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ORIGINAL ARTICLE

Uric acid is not associated with decline in renal function or time to renal replacement therapy initiation in a referred cohort of patients with Stage III, IV and V chronic kidney disease

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ABSTRACT

Background. Although many studies have suggested an association between higher uric acid (UA) and both development of chronic kidney disease (CKD) and faster decline in renal function in Stage I and II CKD, it is not clear whether this effect is consistent throughout higher CKD stages. The aim of this study was to investigate the association between baseline UA and renal outcomes in patients with established CKD (Stages III–V).

Methods. We analysed data in the Swedish Renal Registry–Chronic Kidney Disease (SRR-CKD), which is a nationwide registry of referred CKD patients. Patients with a visit between January 1st, 2005 and December 31st, 2011 were followed until initiation of renal replacement therapy (RRT), death, referral to primary care or end of follow-up. Decline in renal function was assessed with a linear mixed model using all estimated glomerular filtration rate (eGFR) assessments recorded during median 28 months of follow-up, adjusting for important confounders such as demographic factors, primary renal disease, age, sex, relevant medication, diet, blood pressure and body mass index.

Results. There were 2466 patients with a baseline UA measurement {mean [standard deviation (SD)] of 7.81 [1.98] mg/dL}. The mean decline in renal function was −1.48 (95% CI −1.65; −1.31) mL/min/1.73 m^2 per year. The overall adjusted change in decline in renal function per unit increase in baseline UA was 0.08 (95% CI −0.01; 0.17) mL/min/1.73 m^2 per year indicating no association between higher UA levels and decline in renal function. In Stage III, IV and V CKD patients, the mean decline in renal function was −1.52 (95% CI −1.96; −1.08), −1.52 (95% CI −1.72; −1.32) and −1.19 (95% CI −1.75; −0.64) mL/min/1.73 m^2 per year, respectively. The adjusted change in the decline in renal function per unit increase in baseline UA was −0.09 (95% CI −0.30; 0.13) in Stage III CKD, 0.16 (95% CI 0.04; 0.28) in Stage IV CKD and 0.18 (95% CI −0.09; 0.45) in Stage V CKD. The overall adjusted hazard ratio for start of RRT was 0.97 (95% CI 0.93–1.02). For Stage III, IV and V CKD, it was 0.99 (95% CI 0.73–1.34), 0.97 (95% CI 0.91–1.03) and 0.99 (95% CI 0.91–1.07), respectively.

Conclusion. UA is not associated with the rate of decline in renal function or time to start of RRT in Stage III, IV and/or V CKD patients.

Keywords: (progression of) CKD, hyperuricaemia

INTRODUCTION

Humans have relatively high levels of uric acid (UA) in serum compared with other mammals. The reason for this lies 13–24

million years in the past, when mutations in the uricase gene resulted in an inactive uricase enzyme in humans. Normally, the uricase enzyme is responsible for converting UA into allantoin [1]. Today, the non-functional human uricase enzyme results in high levels of UA, which is the reason why humans can spontaneously develop gout [2].

Besides gout, UA has been linked to a wide variety of other diseases such as cardiovascular disease (CVD) [3, 4], diabetes mellitus [5–7], hypertension [8, 9], metabolic syndrome [6, 10] and chronic kidney disease (CKD) [9, 11]. Interest in the association between UA and CKD dates back as far as the 19th century [12]. Although multiple epidemiological studies have suggested an association between higher UA and both the development of CKD and faster decline in renal function for Stage I and II CKD patients, there are conflicting results for later CKD stages (III–V) [13–16]. For patients with later stages (III–V) of CKD, new evidence shows an association between the genetic markers (the rs734553 polymorphism in the SLC2A9 gene) that predict UA levels and CKD (progression) [17, 18]. However, studies fail to find an association between the actual UA levels and CKD progression in the same population [17]. The large body of evidence in this group of patients consists of epidemiological studies in which the majority fails to find an association [11]. It has been theorized that demonstrating a causal relation between UA and CKD in Stage III–V CKD patients is impossible in epidemiological studies, because the relatively high progressed stage of the disease would mask any effect of UA [11]. Indeed, theoretically it is possible that the deleterious effect of UA is more pronounced in patients where the kidney has not yet sustained considerable damage [11, 19–22]. If this is true, the plausible impact of UA on CKD should diminish as kidney damage—expressed as the stage of CKD—progresses.

