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ORIGINAL ARTICLE

Prevalence and correlates of gout in a large cohort of patients with chronic kidney disease: the German Chronic Kidney Disease (GCKD) study

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ABSTRACT

Background. Reduced kidney function is a risk factor for hyperuricaemia and gout, but limited information on the burden of gout is available from studies of patients with chronic kidney disease (CKD). We therefore examined the prevalence and correlates of gout in the large prospective observational German Chronic Kidney Disease (GCKD) study.

Methods. Data from 5085 CKD patients aged 18–74 years with an estimated glomerular filtration rate (eGFR) of 30–<60 mL/min/1.73 m^2 or eGFR ≥60 and overt proteinuria at recruitment and non-missing values for self-reported gout, medications and urate measurements from a central laboratory were evaluated.

Results. The overall prevalence of gout was 24.3%, and increased from 16.0% in those with eGFR ≥60 mL/min/1.73 m^2 to 35.6% in those with eGFR <30. Of those with self-reported gout, 30.7% of individuals were not currently taking any gout medication and among gout patients on urate lowering therapy, 47.2% still showed hyperuricaemia. Factors associated with gout were serum urate, lower eGFR, advanced age, male sex, higher body mass index and waist-to-hip ratio, higher triglyceride and C-reactive protein (CRP) concentrations, alcohol intake and diuretics use. While lower eGFR categories showed significant associations with gout in multivariable-adjusted models (prevalence ratio 1.46 for eGFR <30 compared with eGFR ≥60, 95% confidence interval 1.21–1.77), associations between gout and higher urinary albumin-to-creatinine ratio in this CKD population were not significant.

Conclusions. Self-reported gout is common among patients with CKD and lower GFR is strongly associated with gout. Pharmacological management of gout in patients with CKD is suboptimal. Prospective follow-up will show whether gout and hyperuricaemia increase the risk of CKD progression and cardiovascular events in the GCKD study.

Keywords: chronic kidney disease, correlates, estimated glomerular filtration rate, GCKD study, gout epidemiology, observational study

ORIGINAL ARTICLE

INTRODUCTION

Gout is a common and painful inflammatory arthritis [1–3], caused by urate crystal deposition in tissues and joints when local concentrations of urate exceed its physiological solubility threshold [4]. The burden of gout in the general population is increasing worldwide [5–8], with reported prevalence between 0.53 and 6.1% [9]. Due to the high morbidity, treatment and consequences associated with gout, this inflammatory arthritis poses a substantial financial burden to the health-care system [10, 11]. The management of gout is reported to be suboptimal [5], and a better understanding of the pathophysiology of gout and its correlates is a first step to improve diagnosis and treatment.

Correlates for gout have been examined in numerous studies. The most clinically relevant correlates are male sex, obesity, the metabolic syndrome and its components, dietary factors, hypertension and the current use of diuretics [12–19]. Reduced kidney function leads to accumulation of urate in the blood since renal elimination is the main endogenous mechanism of regulating serum urate concentrations [20]. Numerous studies have demonstrated that hyperuricaemia is associated with a reduced estimated glomerular filtration rate (eGFR) in population-based settings, and one study suggested that adults with eGFR <60 mL/min/1.73 m^2 are at a 2-fold increased risk of developing hyperuricaemia [21]. However, only a limited number of studies have investigated gout in individuals with chronic kidney disease (CKD), although they represent a high-risk population for the condition [22–24]. Moreover, many studies only evaluated the effect of reduced eGFR on the risk of hyperuricaemia or gout [7, 25], whereas the urinary albumin-to-creatinine ratio (UACR) is also used to define CKD [26]. Of previous population-based studies, an association between higher albuminuria and the prevalence or risk of gout or hyperuricaemia has been reported in some [22] but not all studies [27]. In CKD populations, levels of albuminuria are typically much higher compared with the general population. Thus, the study of gout in populations with CKD and specifically the relationship of both eGFR and albuminuria with gout deserve further investigation.

We therefore examined the prevalence, correlates and management of gout in a large cohort of 5085 participants of the German Chronic Kidney Disease (GCKD) study. Our objectives were (i) to quantify the prevalence of hyperuricaemia and gout as well as their pharmacological treatment; (ii) to assess the association of both kidney function parameters eGFR and UACR and the underlying cause of disease with the prevalence of gout and serum urate levels/hyperuricaemia and (iii) to identify correlates of gout in the setting of CKD that may be modifiable.

