, done by Toprak et al. [16], tried to define the risk of hyperuricaemia for contrast-induced nephropathy in a group of patients with chronic kidney disease, in a prospective cohort study in patients undergoing coronary angiography. A higher prevalence of contrast-induced nephropathy in hyperuricaemic patients vs a normouricaemic group was reported. Also the length of hospital stay and contrast-induced nephropathy requiring renal replacement therapy was higher in the hyperuricaemic group, and serum uric acid was found to be an independent risk factor for contrast-induced nephropathy in patients with serum creatinine $\geq 1.2$ mg/dl who are undergoing coronary angiography. Serum uric acid levels of $\geq 7$ mg/dl in males and $\geq 5.9$ mg/dl in females were the best cut-off points for the prediction of contrast-induced nephropathy. Multivariate analysis was done including the known risk factors for contrast induced nephropathy (CIN) such as age, diabetes mellitus, congestive heart failure and renal disease. It is important to mention that the prevalence of congestive heart failure was comparable in both groups. Since hypovolaemia is an important risk factor in the development of the CIN, both groups received intravenous fluids before and after the procedure and no signs and symptoms of dehydration were found in any of the patients. Limitations of this study were the small size of population, and also the GFR was calculated from the Cockcroft–Gault equation and not through serum inulin or any other more sensitive estimate of renal function. Hyperuricaemic patients had a more extensive coronary artery disease which could also cause a difference in the term of procedure between two groups, which was not measured, although the contrast amount was almost identical in both groups.
Pharmacological intervention studies

There is also some controversy whether the treatment of the asymptomatic hyperuricaemia would be beneficial regarding kidney function. Although Campion et al. [5] in light of the relatively low risk for poor outcomes they observed, supported conservative management of asymptomatic hyperuricaemia, other studies confirmed improvement of renal function after proper treatment.

Siu et al. [17] performed a prospective, randomized, controlled study to investigate the renal effects of allopurinol treatment in hyperuricaemic patients with chronic kidney disease. Serum uric acid levels decreased significantly in subjects treated with allopurinol, while serum uric acid level remained elevated throughout the study in the control group. In the treatment group, 84% of patients maintained stable renal function, while 16% had worsening of renal function, while in the control group only 53.8% had stable kidney function and 46.1% had worsening of the renal function. There was a significant decrease in the kidney function in the control group. Proteinuria was measured as an outcome of this study too, and at the end of the study period of 1 yr no statistical difference between the two groups was seen. The reason for this could be that all patients had established renal diseases with long-standing impaired renal function. Structural damage to the arteries and kidneys had occurred and proteinuria probably was multifactorial in pathogenesis. In this study, anti-hypertensive agents were used in the treatment of hypertension and although there were no differences in the use of angiotensin-converting enzyme/angiotensin receptor antagonists in both studied groups during all the study period, the beneficial effect contributed by the anti-hypertensive medications in the preservation of kidney function could not be completely ruled out.

Neal et al. [18] in a study of hyperuricaemia in liver transplant patients indirectly observed that the serum creatinine improved significantly in the eight patients with gout and 10 patients with hyperuricaemia without gout after the treatment with allopurinol over a median period of 3 months. This improvement of serum creatinine in hyperuricaemic patients suggests that hyperuricaemia contributed to renal dysfunction.

Although it could be argued that the effect of lowering serum uric acid in the context of established renal disease or gout might be different than that in asymptomatic hyperuricaemia, given the low incidence of renal dysfunction in the general population an extraordinarily large study will be needed to test the hypothesis in the latter population. Another question this study raises is whether the observed benefits of allopurinol are mediated through uric acid reduction or by some other mechanism.