The aim of this study was to investigate the effect of UA on CKD progression (expressed as decline in renal function) in patients with CKD Stages III–V combined and in patients with CKD Stages III, IV and V separately, and to test whether this effect is different between the stages.

ORIGINAL ARTICLE

MATERIALS AND METHODS

Study population

To study the association between UA and the annual rate of decline in renal function, both in CKD Stages III–V combined and separately, we used data collected in the Swedish Renal Registry—Chronic Kidney Disease (SRR-CKD). The SRR is an ongoing web-based data registry that contains clinical data of referred patients with CKD and end stage renal disease (ESRD) in Sweden [23]. The SRR-CKD is a part of the SRR, where non-dialysis CKD patients treated at 50 nephrology clinics (out of 53 in Sweden) are registered. Most nephrology clinics register patients when the estimated glomerular filtration rate (eGFR) declines below 30 mL/min/1.73 m^2, whereas some clinics choose to register patients earlier. Patients are then followed in the registry during their progressive disease, through start of dialysis, changes between dialysis modalities and kidney transplantation. Upon registration, information about demographic factors, primary renal disease (PRD), age, sex and other relevant clinical parameters such as important medication, diet, blood pressure and body mass index (BMI) are gathered. In this study, we included patients above 18 years of age with a recorded first visit in SRR-CKD between January 1st, 2005 and December 31st, 2011. All visits were part of the routine follow-up. Patients were followed until start of renal replacement therapy (RRT), death, referral to primary care or until December 31st, 2012 (end of the follow-up), whichever came first. The data were linked to the national registry of prescribed drugs, which contains information on all dispensed drugs, using the unique individual national identification number all Swedish citizens have. From this registry, we received information on drugs to treat hyperuricaemia and gout. Data were decoded and analysed anonymously. All patients were informed about registration into SRR and had the right to decline participation. The study protocol was approved by the regional ethics committee.

Measurement and definitions

CKD Stages III–V were constructed based on the Kidney Disease Outcomes Quality Initiative criteria for CKD stages (i.e. Stage III eGFR 30–59 mL/min/1.73 m^2, Stage IV eGFR 15–29 mL/min/1.73 m^2 and Stage V eGFR < 15 mL/min/1.73 m^2) [24]. UA values at the first visit were regarded as the baseline UA values. The eGFR was estimated using the four-variable Modification of Diet in Renal Disease (MDRD) equation, taking into account age, sex and serum creatinine [25]. Since 2003, all laboratories in Sweden are urged to report serum creatinine standardized according to isotope dilution mass spectrometry. Ethnicity is not reported in SRR, and thus all MDRD values were assumed to be non-black. Pulse pressure was defined as the difference between systolic and diastolic blood pressure measured at the clinical visit, mean arterial pressure (MAP) was estimated by dividing the sum of the systolic blood pressure and twice the diastolic blood pressure by three and protein-reduced diet was defined as any prescribed diet with a protein intake at or lower than 0.6 g/kg body weight/day with or without supplementary amino acids. Information on diuretics and lipid-lowering drugs were collected from the SRR-CKD, while information on anti-hyperuricaemic drugs were collected from the registry on dispensed drugs. Any drugs with the anatomical therapeutical chemical codes M04AA01 (allopurinol/Zyloric®) and M04AB01 (probenecid) and dispensed before the first visit were regarded as UA-lowering drugs.