MATERIALS AND METHODS

Study population

The GCKD study is an ongoing prospective observational study. To systematically investigate correlates and consequences of CKD, 5217 Caucasian patients aged 18–74 years with an eGFR ranging from 30 to 60 mL/min/1.73 m^2 or overt proteinuria in the setting of eGFR >60 mL/min/1.73 m^2 were enrolled across Germany between 2010 and 2012 as described previously [28]. Patients provided written informed consent, and the study was approved by the Ethics Boards of all nine participating study centres. For the present study, we analysed data from 5085 patients with non-missing values for self-reported gout, urate measurements, eGFR and UACR at the baseline visit.

Assessment of gout

Gout status was ascertained through a standardized interview administered by trained interviewers. Gout was considered present when a patient gave an affirmative answer to the question 'have you ever been told by a physician that you have gout?' Self-reported gout has been described as reliable in previous epidemiologic studies in the general population [29]. Uric acid was measured from serum using an enzymatic colorimetric test (UA Plus, Roche/Hitachi Diagnostics GmbH, Mannheim, Germany). Hyperuricaemia was defined as >420 μmol/L (7 mg/dL) in men and >357 μmol/L (6 mg/dL) in women [22, 30].

Glomerular filtration rate and albuminuria

Serum and urine creatinine were measured using the CREA plus (Roche/Hitachi Diagnostics GmbH, Mannheim, Germany) assay and urine albumin using the ALBU-XS assay (Roche/Hitachi Diagnostics GmbH, Mannheim, Germany). Estimated GFR was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration formula [31]. The UACR (mg/g) was based on urine albumin (mg/dL)/urine creatinine (g/dL). According to the Kidney Disease: Improving Global Outcomes CKD guidelines [26], GFR categories were defined as follows: ≥60 mL/min/1.73 m^2 (G1/2), 45–59 (G3a), 30–44 (G3b) and <30 (G4/5), while UACR was categorized into

A1 (<30 mg/g, normoalbuminuria), A2 (30-<300 mg/g, microalbuminuria) and A3 (≥300 mg/g, macroalbuminuria).

Assessment of renal diagnosis

To obtain information on the underlying cause of CKD, the patient's treating nephrologists were asked to choose from a given list of aetiologic categories, which were summarized into the groups diabetic nephropathy, nephrosclerosis, primary glomerular disease, interstitial nephropathy, acute kidney injury, systemic diseases, solitary kidney, hereditary diseases, obstructive urophathy or miscellaneous.

Assessment of demographic, anthropometric and medical covariates

Age, gender and menopausal status were recorded at study entry, and weight, height, waist, hip circumference and blood pressure (BP) were measured by trained and certified study personnel in a standardized way. BP was measured three times after 5 min of rest in a sitting position using Omron M5 Professional devices (article number: Art.-Nr. HEM-7213-D, http://www.omron-medizintechnik.de/). Uric acid, cholesterol, high-density lipoprotein cholesterol, triglycerides, C-reactive protein (CRP) and other laboratory parameters were measured in a central laboratory from blood and urine collected at the enrolment visit. Every medication currently taken by a patient was recorded, and active ingredients were coded using the latest Anatomical Therapeutic Chemical (ATC) codes (http://www.wido.de/amtl_atc-code.html, version for 2013). The intake of gout medication was based on the codes M04AA, M04AB, M04AC, M04AH and M04AX. Codes C09A and C09B were used to define angiotensin-converting enzyme inhibitor intake, and C03 represented diuretics intake.

Body mass index (BMI, kg/m^2) was calculated from patient weight and height, and obesity was defined as BMI >30 kg/m^2. Waist-to-hip ratio (WHR) was calculated from measured values. Systolic and diastolic BP was calculated as the mean of three measurements per person, where hypertension was defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg and/or use of antihypertensive medications. Diabetes was defined as HbA1c ≥6.5% or current use of at least one anti-diabetic medication. Coronary heart disease (CHD) was defined as present based on self-reported history of myocardial infarction or coronary reperfusion procedure (bypass or angioplasty). Alcohol intake was dichotomized as 'no or little' (alcohol consumption on <3 days/week) or 'moderate to large amount.'

