World Journal of Nephrology

Online Submissions: http://www.wjgnet.com/esps/
wjnephrol@wjgnet.com
doi:10.5527/wjn.v2.i2.17

World J Nephrol 2013 May 6; 2(2): 17-25
ISSN 2220-6124 (online)

EDITORIAL

Uric acid and chronic kidney disease: A time to act?

Gianni Bellomo

Gianni Bellomo, Department of Nephrology, San Giovanni Battista Hospital, 06034 Foligno, Italy
Author contributions: Bellomo G solely contributed to this manuscript.
Correspondence to: Gianni Bellomo, MD, Department of Nephrology, San Giovanni Battista Hospital, Via Arcamone 1, 06034 Foligno, Italy. assidial@tin.it
Telephone: +39-742-3397083 Fax: +39-742-3397083
Received: February 7, 2013 Revised: March 25, 2013
Accepted: April 10, 2013
Published online: May 6, 2013

Abstract

A role for uric acid in the pathogenesis and progression of renal disease had been proposed almost a century ago, but, too hastily dismissed in the early eighties. A body of evidence, mostly accumulated during the last decade, has led to a reappraisal of the influence of uric acid on hypertension, cardiovascular, and renal disease. The focus of this review will be solely on the relationship between serum uric acid and renal function and disease. We will review experimental evidence derived from animal and human studies, evidence gathered from a number of epidemiological studies, and from the few (up to now) studies of uric-acid-lowering therapy. Some space will be also devoted to the effects of uric acid in special populations, such as diabetics and recipients of kidney allografts. Finally we will briefly discuss the challenges of a trial of uric-acid-lowering treatment, and the recent suggestions on how to conduct such a trial.

Key words: Uric acid; Urate; Chronic kidney disease; Allopurinol; Febuxostat; Diabetes; Renal transplantation

Core tip: The evidence presented so far, derived from experimental, epidemiological, and a few, small, intervention studies, points towards a role for uric acid in the progression of chronic kidney disease and deterioration of renal function. However, conclusive proof, such as that coming from a randomized clinical trial, is lacking. Finally we will briefly discuss the challenges of a trial of uric-acid-lowering treatment, and the recent suggestions on how to conduct such a trial.

Bellomo G. Uric acid and chronic kidney disease: A time to act? *World J Nephrol* 2013; 2(2): 17-25 Available from: URL: http://www.wjgnet.com/2220-6124/full/v2/i2/17.htm DOI: http://dx.doi.org/10.5527/wjn.v2.i2.17

INTRODUCTION

Recent evidence, accumulated in the last decade, has led to a reappraisal of the role of uric acid (UA), in the deterioration of renal function and progression of chronic kidney disease (CKD). In this review, after providing a background concerning UA physiology, we will focus on evidence deriving from experimental, epidemiological and intervention studies linking UA to renal disease; we will also briefly review the role of UA in special populations, such as patients with diabetes and those with solid organ transplantation. In this review, we will use (although not completely correct) the terms urate and uric acid interchangeably.

PHYSIOLOGY OF UA

UA, an organic compound comprised of carbon, nitrogen, oxygen and hydrogen, is the oxidation end-product of purine metabolism in man and higher primates. Its elimination is urinary for approximately 70% and for the remaining part occurs through the gastroenteric tract. In most other mammals, with the exception of the Dalmatian dog, the enzyme uricase (urate oxidase) further oxidates UA into allantoin, a more soluble molecule. However, in man and higher primates, mutations in the uricase gene occurred during evolution and, making the enzyme non-functional, resulted in higher levels of serum UA in hominids than in other mammals[1]. The vari-

Table 1 Causes of hyperuricemia

Drugs: Diuretics, salicylates, pirazinamide, cyclosporine, nicotinic acid
Diet: Excess intake of purine rich foods, such as animal internal organs, sweetbreads, anchovies, sardines, liver, beef kidneys, brains, meat extracts, herring, mackerel, game meats, beer and alcoholic beverages
High dietary fructose intake
Ketogenic diet
Starvation
Reduced excretion due to chronic kidney disease
Malignancies, polycythaemia vera, haemolytic anaemias and other conditions with a rapid cellular turnover
Genetic causes: Mutations in enzymes involved in purine metabolism, such as xanthine oxidase, urate transporter/channel, organic anion transporters 1 and 3 and urate transporter 1, UMOD associated renal diseases, phosphofructokinase deficiency
Lead toxicity

ability in serum UA levels is multifactorial and influenced by both environmental and genetic factors[2]. As already mentioned, renal elimination accounts for the disposal of the greatest part of UA daily load. Dietary factors, such as purine intake, may also be important determinants of serum UA levels. Serum UA can also rise due to high dietary fructose intake or reduced excretion by diseased kidneys[3]. Table 1 displays the principal causes of hyperuricemia in man.

Renal handling of UA is complex: in humans, only 5%-10% of the filtered UA is finally excreted, the largest part being reabsorbed at the tubular level, mostly by the proximal convoluted tubule. Earlier studies had suggested that UA is almost completely reabsorbed and that the amount excreted by the kidney results from active tubular secretion. However, recent evidence suggests that secretion plays a negligible role, and that excreted UA represents the amount filtered, escaping reabsorption[4]. Since UA is poorly soluble, it must be transported across cell membranes. Recently, four protein complexes that may act as UA transporters across the tubular cell membranes, have been identified: urate transporter/channel (UAT), two members of the family of organic anion transporters (OAT1 and OAT3) related to the tubular secretion, and urate transporter 1 (URAT1), which is the main protein responsible for tubular reabsorption, located at the apical membrane of the proximal tubular cells[5-14]. Although filtered UA is reabsorbed mainly *via* the URAT1 (coded by SLC22CA12), to a lesser extent it may be also secreted directly into the tubular lumen *via* the multidrug resistance peptide 4 pump[14]. Single nucleotide polymorphisms in URAT1, may be implicated in increased serum UA[15,16]. Accordingly, several mutations in *SLC22A12* gene have been associated with primary gout[16,17]. It has also been reported that the mutation of 5-methylenetetrahydrofolate reductase C677T may contribute to increased levels of serum UA in both genders[18]. Although genetic factors affecting UA metabolism are mostly unknown, mutations in all of the proteins involved in the synthesis and secretion of urate, especially xanthine oxidase (XO) inhibitor, URAT1, MRP4, OAT1, and OAT3 could potentially be involved and may prove interesting targets for future drug development[14].