Outcomes

The association between UA and renal function was investigated through two studied outcomes: decline in glomerular filtration rate (GFR) and time to start of RRT. Our primary outcome, decline in renal function, is presented as a negative number. Hence, a larger negative number indicates faster decline. We calculated the effect of a unit increase in UA at baseline on the decline in renal function. To this end, we report the absolute change in yearly rate of decline in renal function that can be attributed to a unit increase in UA at baseline. A negative change indicates a larger negative number and thus faster decline, whereas a positive change indicates a smaller negative number and thus slower decline. To calculate the change in

the rate of decline in renal function, all available eGFR measurements during the follow-up were used. For the secondary outcome, start of RRT, we used the date of the first registered dialysis or primary kidney transplantation.

Statistical analysis

Categorical variables are presented as percentages, continuous variables are presented as mean ± SD and skewed variables are presented as median (boundaries of interquartile range, IQR). Baseline characteristics are presented for the total study population and stratified by CKD stage.

A linear mixed model (LMM) was used to estimate the change in the rate of decline in renal function with each unit increase in baseline UA. Multivariable analysis was used to adjust for potential confounders: age, sex, PRD, BMI, MAP, protein-restricted diet, statin use, diuretic use and UA-lowering therapy use, presence of diabetes, arrhythmia, CVD, interstitial heart disease (IHD), hypertension, pulmonary disease and chronic heart failure (CHF). A negative change (−) indicates faster decline [26]. To investigate and test differences between the CKD stages, two- and three-way interactions between baseline UA, CKD stage and follow-up time were used. The coefficients for the three-way interaction terms estimate the differences between the CKD stages in the change in the rate of decline in renal function with each unit increase in baseline UA. In contrast to a standard linear model, the LMM takes into account that repeated eGFR measurements of the same patient are correlated. In our model, this was done by allowing a random intercept and a random slope for follow-up time.

The hazard ratio (HR) for start of RRT for 1 mg/dL increase in baseline UA was estimated by Cox proportional hazards regression [27]. Follow-up time in the Cox analysis was the time between baseline UA measurement and the start of RRT. Censored events were death, referral to a non-participating centre or primary care and end of the follow-up (31 December 2012). The same set of confounders was used in the Cox model as in our primary outcome analysis.

Missing values of potential confounders at baseline were imputed for patients with a baseline UA value using multiple imputations with 10 repetitions. The imputations were based on all known information of each individual [28]. Besides, the potential confounders, presence of gout, baseline eGFR, serum albumin, haemoglobin (Hb), parathyroid hormone (PTH), pulse pressure, follow-up time and whether patient started dialysis or not were used for imputation. The follow-up time was logarithmically transformed before entering in the imputation model.

Four sensitivity analyses were performed in order to test the robustness of our results. First, the main analyses were repeated without imputing for missing confounders. Second, in three separate analyses, UA values were categorized according to above and below the median values of UA (in men and women separately), above and below normal values (i.e. 7.06 mg/dL for men and 5.72 mg/dL for women) and according to tertiles of UA (in men and women separately). Then, in a subset of patients where this information was available, we additionally adjusted for albumin creatinine ratio (ACR) and use of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs). Last, the analysis was stratified for patients using UA-lowering medication versus patients not using those medications at baseline and, separately, for patients with baseline UA > 7 mg/dL versus patients with baseline UA ≤ 7 mg/dL.

P-values are two tailed, and $P < 0.05$ was considered statistically significant. All analyses were performed in PASW/SPSS version 20.0 for Windows.

RESULTS

Patient characteristics

There were 2466 patients included between January 1st, 2005 and 31 December 2011 for whom UA values at baseline were available and a rate of decline in renal function could be estimated. Of these patients, 618 had CKD Stage III, 1507 patients had CKD Stage IV and 341 patients had CKD Stage V. The baseline characteristics for the whole population and for CKD Stages III, IV and V separately are shown in Table 1. Mean (SD) age for the whole population was 69.0 (13.6) years, and 65% were male. Mean (SD) overall UA value was 7.81 (1.98) mg/dL. The mean (SD) UA was 7.68 (1.95), 7.94 (1.97) and 7.47 (2.02) mg/dL for patients with CKD Stages III, IV and V, respectively. Patients with CKD Stage IV were on average 69.9 years old and older than the patients with CKD Stage III or V, and presented more often with diabetic nephropathy and nephrosclerosis as their PRD. CKD Stage IV patients also used diuretics more often than Stage III and V CKD patients, while the patients with Stage III CKD more often used statins compared with the patients with Stage IV or V CKD (Table 1).