Statistical analysis

Characteristics of the GCKD population by gout status or eGFR and UACR categories were compared using *t*- and χ^2 tests for continuous and categorical variables as appropriate. Variables that were clearly not normally distributed were compared across categories using Wilcoxon tests.

Gout prevalence was obtained by tabulation across categories of eGFR and UACR. Modified Poisson regression models were used to estimate prevalence ratios (PRs) [32] for gout according to kidney function measures, and compared with those from logistic regression analyses. Linear regression analyses were employed to model the relationship between uric acid and kidney function measures. All regression analyses evaluated three separate models: model 1 was unadjusted, model 2 adjusted for age, sex and study centre as covariates and model 3 included a full set of known gout correlates: age, sex, study centre, BMI, WHR, systolic BP, triglycerides, CRP, high-density lipoprotein (HDL) cholesterol, alcohol intake, diuretics use, CHD and diabetes. Among variables in model 3, triglycerides, CRP and UACR were log transformed, and WHR was examined per standard deviation (SD) increase, age per 5-year intervals and systolic BP per 10-mmHg increase. Gout medication use, cholesterol and hypertension were not included in the multivariate regression models due to high correlations with gout, HDL cholesterol and systolic BP, respectively. To allow for a direct comparison between models, the study population of models 1 and 2 was restricted to individuals with complete information for model 3.

To evaluate the impact of uric acid as a mediator of the association between kidney function and gout, additional regression models included serum urate concentrations as a covariable. Likelihood ratio tests were used to check the difference between models with and without the inclusion of serum urate concentrations and gout medication intake. Subgroup analyses were conducted across strata of gout medication intake.

Scatter and line plots were used to illustrate the correlation between uric acid and eGFR or UACR by gender. The proportion of the GCKD baseline population with gout and hyperuricaemia was illustrated across the range of eGFR using a linear spline with knots at 30, 60 and 90. In addition, the distribution of GFR and UACR by gout status and gout medication was plotted using kernel density plots. All analyses were conducted using Stata 13.0 (Stata Corp LP, College Park, TX).

RESULTS

Characteristics of the study population and gout medication intake

The study sample characteristics of up to 5085 patients with non-missing information on gout, urate measurements, eGFR and UACR are shown in Table 1; overall, 1238 of 5085 patients (24.3%) reported to have gout. The prevalence, mean or median of most correlates was clearly higher in gout patients compared with those without gout. However, both serum urate concentrations and the prevalence of hyperuricaemia were similar between the two groups, which may have resulted from the higher proportion of gout medication use among CKD patients with gout compared with those without.

Table 2 gives an overview of the current use of gout medications, both overall and separately for CKD patients with and without gout. Of all 5085 GCKD participants, 32.5% currently use gout medication (69.3% of those with and 20.7% of those without gout, P < 0.001), which means that approximately one-third of the patients with self-reported gout were not currently taking any gout medication. Uricostatics identified by ATC codes were by far the most common medication category, and allopurinol accounted for >97% of the uricostatic treatment. Uricosurics, especially benzbromarone, were used by few individuals (2.8% of