EXPERIMENTAL STUDIES

Using a rat animal model in which hyperuricemia was induced by the administration of the uricase inhibitor oxonic acid, a renal vascular disease that includes cortical vasoconstriction, afferent arteriolar swelling, and glomerular hypertension has been induced[19,20]. These physiological abnormalities were at least partially reversible by the administration of the XO inhibitor febuxostat[21]. Several mechanisms have been postulated and are under investigation for explaining these perceived endothelial abnormalities induced by elevated serum UA. Incubation of vascular smooth muscle cells with uric acid has been found to stimulate proliferation, angiotensin Ⅱ production, and oxidative stress. These changes were reversed by the addition of captopril or losartan, which suggested an effect mediated through the renin-angiotensin system[22]. Hemodynamic abnormalities found in the hyperuricemic rat model were reversed by the administration of a superoxide scavenger, lending additional support to a link between elevated urate levels and damage induced by reactive-oxygen species (oxidative stress)[23]. Alterations in the expression of endothelin-1[24], which has been consistently associated with cardiovascular disease, have also been postulated as a potential mechanism of an association between hyperuricemia and cardiovascular conditions.

Endothelin-1 exerts a powerful vasoconstrictive effect by binding to the receptors ET-A and ET-B in human vascular cells[24]. How urate, known as an extracellular molecule, gains entry into vascular endothelial cells is still unknown but is possibly related to the demonstrated capacity of afferent renal arterioles to express URAT1[25]. This molecule is a urate-anion exchange transporter, expression of which had been previously described only in the renal tubular epithelium. The presence of URAT1 in endothelial cells may allow for explanations of intracellular effects of urate.

From a pathological standpoint, in hyperuricemic rats, light microscopy (PAS staining) of the kidney shows minor, non specific, changes consisting of tubular dilatation and atrophy in the renal cortex[19] and some glomerular sclerosis. However, on careful examination, one can also observe thickening of the afferent arterioles and some interlobular arteries, with sparing of the larger vessels.

Table 2 Epidemiological studies linking uric acid to chronic kidney disease

Ref.	Numerosity	Major findings
Madero *et al*[28]	840	CKD 3–4 and uric acid correlate with death but not with ESRD
Domronggkitchaiporn *et al*[29]	3499	Hyperuricemia (> 6.29 mg/dL) associated with increased odds (1.68) of reduced renal function
Iseki *et al*[30]	48177	Uric acid > 8 mg/dL increased CKD risk three-fold in men and 10-fold in women
Obermayr *et al*[31]	21475	Uric acid > 7 mg/dL increased risk of CKD 1.74-fold in men and 3.12-fold in women
Hsu *et al*[32]	177750	Higher uric acid quartile conferred 2.14-fold increased risk of ESRD over 25 years
Borges *et al*[33]	385	Elevated uric acid associated with 2.63-fold increased risk of CKD in hypertensive women
Chen *et al*[34]	5722	Uric acid associated with prevalent CKD in elderly
Sturm *et al*[35]	227	Uric acid predicted progression of CKD only in unadjusted sample
Weiner *et al*[36]	13338	Each 1 mg/dL increase in uric acid increased risk of CKD 7%–11%
Chonchol *et al*[37]	5808	Uric acid strongly associated with prevalent but weakly with incident CKD
Bellomo *et al*[38]	900	Each 1 mg increase in uric acid associated with 1.28 odds ratio of reduced e-GFR at 5 years
Ben-Dov *et al*[39]	2449	Uric acid > 6.5 mg/dL in men and > 5.3 mg/dL in women, associated with hazard ratios of 1.36 for all-cause mortality and 2.14 for incident CKD

CKD: Chronic kidney disease; ESRD: End stage renal disease; e-GFR: Estimated glomerular filtration rate.

In humans, besides crystal deposition nephropathy, which is rare, chronic hyperuricemia is characterized by crystal-independent renal damage. As early as in 1928, Gudzent 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[26]. This lesion consists of interstitial fibrosis, glomerulosclerosis and renal arteriolosclerosis and arterial wall thickening, caused by intimal fibrosis, which resembles the lesion observed in hyperuricemic rats. Similar, non-specific, alterations also occur in patients with familial juvenile hyperuricemic nephropathy type 1 (FJHN-1), clinically characterized by the early onset of hyperuricemia, and sometimes gout, leading to end stage renal disease (ESRD) by the 4th and 7th decade of life[27]; FJHN-1 is associated with mutations in the uromodulin gene, and is inherited in an autosomal dominant manner.

EPIDEMIOLOGY

Table 2 summarizes the most relevant studies investigating the relationship between serum UA levels and renal function, incidence and/or progression of renal disease[28-39], which generally support a significant role of UA, although not all the studies are concordant in this respect[28,37]. A recently published study has clarified the contribution of urate as an independent risk factor in the development of incident stage 3 CKD, defined as a calculated glomerular filtration rate $\leqslant$ 60 mL/min[31]. The study divided the participants (n = 21475 healthy volunteers followed for a median period of time of 7 years) into three categories of serum urate levels: < 7.0 mg/dL, 7.0 to 9.0 mg/dL, and > 9.0 mg/dL. After adjustment for identified confounders, both higher categories of serum urate were associated with significant risks of developing stage 3 CKD [odds ratio = 1.74 (95%CI: 1.45-2.09) for the intermediate category of serum urate, odds ratio = 3.12 (95%CI: 2.29-4.25) for the higher category of serum urate]. Additional data showed that the adjusted odds ratio increased linearly up to a level of serum urate approaching 7 mg/dL, after which the slope of the curve increased. This implied considerably greater risk for developing the outcome at serum urate levels > 7 mg/dL. A large study including 177570 individuals for a total of 5275957 person-years of follow-up, showed UA to be associated with an increased hazard ratio for incident ESRD[32]. Our group, also showed, in 900 healthy normotensive subjects, an inverse relation between serum UA and epidermal growth factor receptor (e-GFR) at 5 years, and an increased risk of e-GFR reduction at follow-up, in hyperuricemic subjects[38]. Finally, in the recently published Jerusalem Lipid Research Clinic Cohort Study[39], the authors demonstrated an association between serum UA and long-term all-cause mortality, incident chronic and acute renal failure. Finally, on the other side, a recent study by Madero *et al*[28], performed in patients with advanced CKD, found a significant association between serum UA and mortality, but no independent association with the risk of progression to ESRD.