Twenty-four variables were used to impute the missing values of potential confounders at baseline. Sixteen of these 24 variables were complete. The remaining eight variables had missing values, with an average percentage missing of <10%.

The rate of decline in renal function per GFR stage

The median (IQR) duration of the follow-up was 26.0 (16.3–38.6) months, and the mean (SD) number of eGFR (MDRD) measurements was 5.2 (3.1). For patients included at Stage III CKD, the median (IQR) follow-up was 28.2 (17.0–38.6) months, while it was 27.3 (17.5–39.9) and 17.6 (10.3–28.9) months, respectively, for patients in Stage IV and V CKD. The mean (SD) numbers of eGFR (MDRD) measurements in Stage III, IV and V CKD were 4.3 (2.3), 5.5 (3.3) and 5.3 (3.5), respectively. Baseline eGFR (MDRD) was available in all patients and had a mean (SD) value of 25.0 (9.8) mL/min/1.73 m^2.

The (adjusted) change in the rate of decline in renal function associated with a unit increase in UA at baseline can be found in Table 2. The mean overall rate of decline in renal function was −1.48 (95% CI −1.65; −1.31) mL/min/1.73 m^2 per year. A 1 mg/dL increase in UA at baseline led to a change in the rate of eGFR decline of 0.08 (95% CI −0.01; 0.17) mL/min/1.73 m^2 per year: the higher the UA at baseline, the slower the decline in renal function. Adjusted for age, sex, PRD, BMI, MAP, protein-restricted diet, use of diuretics, statins and/or UA-

Table 1. Characteristics of patients with stage III-V CKD

	CKD III–V ($n = 2466$)	CKD III ($n = 618$)	CKD IV ($n = 1507$)	CKD V ($n = 341$)
UA (SD) (mg/dL)	7.81 (1.98)	7.68 (1.95)	7.94 (1.97)	7.47 (2.02)
Age (SD) (years)	68.98 (13.59)	67.39 (13.67)	69.85 (13.32)	68.00 (14.28)
Sex (% male)	65.4	27.3	36.1	41.1
PKD				
% Diabetes	17.7	15.7	18.8	16.4
% Glomerulonephritis	10.2	9.9	9.6	13.5
% Nephrosclerosis	16.3	16.5	18.7	5.6
% Other	11.8	11.3	11.3	15.0
BMI (SD) (kg/m^2)	28.13 (5.64)	28.67 (5.61)	28.00 (5.53)	27.76 (6.14)
eGFR* (SD) (MDRD)	24.95 (9.80)	38.18 (7.19)	22.50 (4.21)	11.78 (2.38)
MAP† (SD) (mm Hg)	97.27 (12.70)	95.75 (12.44)	97.31 (12.67)	99.87 (12.96)
Protein-restricted diet (%)	4.7	0.8	4.0	14.4
Diuretics use (%)	72.5	66.8	75.0	71.7
Statin use (%)	50.2	57.7	48.4	44.2
UA lowering drugs (%)	39.3	40.5	39.6	36.1
Diabetes Mellitus (%)	36.0	36.4	36.9	31.1
Arrhythmia (%)	19.3	22.3	19.4	13.2
CVD (%)	14.5	16.3	13.7	15.0
IHD (%)	26.0	26.5	26.4	23.5
Hypertension (%)	72.9	77.8	71.4	70.7
Pulmonary disease (%)	11.4	13.9	10.7	10.0
CHF (%)	21.2	22.3	21.9	15.8
Gout (%)	10.0	11.5	10.2	6.5
RRT initiation (n)	530	21	324	190
RRT modality				
%HD	311	10	192	109
%PD	175	7	97	71
%Tx	44	4	30	10

PKD, primary kidney disease.
*In ml/min/1.73 m^2.
†Calculated as [(2/3*Systolic blood pressure) + (1/3*diastolic blood pressure)/2].