Table 1. Characteristics of the GCKD population by gout status

Characteristic	Overall (n = 5085)	No gout (n = 3847)	Gout (n = 1238)	P value	n
Serum urate, mg/dL	7.21 ± 1.91	7.20 ± 1.91	7.22 ± 1.93	0.685	5085
Hyperuricaemia	61.0%	62.2%	57.4%	0.003	5085
Gout medication use	32.5%	20.7%	69.3%	<0.001	5085
Female	39.9%	44.5%	25.7%	<0.001	5085
Postmenopausal	80.0%	77.9%	91.1%	<0.001	1989
Age, years	60.1 ± 12.0	59.1 ± 12.6	63.1 ± 9.0	<0.001	5085
BMI, kg/m^2	29.8 ± 6.0	29.2 ± 5.8	31.5 ± 6.1	<0.001	5028
Obesity	42.8%	38.8%	55.4%	<0.001	5028
Waist-to-hip ratio	0.94 ± 0.09	0.93 ± 0.09	0.97 ± 0.08	<0.001	4945
Systolic blood pressure, mmHg	139.5 ± 20.3	138.8 ± 20.1	141.4 ± 20.9	<0.001	5056
Cholesterol, mg/dL	211.4 ± 53.0	213.2 ± 53.3	206.0 ± 51.5	<0.001	5083
HDL cholesterol, mg/dL	52.0 ± 18.2	53.5 ± 18.5	47.2 ± 16.2	<0.001	5080
Triglycerides, mg/dL	168.4 (118.0, 239.9)	161.8 (114.0, 230.6)	192.4 (131.0, 270.1)	<0.001	5076
CRP, mg/L	2.3 (1.0, 5.0)	2.1 (1.0, 4.6)	3.0 (1.4, 6.5)	<0.001	5082
Diabetes	36.8%	33.8%	46.3%	<0.001	5085
Coronary heart disease	19.8%	17.6%	26.7%	<0.001	5085
Hypertension	95.1%	94.3%	97.4%	<0.001	5085
Alcohol intake, moderate to large amount	18.9%	17.3%	24.0%	<0.001	5057
ACE inhibitor use	47.1%	47.0%	47.6%	0.711	5085
Angiotensin receptor blocker use	38.9%	38.1%	41.2%	0.053	5085
Diuretics use	60.2%	56.0%	73.3%	<0.001	5085
UACR, mg/g	50.9 (9.6, 391.3)	48.8 (9.4, 385.4)	60.3 (10.0, 405.7)	0.989	5085
eGFR, mL/min/1.73 m^2	49.4 ± 18.2	50.9 ± 19.0	44.9 ± 14.9	<0.001	5085

Numbers are mean and SD or proportion. For triglycerides, UACR and CRP, median and the 25th and 75th percentile are shown.

Table 2. Prevalence of uric acid lowering medication intake

Medications	Overall (n = 5085)	No gout (n = 3847)	Gout (n = 1238)	P value	ATC code
Any gout medication	32.5% (1653)	20.7% (795)	69.3% (858)	<0.001	M04
Uricostatics	31.4% (1598)	20.0% (769)	67.0% (829)	<0.001	M04AA
Allopurinol	30.7% (1562)	19.7% (757)	65.0% (805)	<0.001	M04AA01; M04AA51
Febuxostat	0.77% (39)	0.31% (12)	2.18% (27)	<0.001	M04AA03
Uricosurics	1.2% (62)	0.70% (27)	2.8% (35)	<0.001	M04AB
Benzbromarone	1.2% (62)	0.70% (27)	2.8% (35)	<0.001	M04AB03
Colchicine	0.41% (21)	0.05% (2)	1.5% (19)	<0.001	M04AC01

patients with gout). Other gout medications such as tisopurine, probenecid, sulfinpyrazone and isobromindione were not used by any patient. Figure 1 shows that the proportion of patients with gout increases with lower eGFR, but even at eGFR within the normal range, a substantial fraction of patients with gout are not treated. Moreover, of all gout patients using a urate-lowering therapy, 47.2% still had hyperuricaemia. Supplementary data, Figure S1 shows that individuals not currently taking any gout medication had generally higher levels of eGFR than individuals who were taking gout medication, consistent with the prescription of gout medication in response to an increase in serum urate concentrations at lower levels of GFR. Individuals with gout had lower eGFR compared with individuals without, a finding that was observed overall and also among those not currently taking any gout medication.

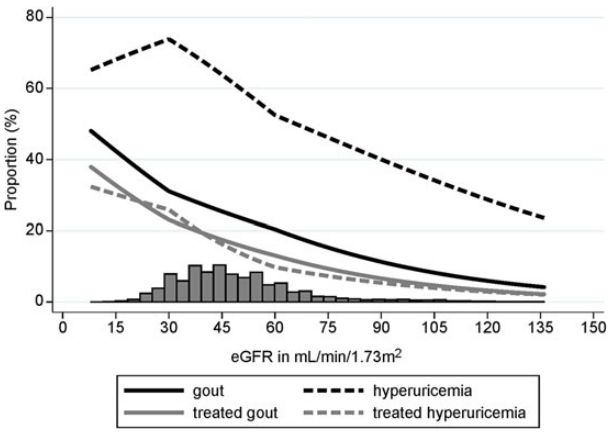

FIGURE 1: Linear spline graph of the proportion of the GCKD baseline population with gout (solid line) or hyperuricaemia (dashed line), stratified by the current use of gout medication, according to eGFR. The distribution of eGFR among all GCKD participants is shown as a histogram.