SPECIAL POPULATIONS-DIABETES

In diabetes, the effect of serum UA levels on both the initiation and progression of diabetic nephropathy has recently been evaluated by several prospective observational studies. In a study from the Steno Diabetes Center, where a cohort of patients with type-1 diabetes was followed up from onset of diabetes and for a median of 18 years, serum UA was measured 3 years after onset of diabetes before any patient developed microalbuminuria[40]. At that time, all patients had serum UA levels within the normal range, however, the mean level of serum UA was significantly higher in those who eventually progressed to overt diabetic nephropathy, that is, persistent macroalbuminuria, compared to those who remained normoalbuminuric or who later progressed to microalbuminuria only. When segregating the patients according to quartiles of UA measured close to onset of diabetes and before development of micro- or macroalbuminuria, there was a significantly higher proportion of patients who developed overt nephropathy among those with serum UA levels in the highest quartile (4.2 mg/dL, still within the nor-

mal range) and with cumulative incidence of persistent macroalbuminuria of 22.3% as compared with the 9.5% among patients with uric acid in the three lower quartiles. In a Cox proportional hazard model including gender and age as fixed covariates, UA was independently associated with subsequent development of persistent macroalbuminuria (hazard ratio, 2.37 per each 1.7 mg/dL increase in UA level). Adjustment for confounders did not change the estimate significantly. In a recent study, Jalal *et al*[41] confirmed these findings by showing that serum UA was a strong predictor of the development of albuminuria in a prospective follow-up study of 324 patients with type-1 diabetes who were followed up for 6 years. The risk of micro- or macroalbuminuria was found to increase by 1.8-fold per each 1 mg/dL increase in serum UA. In this study, no separate analysis of patients either remaining in the microalbuminuric range or progressing further to macroalbuminuria was performed, because these groups were pooled together in the analysis. These two studies performed early in the course of type-1 diabetes, concurrently found serum UA to be significantly, after adjustment for confounders, associated with later development of persistent macroalbuminuria, thereby supporting the hypothesis that UA may be involved in the pathogenesis of microvascular complications in diabetes. However, a clear association with development of persistent microalbuminuria only, has not yet been established. In their study, Jalal *et al*[41] reported micro- and macroalbuminuria as a combined endpoint, whereas Hovind *et al*[40] were not able to find an association, which may be explained by the observation that patients progressing to microalbuminuria may be a more heterogeneous group than previously assumed, as not all patients progress to nephropathy. In an observational, cross-sectional study, Rosolowsky *et al*[42] found serum UA in the high-normal range to be associated with impaired renal function, in patients with type-1 diabetes and normo- or microalbuminuria. A recently published follow-up of a selected subgroup of the patients (excluding 183 patients with very low urinary albumin excretion rate), confirmed the results, extending them to show a clear dose-response relationship between serum UA and early decline in renal function evaluated by the serum concentration of cystatin C in 355 patients followed up for 4 to 6 years[43]. However, the study did not find any association between serum UA and progression or regression of urinary albumin excretion rate. Quite surprisingly, the significant decline in kidney function observed before proteinuria developed in 79 of 355 patients. These findings are discordant with those from a Japanese population study[44], where no association between UA and progression of diabetic kidney disease in 1622 Japanese patients with diabetes and chronic kidney disease was found. In the latter study, however, the patients had more advanced kidney disease.

As far as type 2 diabetes is concerned, despite its increasing worldwide prevalence, and its leading role as a cause of end stage renal disease, few studies of the effect of UA on the progression of renal dysfunction in this population of patients have been conducted. In a post hoc analysis of 1342 patients with type 2 diabetes mellitus and nephropathy participating in the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan Trial[45], Zoppini *et al*[46] estimated that 22% (95%CI: 6-35) of the renoprotective effect of losartan was attributable to its urate-lowering effect. In another study, including 1449 patients with type 2 diabetes and preserved baseline renal function, followed for 5 years, hyperuricemia was associated with an adjusted odds ratio of 2.1 (95%CI: 1.16-3.76) for developing incident CKD. Finally, a recent study conducted on 1213 type 2 diabetics in Japan[47], after a 12-mo follow-up showed an increased incidence of incident nephropathy (odds ratio = 2.79, 95%CI: 1.90-4.12).

UA AND RENAL TRANSPLANTATION

The relationship between serum UA and renal function and graft survival in kidney transplant recipient is complex and controversial. Hyperuricemia is a common complication in organ transplant recipients, and frequently associated with chronic cyclosporine immunosuppressive therapy. Risk factors for hyperuricemia include decreased GFR, diuretic use, and preexistent history of hyperuricemia. The influence of hyperuricemia in patient and graft survival is unclear because uric acid is not usually considered a common risk factor for cardiovascular disease that affects graft and patient survival. Table 3 summarizes the most relevant studies exploring this relationship[48-59]. Although most studies tend to favour an influence of UA on graft function and survival, there are notable exceptions: for instance, Meier-Kriesche *et al*[55], reviewing their data from the SYMPHONY Study, in which a cohort of 1645 was followed-up for 3 years, found that the association of baseline UA with follow-up e-GFR, disappeared when adjusting for baseline e-GFR. Conversely, in the study by Haririan *et al*[56], after a mean 68 mo follow-up, hyperuricemia was associated with a 1.26 (95%CI: 1.03-1.53) hazard ratio of graft loss. Kim *et al*[58] recently reported their review of patients transplanted between 1990 and 2009, and they observed that hyperuricemia conferred an 1.45 ($P < 0.001$)hazard ratio of graft loss. Other studies have yielded conflicting results, although those with a longer follow-up, and those assessing graft survival (rather than e-GFR) as an end-point, tend to favour an adverse effect of hyperuricemia. The reason for the discrepancies among studies are not completely clear, however differences in the definition of hyperuricemia, duration of follow-up, end-points evaluated, and in adjustment for confounders and comorbidity may have played a role.