Table 2. The rate of decline in renal function (95% CI)

	CKD III–V ($n = 2466$)	CKD III ($n = 618$)	CKD IV ($n = 1507$)	CKD V ($n = 341$)	
Mean decline[a]	−1.48 (−1.65; −1.31)	−1.52 (−1.96; −1.08)	−1.52 (−1.72; −1.32)	−1.19 (−1.75; −0.64)	
Change in eGFR decline per mg/dL increase in UA at baseline (negative = extra decline)[a]					
Crude	0.08 (−0.01; 0.17)	−0.09 (−0.31; 0.12)	0.14 (0.03; 0.26)	0.10 (−0.17; 0.37)	0.20*
Adjusted[b]	0.09 (−0.01; 0.19)	−0.09 (−0.30; 0.13)	0.16 (0.04; 0.28)	0.18 (−0.09; 0.45)	0.12

[a]In mL/min/1.73 m^2 per year.
[b]Adjusted for age, sex, PRD, BMI, MAP, protein-restricted diet, diuretics use, statin use and UA-lowering medication use, diabetes, arrhythmia, dementia, CVD, IHD, hypertension, pulmonary disease and CHF.
*P-value for difference in the change in the rate of renal function decline between CKD stages.

lowering medication, presence of diabetes, arrhythmia, CVD, IHD, hypertension, pulmonary disease and CHF, the change in the rate of renal function decline became 0.09 (95% CI −0.01; 0.19) mL/min/1.73 m^2 per year per unit increase in baseline UA (slower decline).

The mean rates of decline in renal function were not significantly different between the three CKD stages. They were −1.52 (95% CI −1.96; −1.08), −1.52 (95% CI −1.72; −1.32) and −1.19 (95% CI −1.75; −0.64) mL/min/1.73 m per year for patients in Stages III, IV and V, respectively. The adjusted change in the yearly rate of decline in renal function associated with a unit increase in baseline UA was −0.09 (95% CI −0.30; 0.13) in Stage III CKD, 0.16 (95% CI 0.04; 0.28) in Stage IV CKD and 0.18 (95% CI −0.09; 0.45) in Stage V CKD, and the difference in the change in the rate of decline in renal function between CKD stages is not statistically significant (P = 0.12).

Time to start of renal replacement therapy

A total of 530 (21.5%) from 2466 patients started RRT during the follow-up, of which 311 (12.6%) started with haemodialysis (HD), 175 (7.1%) with peritoneal dialysis (PD) and 44 (1.8%) were transplanted (Tx). For patients with Stage III CKD ($n = 618$), 21 (3.4%) started RRT [10 (1.6%) with HD, 7 (1.1%) with PD and 4 (0.6%) were transplanted)]. Of the 1507 patients with Stage IV CKD, 324 (21.5%) started RRT [192 (12.7%) with HD, 97 (6.4%) with PD and 30 (2.0%) were transplanted)]. For Stage V CKD patients, 190 (55.7%) of 341 started with RRT during the follow-up [109 (32%) with HD, 71 (20.8%) with PD and 10 (2.9%) were transplanted)]. During pre-dialysis care, 652 (26.4%) patients died [130 (21%) patients with Stage III CKD, 433 (28.7%) patients with Stage IV CKD died and 189 (26.1%) patients with Stage V CKD].

Table 3. HR (95% CI) for start of dialysis per unit (mg/dL) increase in baseline UA

	CKD III–V	CKD III	CKD IV	CKD V
Crude HR	0.96 (0.92–1.01)	1.25 (1.02–1.52)	0.94 (0.88–1.00)	1.01 (0.94–1.09)
Adjusted[a]	0.97 (0.93–1.02)	0.99 (0.73–1.34)	0.97 (0.91–1.03)	0.99 (0.91–1.07)

[a]Adjusted for age, sex, BMI, protein-restricted diet, diuretics, lipid-lowering medication, MAP, PRD, allopurinol use, diabetes, arrhythmia, CVD, IHD, hypertension, pulmonary disease and CHF.