Distribution of serum urate concentrations and gout prevalence

The distribution of serum urate concentrations is shown across the range of eGFR (Supplementary data, Figure S2A) and UACR values (Supplementary data, Figure S2B). While serum urate concentrations showed a negative correlation with eGFR (Pearson correlation coefficient −0.254, P < 0.0001), there was no relevant correlation with UACR (Pearson correlation coefficient 0.037, P = 0.011). The good fit of the linear

Table 3. Prevalence of gout by kidney function measure

Gout	Prevalence		Model 1		Model 2		Model 3	
	n	%	PR	95% CI	PR	95% CI	PR	95% CI
G1/2	1102	16.0% (176)	Ref	Ref	Ref	Ref	Ref	Ref
G3a	1686	23.2% (391)	1.42	1.21–1.68	1.17	0.99–1.38	1.13	0.96–1.33
G3b	1842	27.6% (509)	1.65	1.41–1.93	1.33	1.13–1.56	1.22	1.04–1.43
G4/5	455	35.6% (162)	2.17	1.80–2.61	1.70	1.41–2.06	1.46	1.21–1.77
A1	2170	23.2% (503)	Ref	Ref	Ref	Ref	Ref	Ref
A2	1483	25.6% (379)	1.08	0.96–1.22	1.09	0.97–1.22	1.10	0.98–1.23
A3	1432	24.9% (356)	1.05	0.93–1.19	1.09	0.96–1.24	1.09	0.96–1.24

Model 1 did not contain co-variables; model 2 adjusted for age, sex and study centre and model 3 adjusted additionally for BMI, waist-to-hip ratio, systolic blood pressure, triglycerides, CRP, HDL cholesterol, alcohol intake, diuretics use, CHD and diabetes. Sample size was 4836 patients with full covariable information. PR: prevalence ratio, CI: confidence interval. G and A refer to the CKD stages (see Materials and Methods).

Table 4. Correlates of gout in the overall population and among those not currently using gout medication

Characteristic	Overall (4836)			Without gout medication (3259)		
	PR	95% CI	P value	PR	95% CI	P value
eGFR, G1	ref					
eGFR, G2	1.13	0.96–1.33	0.128	1.13	0.84–1.52	0.428
eGFR, G3	1.22	1.04–1.43	0.013	1.19	0.88–1.60	0.253
eGFR, G4/5	1.46	1.21–1.77	<0.001	1.43	0.98–2.11	0.065
UACR, A1	ref			ref		
UACR, A2	1.10	0.98–1.23	0.117	1.02	0.81–1.29	0.864
UACR, A3	1.09	0.96–1.24	0.169	1.08	0.84–1.40	0.543
Male Sex	1.47	1.27–1.71	<0.001	1.44	1.09–1.91	0.011
Age, per 5 years	1.08	1.05–1.11	<0.001	1.13	1.07–1.20	<0.001
BMI, kg/m^2	1.03	1.02–1.04	<0.001	1.01	0.99–1.04	0.180
Waist-to-hip ratio, per SD increase	1.11	1.03–1.19	0.003	1.10	0.96–1.27	0.161
Systolic blood pressure, per 10 mmHg	1.01	0.98–1.03	0.616	1.03	0.98–1.08	0.304
HDL cholesterol, mg/dL	1.00	0.99–1.00	0.191	1.00	0.99–1.01	0.866
ln(Triglyceride), mg/dL	1.19	1.07–1.32	0.001	1.46	1.19–1.78	<0.001
ln(CRP), mg/L	1.09	1.04–1.14	<0.001	1.15	1.05–1.26	0.002
Diabetes	0.93	0.84–1.04	0.210	0.90	0.72–1.12	0.328
Coronary heart disease	1.05	0.94–1.17	0.429	1.19	0.95–1.50	0.135
Alcohol (moderate to large amount)	1.21	1.08–1.35	0.001	1.14	0.89–1.45	0.295
Diuretics use	1.32	1.17–1.49	<0.001	1.33	1.07–1.66	0.011

Estimates are derived from the full model (model 3). PR: prevalence ratio, CI: confidence interval. G and A refer to the CKD stages (see Materials and Methods). The study centres Heidelberg and Aachen also showed significant association with increased gout prevalence, but adjustment was included for all study centres.

prediction of serum urate concentrations with the corresponding lowess smoother in Supplementary data, Figure S2 indicates that the relationship between eGFR and serum urate was approximately linear across the range of eGFR values. Whereas serum urate was higher in males than in females across the range of UACR, the sex difference for serum urate concentrations decreased with lower eGFR and was not observed anymore as eGFR approached ~40 mL/min/1.73 m^2. Supplementary data, Table S1A and B show baseline study characteristics by category of eGFR and UACR, respectively, and support the observation that serum urate concentrations increase with lower eGFR but not higher UACR.