Discussion

Multiple laboratory experiments done in the last decade suggested a pathogenic role of uric acid in the kidney dysfunction and different possible mechanisms of action. Hyperuricaemia was induced in rats by providing low doses of oxonic acid, a uricase inhibitor, which led to mild hyperuricaemia without intrarenal crystal deposition [19]. It was observed that subtle interstitial renal injury developed, which was associated with activation of the renin angiotensin system (RAS) and development of hypertension. Also an afferent arteriolaropathy was observed, which was independent of changes in blood pressure. This afferent arteriolaropathy is caused by direct effect of uric acid in induction of the vascular smooth muscle cell (VSMC) proliferation and by activation of the RAS. VSMCs show de novo expression of COX-2 messenger RNA after incubation with uric acid. COX-2 expression correlated with both uric acid levels and with the degree of the VSMC proliferation. When thickening of the afferent arterioles and infiltration of the macrophages in the vascular wall are induced then the preglomerular vasculopathy causes renal injury by causing ischaemia in the post-glomerular circulation [20]. Another mechanism of pathogenesis proposed was that hyperuricaemia inhibits nitric oxide system in the kidney and increases endothelin-1 levels, contributing this way to the vasoconstriction that reduces renal medullary blood flow inducing renal dysfunction [21]. In other experimental studies, it was found that hyperuricaemia accelerated cyclosporin-induced vascular injury and interstitial renal disease [22]. This exacerbation was associated with increased activation of RAS and the blockade of specific nitric oxide pathways (Fig. 1). The pathogenic mechanism of uric acid in the progression of chronic kidney disease was studied in remnant kidney (RK) rats (equivalent of chronic renal disease). It was shown that glomerulosclerosis and interstitial fibrosis were more common in RK + OA rats than in the RK alone. Allopurinol prevented the increase in both glomerulosclerosis and interstitial fibrosis. Also the number of smooth muscle cells in pre-glomerular arteries in RK + OA rats was higher compared with the RK rats with comparable blood pressure, suggesting that the increase in blood pressure in RK + OA rats does not account for the differences observed in vascular injury [19, 20].

While the data summarized above suggest that the link between hyperuricaemia and renal dysfunction is likely to be independent and consistent across studies, the question of causality requires more rigorous benchmarks. Sir Bradford Hill has suggested a checklist of study characteristics that suggest a causal relationship between environmental factors and disease. We applied these criteria to hyperuricaemia and renal disease and judged how well each criterion is met:

(i) Strength of association between hyperuricaemia and renal dysfunction: moderate to high.
(ii) Dose-dependence: modest. Few studies had the range of serum uric acid and adequate number of events in all these categories in order to establish dose dependency.
(iii) Consistency: moderate to high consistency across disparate populations.
(iv) Specificity: moderate. Satisfaction of this criterion means that after exclusion of other risk factors for kidney disease, uric acid still needs to remain a risk for development or progression of kidney disease; but as mentioned in the Results section, although an effort was done in these studies to exclude all other risk factors for kidney disease, still some of the confounding factors could not be excluded.
(v) Temporal relation: moderate to high. Elevated uric acid preceded renal dysfunction in all the longitudinal studies that we reviewed.

(vi) Biological plausibility: moderate. A plausible biological mechanism linking hyperuricaemia and renal dysfunction exists.

(vii) Coherence: modest to moderate. This theory is coherent with knowledge. However, given the link between existing renal dysfunction and consequent hyperuricaemia, the 'chicken-or-egg' question is not entirely ruled out.

(viii) Experiment: moderate to high. Treatment of hyperuricaemia in rats and humans resulted in improvement in renal function.

(ix) Analogy: modest. A good analogy of hyperuricaemia–renal dysfunction is not available; a close one might be that between hyperglycaemia and renal dysfunction; high levels of the latter are associated with worse renal outcomes.

Conclusion

Based on our review of literature, we conclude that serum uric acid can be a useful marker for worsening renal function in ‘healthy’ individuals as well as those with specific renal diseases. One does not need to prove causality in order to leverage the prognostic utility of this simple blood test. Strength of literature does not permit recommendation for uric acid reduction treatment for individuals, especially those without renal dysfunction. The prevalence of hyperuricaemia has been increasing over time in most of the developed nations and more research on the impact of hyperuricaemia and its treatment is warranted.

Disclosure statement

E.K. has received grant funding from TAP pharmaceuticals and currently sits on the advisory board and holds stocks in Savient Pharmaceuticals. The other author has declared no conflicts of interest.

References