URATE LOWERING THERAPY AND RENAL FUNCTION

Among drugs capable of lowering serum UA levels (Table 4)[60], uricosuric agents, with the possible excep-

Table 3 Studies investigating the association between serum uric acid and renal function/graft survival in patients with kidney transplantation

Ref.	Numerosity	Major findings
Gerhardt *et al*[48]	375	Hyperuricemia (> 8.0 mg/dL in men and > 6.2 mg/dL in women), associated with reduced graft survival
Armstrong *et al*[49]	90	UA independent predictor of follow-up e-GFR, but not of e-GFR change over time
Akgul *et al*[50]	133	No association found between serum UA and the development of chronic allograft nephropathy
Saglam *et al*[51]	34	Serum UA associated to development of cyclosporine A nephropathy (biopsy proven)
Akalin *et al*[52]	307	Hyperuricemia 6 mo after transplantation significantly associated with new cardiovascular events and graft dysfunction
Bandukwala *et al*[53]	405	Hyperuricemia associated with cardiovascular events, and, inversely with e-GFR
Karbowska *et al*[54]	78	Hyperuricemia associated with markers of endothelial dysfunction and inflammation
Meier-Kriesche *et al*[55]	1645	UA levels one month after transplantation not associated with follow-up e-GFR, after adjustment for baseline renal function
Haririan *et al*[56]	212	Serum UA during the first six months postransplant, is an independent predictor of graft survival
Boratyńska *et al*[57]	100	Serum UA not associated to graft survival during 30 mo of follow-up
Kim *et al*[58]	556	Serum UA levels affect graft function, even after adjustment for baseline e-GFR
Wang *et al*[59]	524	Retrospective study: UA significantly lower in patients with longer graft survival

e-GFR: Estimated glomerular filtration rate; UA: Uric acid.

Table 4 Urate lowering drugs

Pharmacologic options for the treatment of hyperuricemia
Xanthine-oxidase inhibitors: Allopurinol, febuxostat
Uricosuric agents: Probenecid, sulfinpyrazone, benzbromarone
Uricase: Rasburicase, pegloticase
Drugs and contrast media with hypouricemic properties, not primarily intended for the treatment of hyperuricemia
Acetohexamide, azauridine, chlorprothixene, dicumarol, estrogens, fenofibrate, glyceryl guaiacolate, iopanoic acid, losartan,meglumine iodapamide, phenylbutazone, salicylates and other NSAIDs, sodium diatrizoate, trimetoprim-sulfamethoxazole

NSAIDs: Nonsteroidal anti-inflammatory drugs.

tion of losartan, are mostly not indicated, or ineffective, in patients with CKD and/or kidney stones, uricase and its analogues are expensive, must be administered parenterally, and have important side effects; thus, long-term treatment of hyperuricemia relies mainly on xantine-oxidase inhibitors.

Only a few studies evaluating the effects of urate lowering therapy in patients with CKD, or its influence on renal function, have been published (Table 5)[61-68]. Short-term studies suggest that lowering serum UA levels with allopurinol may have beneficial effects on renal function. In a retrospective study of 134 liver transplant recipients, Neal *et al*[61] evaluated eight patients with gout and 10 patients with asymptomatic hyperuricemia who received allopurinol. Over a median follow-up period of 3 mo, mean serum creatinine concentration decreased from 2.0 ± 0.2 to 1.8 ± 0.2 mg/dL (P = 0.01). Although these results are encouraging, the effect size is small, and the study has limitations (Table 4).

Although limited by its uncontrolled and non-randomized design, the study by Fairbanks *et al*[62], involving patients with FJHN, is important, for its long duration of follow-up, and for evaluating a chronic disease, characterized by hyperuricemia since childhood, and almost invariably evolving to ESRD later in life.

Siu *et al*[63] studied the effect of the lowering of serum UA level on progression of CKD in an open-label randomized, controlled trial of allopurinol (100-200 mg daily) for 12 mo in 54 patients with proteinuria > 0.5 g per day and creatinine > 1.4 mg/d. At baseline, mean serum creatinine concentrations in the allopurinol and control group were 1.65 ± 0.6 and 1.85 ± 0.7 mg/dL, respectively. After 12 mo, mean serum creatinine increased in the control arm, but remained unchanged in the allopurinol arm (Table 5). Allopurinol had no effect on proteinuria. Overall, 12% of patients in the allopurinol arm experienced worsening of kidney function, compared with 42% in the controls. This trial was also limited by inadequate power and its open-label study design.

In a very intriguing study, Goicoechea *et al*[65] randomized 113 patients with CKD (e-GFR < 60 mL/min per 1.73 m^2) to allopurinol 100 mg daily or no study medication. After 24 mo, e-GFR decreased by 3.3 ± 1.2 mL/min per 1.73 m^2 in the control group and increased by 1.3 ± 1.3 mL/min per 1.73 m^2 in the allopurinol group (P = 0.018). No differences in blood pressure between groups were reported. Fifteen of 56 patients in the control and seven of 57 patients in the allopurinol arm experienced a cardiovascular event (hazard ratio = 0.29, 95%CI: 0.09-0.86). Allopurinol was withdrawn in two patients as a result of gastrointestinal symptoms. No other serious adverse events were reported. Kao *et al*[66] assessed the effects of allopurinol 300 mg daily on cardiovascular surrogate measures over 9 mo in 53 patients with stage 3 CKD and left ventricular hypertrophy in a double-blind, placebo-controlled RCT. Compared with placebo, treatment with allopurinol was associated with a reduction in left ventricular mass index, and an improvement of the central

Table 5 Studies of uric-acid-lowering therapy in patients with chronic kidney disease

Ref.	Study population	Intervention	Study findings	Limitations
Neal *et al*[61], 2001	18 liver transplant recipients with gout (n = 8) and hyperuricemia (n = 10)	Allopurinol (dose not stated)	Mean serum creatinine decreased from 2.0 to 1.8 mg/dL over a median period of 3 mo	Retrospective study; indication bias; small sample size
Fairbanks *et al*[62], 2002	27 patients with FJHN	Allopurinol (dose not stated)	Early treatment associated with slower decline of renal function	Case series, single center, partially inadequate controls
Siu *et al*[63], 2006	54 CKD patients with proteinuria > 0.5 g per day, serum creatinine > 1.4 mg/dL and serum uric acid > 7.6 mg/dL	Allopurinol 100-200 mg daily or their usual therapy for 12 mo	Lower serum creatinine in the allopurinol arm than the control arm (2.0 ± 0.9 *vs* 2.9 ± 0.9 mg/dL; P = 0.08) and no differences in effect on proteinuria (2.53 ± 4.85 g per day *vs* 2.16 ± 1.93 g per day; P = NS)	Small sample size, open-label design, short duration of follow-up
Shelmadine *et al*[64], 2009	12 prevalent adult hemodialysis patients	Allopurinol 300 mg twice daily for 3 mo	Reduction in LDL cholesterol by 0.36 μmol/L (14 mg/dL) (P = 0.04)	No control arm; small sample size; no safety data; no data on hemodynamic parameters; dose of allopurinol higher than recommended
Goicoechea *et al*[65], 2010	113 CKD patients with eGFR < 60 mL/min per 1.73 m^2	Allopurinol 100 mg daily or no study medication for 24 mo	Allopurinol slowed the decline in eGFR (1.3 ± 1.3 mL/min per 1.73 m^2 *vs* –3.3 ± 1.2 mL/min per 1.73 m^2); no effect on BP	Small sample size; open label and single-center study; allocation concealment unclear; assessor blinding unclear
Kao *et al*[66], 2011	53 stage 3 CKD patients with LVH	Allopurinol 300 mg daily or placebo for 9 mo	Allopurinol reduced LVMI (–1.42 ± 4.67 g/m^2 *vs* 1.28 ± 4.45 g/m^2) and improved brachial artery FMD (1.26% ± 3.06% *vs* -1.05% ± 2.84%); improved augmentation index (P = 0.015)	Surrogate end-points only
Momeni *et al*[67], 2010	40 patients with type 2 diabetes and overt nephropathy (proteinuria > 500 mg/24 h, and serum creatinine < 3.0 mg/dL)	Allopurinol 100 mg or placebo	Treated patients had lower serum UA and 24 h proteinuria after 4 mo of follow-up	Small sample size, single-center, short follow-up, blinding unclear
Kanbay *et al*[68], 2011	30 hyperuricemic subjects *vs* 37 hyperuricemic and 30 normouricemic controls	4 mo treatment with allopurinol, 300 mg *vs* no study medication	Allopurinol treated patients had increased e-GFR with respect to baseline	Small sample size, short duration, blinding unclear