Gout prevalence showed a gradual increase with lower eGFR from 16.0% among those with an eGFR >60 mL/min/1.73 m^2 to 35.6% among those with an eGFR <30 mL/min/1.73 m^2 (Table 3). No difference in gout prevalence was observed across categories of UACR. When eGFR decreased to 30 mL/min/1.73 m^2, the predicted proportions of hyperuricaemia and gout reached 73 and 30%, respectively (Figure 1). Because relatively few participants had an eGFR of <30 mL/min/1.73 m^2, the predictions within this range of eGFR may not be very precise. Table 3 shows that, when compared with an eGFR of ≥60 mL/min/1.73 m^2, the unadjusted PR of gout was significantly increased by 1.42-fold, 1.65-fold and 2.17-fold for those with an eGFR of 45–59, 30–44 and <30 mL/min/1.73 m^2. The significant association between gout and lower eGFR persisted after adjusting for age, sex and study centre as well as upon further extensive adjustment for potential confounders for CKD stages 3b and 4/5, but the magnitude of the ratios decreased. The PR of gout by category of UACR was not significant in unadjusted analyses, and—compared with individuals with normoalbuminuria—showed modest and insignificant associations for both microalbuminuria and macroalbuminuria [PR 1.09, 95% confidence interval (CI) 0.96–1.24, Table 3]. Associations obtained

Table 5. Prevalence of gout by CKD aetiology

Characteristic entities	No gout (n = 3845)	Gout (n = 1238)	Overall (n = 5083)	P value
Diabetic nephropathy, %	24.4	33.8	26.7	<0.001
Nephrosclerosis, %	38.8	48.7	41.2	<0.001
Systemic diseases, %	11.5	12.4	11.8	0.38
Primary glomerular disease, %	23.9	19.8	22.9	0.003
Interstitial nephropathy, %	8.3	9.5	8.6	0.21
Acute kidney injury, %	4.6	5.0	4.7	0.53
Solitary kidney, %	6.3	6.4	6.3	0.89
Hereditary diseases, %	5.1	2.8	4.5	0.001
Obstructive uropathy, %	7.6	6.5	7.3	0.19

Percentages do not sum up to 100% because individuals could be assigned more than a single cause of CKD by their treating nephrologist. P value is obtained from a comparison of the proportion of patients with a specific CKD category among those with and without gout.

from logistic regression models were similar but risk estimates were higher; therefore, the more conservative estimates from Poisson regression models are shown throughout.

Correlates of self-reported gout

To identify factors that are independently associated with gout, regression models were employed that included multiple covariates selected based on the prior literature and gout pathophysiology [9, 33]. As displayed in Table 4, advanced age, male sex, higher BMI, WHR, triglyceride concentrations and CRP, a moderate or large amount of alcohol intake, diuretics use and some of the study centres were significantly associated with gout. Among these correlates, the strongest associations were observed for advanced age, higher BMI and male sex, followed by diuretics use and an eGFR of <30 mL/min/1.73 m^2 (RR 1.46, 95% CI 1.21–1.77). Systolic BP, HDL-cholesterol concentrations, CHD and diabetes did not show significant association with gout upon multivariable adjustment, although they showed association in univariate analyses (see Table 1). Higher UACR categories were not independently associated with gout, and this was true in the overall GCKD population (Table 4) as well as in the patients with eGFR <60 only [n = 3794, PR for microalbuminuria 1.09 (95% CI 0.96–1.23) and for macroalbuminuria 1.09 (0.95–1.25)].