In the adjusted Cox proportional hazards model, the HR for starting RRT of 1 mg/dL increase in baseline UA was 0.97 (95% CI 0.93–1.02). In Stage III, IV and V CKD patients, the HR for start of RRT was 0.99 (95% CI 0.73–1.34), 0.97 (95% CI 0.91–1.03) and 0.99 (95% CI 0.91–1.07), respectively (Table 3).

Sensitivity analyses

The sensitivity analyses demonstrated robustness of our results. First, the results of the LMM without imputing for missing confounder data were similar and in line with the results based on imputed missing confounder data. Second, results did not change after categorizing UA based on median, normal values or tertiles of distribution: no significant effects were found, and directions of effects were the same. Also, adding ACR and use of ACEi/ARB data to the models did not materially change the results. Neither did we observe any substantial change in the results when we stratified on the basis of use of UA-lowering medications nor on the basis of baseline UA (i.e. UA $\leq$ 7 mg/dL versus UA > 7 mg/dL) (Supplementary data, Tables S1, S2a,b and S3a,b).

DISCUSSION

In this large population of Swedish referred CKD III–V patients, we did not observe a statistically significant change in the overall rate of decline in renal function associated with 1 mg/dL increase in UA at baseline [0.08 (95% CI −0.01; 0.17) mL/min/1.73 m^2 per year]. This did not change after adjustment for confounders. Neither did crude analyses of Stage III, IV or V CKD patients show any significant changes in the rate of decline in renal function attributed to UA. We also could not demonstrate that UA levels were in any way linked to initiation of RRT.

Previous studies investigating the association between UA and CKD development and progression have mainly focussed on patients with normal renal function or Stage I and II CKD. As summarized in Supplementary data, Table S4 (partly based on previous systematic reviews [9, 11], most epidemiological studies in Stage I and II CKD patients find a significant association between higher UA and development of CKD [29–46], eGFR decline [31, 43, 47–53] and development of ESRD [54, 55], whereas the results of the studies that included Stage III–V patients diverge [13–16]. It has even been suggested that epidemiological studies are inherently incapable of exposing a causal relation between the UA and CKD progression in CKD Stages III–V. The rationale for this theory depends on the pathophysiology of UA clearance [11] where UA for the most part is cleared by the kidney, and to some extent by the gut. CKD, then, inadvertently leads to UA rise, which cannot be compensated by excretion by the gut. Although UA increases as a result of declining renal function, the studies investigating if increased UA is associated with an additive negative progression have failed to show so. However, none of the epidemiological studies including patients with established CKD III–V have specifically investigated the decline in renal function but instead used incidence in RRT as the outcome alone or in combination with doubling of serum creatinine, or a percentage of decrease in eGFR and/or death. Two of the studies that showed a significant association between higher UA and ESRD [15, 16] were performed in patients with a single PRD, and the results may therefore not be applicable to the whole CKD population. In addition, these two studies also included a majority of CKD I and II patients, which probably affected the outcome. The study that resembles ours the most is a sub-analysis from the MDRD study [14]: the investigators studied the association between UA and kidney failure (defined as the need for RRT or transplantation) and found an HR of 1.02 (95% CI 0.97–1.07) for kidney failure per unit increase (mg/dL) in baseline UA. Unfortunately, the effect of UA on the rate of renal function decline was not reported. Our study, which is the first large study in unselected referred CKD III–V patients, now also suggests that increased levels of UA in later stages of CKD are not associated with the rate of decline in renal function in agreement with the results from the MDRD study.

Our results concerning the time until start of RRT are in line with the results for eGFR decline. The decision to start dialysis is a complex event where nephrologist and patient collaborate to make the best decision with regard to quality of life and survival on dialysis. It is likely that some clinical characteristics are taken into account when making this decision, especially by the physician. However, it is unlikely that high UA levels are a major clinical characteristic that would drive a nephrologist to start RRT, particularly if the hyperuricaemia is asymptomatic.