FJHN: Familial juvenile hyperuricemic nephropathy; CKD: Chronic kidney disease; e-GFR: Estimated glomerular filtration rate; LDL: Low-density lipoprotein; LVH: Left ventricular hypertrophy; FMD: Flow-mediated dilation; LVMI: Left ventricular mass index; UA: Uric acid.

Augmentation index, an indirect measure of arterial rigidity. In a small controlled study of forty type 2 diabetics with overt nephropathy, Momeni *et al*[67] observed a reduction of 24-h proteinuria, following 4-mo treatment with allopurinol (100 mg/d). Finally, Kanbay *et al*[68] in a small controlled trial, along a 4-mo observation period, found that healthy hyperuricemic subjects treated with allopurinol 300 mg, at the end of follow-up, had increased e-GFR, improved endothelial function, and decreased systolic BP with respect to baseline, whereas no change was observed in hyperuricemic and normouricemic controls.

PRACTICAL CONSIDERATIONS

While there exists a general consensus on treating hyperuricemia in patients with gout, in order to keep serum UA levels below 6.0 mg/dL[69], the dilemma whether to treat or not, asymptomatic hyperuricemia remains unresolved. The matter is further complicated by the use of different definitions for hyperuricemia in the various studies, and thus, it is difficult to identify a threshold for serum UA at which treatment should be initiated. In addition, the risk of developing CKD appears to rise as a continuum with increasing serum UA, rather than displaying a threshold effect. Nonetheless, based on the available epidemiologic studies, it seems reasonable to treat UA levels above 7.0 mg/dL in men, and above 6.0 mg/dL in women, with possibly, a lower threshold in people of Asian descent.

CONCLUSION

The evidence presented so far, derived from experimental, epidemiological, and a few, small, intervention studies, points towards a role for UA in the progression of CKD and deterioration of renal function. However, conclusive proof, such as that coming from a randomized clinical trial, is lacking.

Such a trial presents considerable challenges, nonetheless, it is feasible, as recently indicated by Badve *et al*[70], who have proposed a design for such a trial of uric-acid-lowering therapy (with either allopurinol or febuxostat, which has a better safety profile) for slowing the progression of CKD; briefly, they suggest a two-phase trial, with, first, a pilot study, evaluating surrogate end-points

(change in UA level, GFR, proteinuria, systolic and diastolic BP, pulse wave velocity), including a limited number of patients (a few hundredths) and duration of follow-up (24 mo). The results of this pilot studies would help lay out the background (feasibility, power, design) for a subsequent outcome trial, using hard end-points, such as decrease in e-GFR of 50% (or > 25 mL/min per m^2), ESRD requiring renal replacement therapy, and incident cardiovascular events as a secondary outcome. We fully endorse the suggestions of Badve, and heartily hope such a trial will be funded and performed, so that one more effective tool for halting or slowing the progression of renal disease might be supplied to our patients.

REFERENCES

1 **Watanabe S**, Kang DH, Feng L, Nakagawa T, Kanellis J, Lan H, Mazzali M, Johnson RJ. Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. *Hypertension* 2002; **40**: 355-360 [PMID: 12215479 DOI: 10.1161/01.HYP]

2 **Nath SD**, Voruganti VS, Arar NH, Thameem F, Lopez-Alvarenga JC, Bauer R, Blangero J, MacCluer JW, Comuzzie AG, Abboud HE. Genome scan for determinants of serum uric acid variability. *J Am Soc Nephrol* 2007; **18**: 3156-3163 [PMID: 17978310 DOI: 10.681/ASN.2007040426]

3 **Johnson RJ**, Segal MS, Sautin Y, Nakagawa T, Feig DI, Kang DH, Gersch MS, Benner S, Sánchez-Lozada LG. Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. *Am J Clin Nutr* 2007; **86**: 899-906 [PMID: 17921363]

4 **Pascual E**, Perdiguero M. Gout, diuretics and the kidney. *Ann Rheum Dis* 2006; **65**: 981-982 [PMID: 16837492 DOI: 10.1136/ard.2005.049023]

5 **Burckhardt BC**, Burckhardt G. Transport of organic anions across the basolateral membrane of proximal tubule cells. *Rev Physiol Biochem Pharmacol* 2003; **146**: 95-158 [PMID: 12605306 DOI: 10.1007/s10254-002-0003-8]

6 **Sekine T**, Watanabe N, Hosoyamada M, Kanai Y, Endou H. Expression cloning and characterization of a novel multispecific organic anion transporter. *J Biol Chem* 1997; **272**: 18526-18529 [PMID: 9228014 DOI: 10.1074/jbc.272.30.18526]

7 **Sweet DH**, Wolff NA, Pritchard JB. Expression cloning and characterization of ROAT1. The basolateral organic anion transporter in rat kidney. *J Biol Chem* 1997; **272**: 30088-30095 [PMID: 9374486 DOI: 10.1074/jbc.272.48.30088]

8 **Reid G**, Wolff NA, Dautzenberg FM, Burckhardt G. Cloning of a human renal p-aminohippurate transporter, hROAT1. *Kidney Blood Press Res* 1998; **21**: 233-237 [PMID: 9762842 DOI: 10.1159/000025863]