For comparison, Supplementary data, Table S2 shows the corresponding estimates for serum urate concentrations. Mean serum urate concentrations showed a graded and significant increase with lower eGFR, which remained significant upon multivariable adjustment. Significant positive associations between serum urate and higher UACR were observed, but—similar to the associations with gout—were of lesser magnitude than the associations between serum urate and eGFR. To evaluate to which extent serum urate influenced the associations between gout and its correlates, serum urate was included as an additional covariable. While this had little effect in the overall study population, the association between eGFR and gout became insignificant upon adjustment for urate among those not currently using any gout medication (data not shown).

Lastly, we evaluated whether gout prevalence differed by CKD aetiology. The proportions of patients with diabetic nephropathy and nephrosclerosis were significantly higher among patients with gout compared with those without gout, consistent with the epidemiological correlation of gout with diabetes and hypertension (Table 5). The prevalence of hereditary nephropathy was significantly lower among those with gout, consistent with the younger age and specific cause of disease in these patients. The addition of CKD aetiology to the multivariable-adjusted model presented in Table 4 showed that diabetic nephropathy, nephrosclerosis and hereditary nephropathy were not independently associated with gout, suggesting that the different proportion of these CKD aetiologies in patients with and without gout can be explained by one or more of the other known gout correlates such as age.

DISCUSSION

This study is the first epidemiological investigation of gout prevalence among a large CKD patient population, a high-risk group for gout. The prevalence of gout was 24.3% in the overall GCKD population and increased with lower eGFR from 16.0% (eGFR of ≥60 mL/min/1.73 m^2) to 35.6% (eGFR <30 mL/min/1.73 m^2), highlighting the large burden of disease posed by the painful condition of gout and its sequelae. Moreover, we found evidence for significant undertreatment; ∼30% of those with gout received no uric acid lowering medication, and among those who are treated almost half remained hyperuricaemic.

The prevalence of gout in this CKD population is about 10 times greater compared with estimates reported from population-based studies and studies of individuals with normal renal function [23]. A study conducted among individuals with CKD identified in the nationally representative population-based National Health and Nutrition Examination Survey (NHANES) found a similar gout prevalence of 35% among those with stage 4 CKD, but lower gout prevalence of 11% among those with stage 3 CKD compared with our estimate of ∼25% for CKD stages 3a and 3b [22]. A potential reason for these discrepancies is that a diagnosis of CKD stage 3 based on one measurement of serum creatinine in population-based settings such as the NHANES survey is less valid than the verified presence of CKD in patients under nephrological care, the source population of the GCKD study.

Our results of an inverse relationship between eGFR and gout as well as hyperuricaemia are consistent with other studies [21–23], but the association between albuminuria and gout is less clear. In contrast to our study, Juraschek *et al.* [22] found a graded positive relationship between gout and albuminuria, and Krishnan *et al.* [24] stated that proteinuria independently associated with increased risk of gout. A potential explanation for this discrepancy is the fact that most GCKD patients were enrolled because of an eGFR <60 mL/min/1.73 m^2, and the finding that UACR is not an independent correlate of gout in patients with CKD stage 3 or higher may not be representative of the relationship of UACR and gout in healthy

reference and/or non-CKD populations. In addition, very high UACR levels in CKD populations are often found in individuals with primary glomerular diseases, who are often younger and have CKD of auto-immune aetiology compared with older individuals with diabetes who typically have high UACR in population-based studies.

The relationship between gout and CKD is bidirectional. Although reduced kidney function can precede the development of gout [24], gout can also adversely impact renal function [34, 35]. Elevated serum urate concentrations and medication toxicity have been postulated as factors by which these conditions can lead to reduced renal function [36]. In addition, there are numerous shared correlates between the two conditions, with prevalence of 55.4% for obesity, 46.3% for diabetes, 26.7% for CHD and 97.4% for hypertension among the patients with gout in the GCKD study. Prospective studies specifically in CKD populations including different CKD stages and detailed information on medication intake are needed to determine incidence rates and correlates of new-onset gout.