Recently, there have been some promising new studies that have looked at the association between UA and CKD (progression) in the specific group of Stage III–V CKD patients. First, Testa *et al.* [17] performed a Mendelian randomization study in which the rs734553 single-nucleotide polymorphism (SNP) served as an instrument variable for levels of UA. They analysed 755 patients with Stage II–V CKD and demonstrated that CKD patients who harbour the T-allele, which raises UA levels, have a 2.35-fold (95% CI 1.25–4.42) higher risk of CKD progression, which was defined as a >30% decrease in eGFR-MDRD, start of dialysis or transplantation. However, in the same study, there was no association between circulating UA levels and CKD progression. Also, Voruganti *et al.* [18] have investigated the same SLC2A9 gene in the Strong Heart American Study. They included 3604 American Indians and demonstrated that the association between rs734553 SNP and UA holds true for this

population as well. Although they did look at the association between this SNP and eGFR, they did not investigate any measures of CKD progression.

A possible explanation for the discrepancy between the effect of UA in early-stage CKD (I and II) and later-stage CKD (III–V) is that patients with CKD III–V have already sustained considerable damage to the kidney, which leaves little room for UA to cause further harm. It has been proposed that UA eventually leads to kidney damage by causing systemic and glomerular hypertension [11]. However, in more severe CKD stages, systemic and glomerular hypertension is already apparent because of sodium and/or water retention [20–22].

There are several strengths of this study. First, the patients included were part of the SRR-CKD, which intends to include all patients followed up at a nephrology clinic in Sweden and who have an eGFR below 30 mL/min/1.73 m^2. Although representativeness of the CKD part of the registry has not been evaluated in all areas in Sweden, about 80% of all patients entering RRT in Sweden in 2013 had at least one previous CKD visit (www.snronline.se). Patients in the SRR-CKD are followed until either referral back to primary health care or death and through start in any RRT. Another strength is that most patients have several out-patient visits with an eGFR recorded (mean number 5.2), which decreases the intra-individual variability of the slope estimation. Furthermore, in our study, we focus on two end points that both fall under the scope of CKD progression. The fact that both results point in the same direction strengthens the validity of our results.

There are also some limitations. First, the 2466 patients for whom a baseline UA measurement was available form a subset of all patients in the SRR-CKD database and this selection may not be random. However, we do not think that selection bias is a major problem since a physician's decision to measure the UA level in serum is likely to be independent of his/her expectation of the subsequent rate of renal function decline. Also, the rate of decline in the whole SRR-CKD is similar to the decline among the patients with a UA measurement at baseline. Second, as a consequence of the inclusion criteria, the majority of patients were first registered when they reach Stage IV CKD, which means that Stage III CKD patients in the SRR-CKD are underrepresented and possibly unrepresentative of the general referred CKD population. However, the decision to register patients in CKD III or IV is mainly a centre effect based on local resources and tradition, and the baseline characteristics of Stage III, IV and V CKD patients are similar. Finally, confounding by indication should always be considered when analysing observational data. This means that physicians may have treated patients with high levels of UA differently because they think that these patients might have had a different prognosis. We tried to take this into account by adjusting for multiple potential confounders. Still, residual confounding might be present. For instance, we did not have comprehensive data about proteinuria. However, proteinuria is a likely consequence of any risk factor for kidney disease. In other words, any damage to the kidneys caused by UA would certainly lead to proteinuria. Adjusting for markers of proteinuria in the multivariable analyses would, therefore, diminish the magnitude of the effect between UA and CKD progression as it would be adjustment in the causal pathway. This is demonstrated by an earlier study in which the association between UA and CKD disappeared after adjustment for proteinuria [13].

To conclude, in Stage III–V CKD patients, UA levels are not associated with the rate of decline in renal function. Furthermore, there is no significant difference in this effect between Stage III, IV and V CKD patients. Also, UA levels in Stage III–V CKD patients are not associated with the start of RRT. In light of these findings, further studies are warranted to elucidate whether targeting lower UA levels in Stage III–V CKD patients is sensible for delaying CKD progression.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

None declared.

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