9 **Hosoyamada M**, Sekine T, Kanai Y, Endou H. Molecular cloning and functional expression of a multispecific organic anion transporter from human kidney. *Am J Physiol* 1999; **276**: F122-F128 [PMID: 9887087]

10 **Enomoto A**, Takeda M, Shimoda M, Narikawa S, Kobayashi Y, Kobayashi Y, Yamamoto T, Sekine T, Cha SH, Niwa T, Endou H. Interaction of human organic anion transporters 2 and 4 with organic anion transport inhibitors. *J Pharmacol Exp Ther* 2002; **301**: 797-802 [PMID: 12023506 DOI: 10.1124/jpet.301.3.797]

11 **Kusuhara H**, Sekine T, Utsunomiya-Tate N, Tsuda M, Kojima R, Cha SH, Sugiyama Y, Kanai Y, Endou H. Molecular cloning and characterization of a new multispecific organic anion transporter from rat brain. *J Biol Chem* 1999; **274**: 13675-13680 [PMID: 10224140 DOI: 10.1074/jbc.274.19.13675]

12 **Cha SH**, Sekine T, Fukushima JI, Kanai Y, Kobayashi Y, Goya T, Endou H. Identification and characterization of human organic anion transporter 3 expressing predominantly in the kidney. *Mol Pharmacol* 2001; **59**: 1277-1286 [PMID: 11306713]

13 **Cha SH**, Sekine T, Kusuhara H, Yu E, Kim JY, Kim DK, Sugiyama Y, Kanai Y, Endou H. Molecular cloning and characterization of multispecific organic anion transporter 4 expressed in the placenta. *J Biol Chem* 2000; **275**: 4507-4512 [PMID: 10660625 DOI: 10.1074/jbc.275.6.4507]

14 **Enomoto A**, Kimura H, Chairoungdua A, Shigeta Y, Jutabha P, Cha SH, Hosoyamada M, Takeda M, Sekine T, Igarashi T, Matsuo H, Kikuchi Y, Oda T, Ichida K, Hosoya T, Shimokata K, Niwa T, Kanai Y, Endou H. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. *Nature* 2002; **417**: 447-452 [PMID: 12024214]

15 **Hediger MA**, Johnson RJ, Miyazaki H, Endou H. Molecular physiology of urate transport. *Physiology* (Bethesda) 2005; **20**: 125-133 [PMID: 15772301 DOI: 10.1152/physiol.00039.2004]

16 **Shima Y**, Teruya K, Ohta H. Association between intronic SNP in urate-anion exchanger gene, SLC22A12, and serum uric acid levels in Japanese. *Life Sci* 2006; **79**: 2234-2237 [PMID: 16920156 DOI: 10.1016/j.lfs.2006.07.030]

17 **Vázquez-Mellado J**, Jiménez-Vaca AL, Cuevas-Covarrubias S, Alvarado-Romano V, Pozo-Molina G, Burgos-Vargas R. Molecular analysis of the SLC22A12 (URAT1) gene in patients with primary gout. *Rheumatology* (Oxford) 2007; **46**: 215-219 [PMID: 16837472 DOI: 10.1093/rheumatology/kel205]

18 **Golbahar J**, Aminzadeh MA, Al-Shboul QM, Kassab S, Rezaian GR. Association of methylenetetrahydrofolate reductase (C677T) polymorphism with hyperuricemia. *Nutr Metab Cardiovasc Dis* 2007; **17**: 462-467 [PMID: 17010581]

19 **Sánchez-Lozada LG**, Tapia E, Avila-Casado C, Soto V, Franco M, Santamaría J, Nakagawa T, Rodríguez-Iturbe B, Johnson RJ, Herrera-Acosta J. Mild hyperuricemia induces glomerular hypertension in normal rats. *Am J Physiol Renal Physiol* 2002; **283**: F1105-F1110 [PMID: 12372787]

20 **Sánchez-Lozada LG**, Tapia E, Santamaría J, Avila-Casado C, Soto V, Nepomuceno T, Rodríguez-Iturbe B, Johnson RJ, Herrera-Acosta J. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. *Kidney Int* 2005; **67**: 237-247 [PMID: 15610247 DOI: 10.1111/j.1523-1755.2005.00074.x]

21 **Sánchez-Lozada LG**, Tapia E, Soto V, Avila-Casado C, Franco M, Zhao L, Johnson RJ. Treatment with the xanthine oxidase inhibitor febuxostat lowers uric acid and alleviates systemic and glomerular hypertension in experimental hyperuricaemia. *Nephrol Dial Transplant* 2008; **23**: 1179-1185 [PMID: 18048425 DOI: 10.1093/ndt/gfm783]

22 **Corry DB**, Eslami P, Yamamoto K, Nyby MD, Makino H, Tuck ML. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. *J Hypertens* 2008; **26**: 269-275 [PMID: 18192841 DOI: 10.1097/HJH.0b013e3282f240bf]

23 **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. *Am J Physiol Renal Physiol* 2008; **295**: F1134-F1141 [PMID: 18701632 DOI: 10.1152/ajprenal.00104.2008]

24 **Arai H**, Hori S, Aramori I, Ohkubo H, Nakanishi S. Cloning and expression of a cDNA encoding an endothelin receptor. *Nature* 1990; **348**: 730-732 [PMID: 2175396]

25 **Price KL**, Sautin YY, Long DA, Zhang L, Miyazaki H, Mu W, Endou H, Johnson RJ. Human vascular smooth muscle cells express a urate transporter. *J Am Soc Nephrol* 2006; **17**: 1791-1795 [PMID: 16775029 DOI: 10.1681/ASN.2006030264]

26 **Talbott JH**, Terplan KL. The kidney in gout. *Medicine* (Baltimore) 1960; **39**: 405-467 [PMID: 13775026]