Medication to treat and prevent gout is available, but the treatment of gout was reported to be suboptimal by several studies [5, 37]. The necessity to permanently maintain serum urate levels below its saturation point means that often lifelong treatment is required and cost-effective treatments are needed. Typically, the xanthine oxidase inhibitor allopurinol is prescribed as urate-lowering therapy [38], with other medication having less favourable side effect profiles or higher associated costs. The high proportion of patients with gout that showed hyperuricaemia despite treatment would be even higher if the therapeutic target for urate-lowering therapy (ULT) would be <6 mg/dL, a threshold suggested to be associated with the slowing of CKD progression [39]. This is also illustrated in a recent publication that—using a cut-off of 6 mg/dL in a general population-based sample—reported that half of US Americans with gout on urate-lowering therapy were still hyperuricaemic [40], a proportion comparable with the one we report in a CKD population using a higher cut-off of >7 mg/dL in men. These numbers clearly illustrate that pharmacologic management of gout in patients with CKD is suboptimal and underscores the need to achieve better urate treatment target rates using available treatment or additional novel urate-lowering therapies. Of note, however, there is a lack of prospective interventional trials in CKD patients assessing the risk benefit relationship of urate-lowering therapy [41]. This lack of evidence may influence treatment decisions and contribute to the relatively large fraction of patients with gout that remain untreated.

The present study has several limitations. First, a gold-standard definition of gout (crystal aspiration or ACR criteria) was not available and should be obtained for future studies of gout risk in patients with CKD. The use of self-reported physician-diagnosed gout may incorporate some misclassification, which may affect prevalence estimates but should not lead to false-positive correlate associations. Second, no data on dietary intake was available, which likewise should be assessed in future studies among CKD patients. Third, our study was based on data collected at the GCKD study enrolment visit, and we can therefore not answer questions related to the temporality of the association between eGFR and gout, or between the presence of gout and incident health outcomes such as renal replacement therapy. However, this will be possible in the future once prospective data become available. Our current study provides information on the prevalence of gout and which correlates to examine, and therefore facilitates future studies on new-onset gout. Our analyses were conducted using an ethnically homogenous German population of patients with mostly stage 3 CKD at enrolment, and our findings may therefore not be generalizable to other ethnic groups or countries or individuals with other CKD stages. Because of the general health-care coverage in Germany, we believe that access to care should have little impact on our findings, which may be different in other settings. A particular strength is that our results are based on one of the largest cohorts of CKD patients worldwide, and the standardized collection of information provides a sound foundation to the evidence reported here. Because of the substantial morbidity associated with gout, our findings are potentially of high clinical relevance and should stimulate and help design future interventional trials.

In conclusion, gout is a highly prevalent comorbidity in patients with CKD, and prevalence increases with lower eGFR. A third of CKD patients with gout are not treated for the condition, and among those who are treated almost half still show hyperuricaemia. CKD patients represent a high-risk population for gout and screening for and treatment of gout in this population deserves special attention.

SUPPLEMENTARY MATERIAL

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

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CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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ORIGINAL ARTICLE

Urinary exosomes in the diagnosis of Gitelman and Bartter syndromes

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ABSTRACT

Background. Gitelman syndrome (GS) and Bartter syndrome (BS) are hereditary salt-losing tubulopathies (SLTs) resulting from defects of renal proteins involved in electrolyte reabsorption, as for sodium-chloride cotransporter (NCC) and furosemide-sensitive sodium-potassium-chloride cotransporter (NKCC2) cotransporters, affected in GS and BS Type 1 patients, respectively. Currently, definitive diagnosis is obtained through expensive and time-consuming genetic testing. Urinary exosomes (UE), nanovesicles released by every epithelial cell facing the urinary space, represent an ideal source of markers for renal dysfunction and injury, because UE molecular composition stands for the cell of origin. On these assumptions, the aim of this work is to evaluate the relevance of UE for the diagnosis of SLTs.

Methods. UE were purified from second morning urines collected from 32 patients with genetically proven SLTs (GS, BS1, BS2 and BS3 patients), 4 with unclassified SLTs and 22 control subjects (age and sex matched). The levels of NCC and NKCC2 were evaluated in UE by SDS–PAGE/western blotting with specific antibodies.

Results. Due to their location on the luminal side of tubular cells, NCC and NKCC2 are well represented in UE proteome. The NCC signal is significantly decreased/absent in UE of Gitelman patients compared with control subjects (Mann–Whitney *t*-test, $P < 0.001$) and, similarly, the NKCC2 in those of Bartter type 1 ($P < 0.001$). The difference in the levels of the two proteins allows recognition of Gitelman and Bartter type 1 patients from controls and, combined with clinical data, from other Bartter patients. Moreover, the receiver operating characteristic curve analysis using UE NCC densitometric values