27 **Bleyer AJ**, Hart PS. UMOD-Associated Kidney Disease. In: Pagon RA, Bird TD, Stephens K, editors. GeneReviews [In-

ternet]. Seattle (WA): University of Washington, Seattle, 1993
28 **Madero M**, Sarnak MJ, Wang X, Greene T, Beck GJ, Kusek JW, Collins AJ, Levey AS, Menon V. Uric acid and long-term outcomes in CKD. *Am J Kidney Dis* 2009; **53**: 796-803 [PMID: 19303683 DOI: 10.1053/j.ajkd.2008.12.021]
29 **Domrongkitchaiporn S**, Sritara P, Kitiyakara C, Stitchantrakul W, Krittaphol V, Lolekha P, Cheepudomwit S, Yipintsoi T. Risk factors for development of decreased kidney function in a southeast Asian population: a 12-year cohort study. *J Am Soc Nephrol* 2005; **16**: 791-799 [PMID: 15677313]
30 **Iseki K**, Ikemiya Y, Inoue T, Iseki C, Kinjo K, Takishita S. Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. *Am J Kidney Dis* 2004; **44**: 642-650 [PMID: 15384015 DOI: 10.1016/S0272-6386(04)00934-5]
31 **Obermayr RP**, Temml C, Gutjahr G, Knechtelsdorfer M, Oberbauer R, Klauser-Braun R. Elevated uric acid increases the risk for kidney disease. *J Am Soc Nephrol* 2008; **19**: 2407-2413 [PMID: 18799720 DOI: 10.1681/ASN.2008010080]
32 **Hsu CY**, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease: 25-year follow-up. *Arch Intern Med* 2009; **169**: 342-350 [PMID: 19237717 DOI: 10.1001/archinternmed.2008.605]
33 **Borges RL**, Hirota AH, Quinto BM, Ribeiro AB, Zanella MT, Batista MC. Uric acid as a marker for renal dysfunction in hypertensive women on diuretic and nondiuretic therapy. *J Clin Hypertens* (Greenwich) 2009; **11**: 253-259 [PMID: 19534022 DOI: 10.1111/j.1751-7176.2009.00101.x]
34 **Chen N**, Wang W, Huang Y, Shen P, Pei D, Yu H, Shi H, Zhang Q, Xu J, Lv Y, Fan Q. Community-based study on CKD subjects and the associated risk factors. *Nephrol Dial Transplant* 2009; **24**: 2117-2123 [PMID: 19193736 DOI: 10.1093/ndt/gfn767]
35 **Sturm G**, Kollerits B, Neyer U, Ritz E, Kronenberg F. Uric acid as a risk factor for progression of non-diabetic chronic kidney disease? The Mild to Moderate Kidney Disease (MMKD) Study. *Exp Gerontol* 2008; **43**: 347-352 [PMID: 18294794]
36 **Weiner DE**, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS. Uric acid and incident kidney disease in the community. *J Am Soc Nephrol* 2008; **19**: 1204-1211 [PMID: 18337481 DOI: 10.1681/ASN.2007101075]
37 **Chonchol M**, Shlipak MG, Katz R, Sarnak MJ, Newman AB, Siscovick DS, Kestenbaum B, Carney JK, Fried LF. Relationship of uric acid with progression of kidney disease. *Am J Kidney Dis* 2007; **50**: 239-247 [PMID: 17660025 DOI: 10.1053/j.ajkd.2007.05.013]
38 **Bellomo G**, Venanzi S, Verdura C, Saronio P, Esposito A, Timio M. Association of uric acid with change in kidney function in healthy normotensive individuals. *Am J Kidney Dis* 2010; **56**: 264-272 [PMID: 20385436 DOI: 10.1053/j.ajkd.2010.01.019]
39 **Ben-Dov IZ**, Kark JD. Serum uric acid is a GFR-independent long-term predictor of acute and chronic renal insufficiency: the Jerusalem Lipid Research Clinic cohort study. *Nephrol Dial Transplant* 2011; **26**: 2558-2566 [PMID: 21220750 DOI: 10.1093/ndt/gfq740]
40 **Hovind P**, Rossing P, Tarnow L, Johnson RJ, Parving HH. Serum uric acid as a predictor for development of diabetic nephropathy in type 1 diabetes: an inception cohort study. *Diabetes* 2009; **58**: 1668-1671 [PMID: 19411615 DOI: 10.2337/db09-0014]
41 **Jalal DI**, Rivard CJ, Johnson RJ, Maahs DM, McFann K, Rewers M, Snell-Bergeon JK. Serum uric acid levels predict the development of albuminuria over 6 years in patients with type 1 diabetes: findings from the Coronary Artery Calcification in Type 1 Diabetes study. *Nephrol Dial Transplant* 2010; **25**: 1865-1869 [PMID: 20064950 DOI: 10.1093/ndt/gfp740]
42 **Rosolowsky ET**, Ficociello LH, Maselli NJ, Niewczas MA, Binns AL, Roshan B, Warram JH, Krolewski AS. High-normal serum uric acid is associated with impaired glomerular filtration rate in nonproteinuric patients with type 1 diabetes. *Clin J Am Soc Nephrol* 2008; **3**: 706-713 [PMID: 18272826 DOI: 10.2215/CJN.04271007]
43 **Ficociello LH**, Rosolowsky ET, Niewczas MA, Maselli NJ, Weinberg JM, Aschengrau A, Eckfeldt JH, Stanton RC, Galecki AT, Doria A, Warram JH, Krolewski AS. High-normal serum uric acid increases risk of early progressive renal function loss in type 1 diabetes: results of a 6-year follow-up. *Diabetes Care* 2010; **33**: 1337-1343 [PMID: 20332356 DOI: 10.2337/dc10-0227]
44 **Hayashi T,** Babazono T, Nyumura I. Serum uric acid levels and progression of CKD in diabetic patients. J Am Soc Nephrol 2008; 19: 339A
45 **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; **58**: 2-7 [PMID: 21632472]
46 **Zoppini G**, Targher G, Chonchol M, Ortalda V, Abaterusso C, Pichiri I, Negri C, Bonora E. Serum uric acid levels and incident chronic kidney disease in patients with type 2 diabetes and preserved kidney function. *Diabetes Care* 2012; **35**: 99-104 [PMID: 22028277]
47 **Ito H**, Abe M, Mifune M, Oshikiri K, Antoku S, Takeuchi Y, Togane M. Hyperuricemia is independently associated with coronary heart disease and renal dysfunction in patients with type 2 diabetes mellitus. *PLoS One* 2011; **6**: e27817 [PMID: 22125626 DOI: 10.1371/journal.pone.0027817]
48 **Gerhardt U**, Grosse Hüttmann M, Hohage H. Influence of hyperglycemia and hyperuricemia on long-term transplant survival in kidney transplant recipients. *Clin Transplant* 1999; **13**: 375-379 [PMID: 10515217 DOI: 10.1034/j.1399-0012.1999.130502.x]
49 **Armstrong KA**, Johnson DW, Campbell SB, Isbel NM, Hawley CM. Does uric acid have a pathogenetic role in graft dysfunction and hypertension in renal transplant recipients? *Transplantation* 2005; **80**: 1565-1571 [PMID: 16371927 DOI: 10.1097/01.tp.0000183895.88572.13]
50 **Akgul A**, Bilgic A, Ibis A, Ozdemir FN, Arat Z, Haberal M. Is uric acid a predictive factor for graft dysfunction in renal transplant recipients? *Transplant Proc* 2007; **39**: 1023-1026 [PMID: 17524881 DOI: 10.1016/j.transproceed.2007.03.028]
51 **Saglam F**, Celik A, Sarioglu S, Cavdar C, Sifil A, Gulay H, Camsari T. Hyperuricemia influences chronic cyclosporine nephropathy. *Transplant Proc* 2008; **40**: 167-170 [PMID: 18261576 DOI: 10.1016/j.transproceed.2007.11.013]
52 **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; **86**: 652-658 [PMID: 18791445 DOI: 10.1097/TP.0b013e3181814f5b]
53 **Bandukwala F**, Huang M, Zaltzman JS, Nash MM, Prasad GV. Association of uric acid with inflammation, progressive renal allograft dysfunction and post-transplant cardiovascular risk. *Am J Cardiol* 2009; **103**: 867-871 [PMID: 19268747 DOI: 10.1016/j.amjcard.2008.11.042]
54 **Karbowska A**, Boratynska M, Kusztal M, Klinger M. Hyperuricemia is a mediator of endothelial dysfunction and inflammation in renal allograft recipients. *Transplant Proc* 2009; **41**: 3052-3055 [PMID: 19857674 DOI: 10.1016/j.transproceed.2009.07.080]
55 **Meier-Kriesche HU**, Schold JD, Vanrenterghem Y, Halloran PF, Ekberg H. Uric acid levels have no significant effect on renal function in adult renal transplant recipients: evidence from the symphony study. *Clin J Am Soc Nephrol* 2009; **4**: 1655-1660 [PMID: 19713295 DOI: 10.2215/CJN.02700409]
56 **Haririan A**, Nogueira JM, Zandi-Nejad K, Aiyer R, Hurley H, Cooper M, Klassen DK, Weir MR. The independent association between serum uric acid and graft outcomes after kidney transplantation. *Transplantation* 2010; **89**: 573-579 [PMID:

19997058 DOI: 10.1097/TP.0b013e3181c73c18]
57 **Boratyńska M**, Karbowska A, Klinger M. The effect of hyperuricemia on endothelial biomarkers and renal function in kidney allograft recipients. *Transplant Proc* 2010; **42**: 4074-4077 [PMID: 21168631 DOI: 10.1016/j.transproceed.2010.09.069]
58 **Kim KM**, Kim SS, Yun S, Lee MS, Han DJ, Yang WS, Park JS, Park SK. Uric acid contributes to glomerular filtration rate deterioration in renal transplantation. *Nephron Clin Pract* 2011; **118**: c136-c142 [PMID: 21150221 DOI: 10.1159/000320616]
59 **Wang W**, Li XB, Yin H, Yang XY, Liu H, Ren L, Hu XP, Wang Y, Zhang XD. Factors affecting the long-term renal allograft survival. *Chin Med J* (Engl) 2011; **124**: 1181-1184 [PMID: 21542992]
60 **Daskalopoulou SS**, Tzovaras V, Mikhailidis DP, Elisaf M. Effect on serum uric acid levels of drugs prescribed for indications other than treating hyperuricaemia. *Curr Pharm Des* 2005; **11**: 4161-4175 [PMID: 16375738]
61 **Neal DA**, Tom BD, Gimson AE, Gibbs P, Alexander GJ. Hyperuricemia, gout, and renal function after liver transplantation. *Transplantation* 2001; **72**: 1689-1691 [PMID: 11726834 DOI: 10.1097/00007890-200111270-00021]
62 **Fairbanks LD**, Cameron JS, Venkat-Raman G, Rigden SP, Rees L, Van'T Hoff W, Mansell M, Pattison J, Goldsmith DJ, Simmonds HA. Early treatment with allopurinol in familial juvenile hyerpuricaemic nephropathy (FJHN) ameliorates the long-term progression of renal disease. *QJM* 2002; **95**: 597-607 [PMID: 12205338 DOI: 10.1093/qjmed/95.9.597]
63 **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. *Am J Kidney Dis* 2006; **47**: 51-59 [PMID: 16377385 DOI: 10.1053/j.ajkd.2005.10.006]
64 **Shelmadine B**, Bowden RG, Wilson RL, Beavers D, Hartman J. The effects of lowering uric acid levels using allopurinol on markers of metabolic syndrome in end-stage renal disease patients: a pilot study. *Anadolu Kardiyol Derg* 2009; **9**: 385-389 [PMID: 19819789]
65 **Goicoechea M**, de Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincón A, Arroyo D, Luño J. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. *Clin J Am Soc Nephrol* 2010; **5**: 1388-1393 [PMID: 20538833 DOI: 10.2215/CJN.01580210]
66 **Kao MP**, Ang DS, Gandy SJ, Nadir MA, Houston JG, Lang CC, Struthers AD. Allopurinol benefits left ventricular mass and endothelial dysfunction in chronic kidney disease. *J Am Soc Nephrol* 2011; **22**: 1382-1389 [PMID: 21719783 DOI: 10.1681/ASN.2010111185]
67 **Momeni A**, Shahidi S, Seirafian S, Taheri S, Kheiri S. Effect of allopurinol in decreasing proteinuria in type 2 diabetic patients. *Iran J Kidney Dis* 2010; **4**: 128-132 [PMID: 20404423]
68 **Kanbay M**, Huddam B, Azak A, Solak Y, Kadioglu GK, Kirbas I, Duranay M, Covic A, Johnson RJ. A randomized study of allopurinol on endothelial function and estimated glomular filtration rate in asymptomatic hyperuricemic subjects with normal renal function. *Clin J Am Soc Nephrol* 2011; **6**: 1887-1894 [PMID: 21784838 DOI: 10.2215/CJN.11451210]
69 **Neogi T**. Clinical practice. Gout. *N Engl J Med* 2011; **364**: 443-452 [PMID: 21288096]
70 **Badve SV**, Brown F, Hawley CM, Johnson DW, Kanellis J, Rangan GK, Perkovic V. Challenges of conducting a trial of uric-acid-lowering therapy in CKD. *Nat Rev Nephrol* 2011; **7**: 295-300 [PMID: 21321568 DOI: 10.1038/nrneph.2010.186]

P- Reviewer Bellomo G **S- Editor** Gou SX
L- Editor A **E- Editor** Lu YJ