The serum uric acid concentration is not causally linked to diabetic nephropathy in type 1 diabetes

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Previous studies have shown a relationship between uric acid concentration and progression of renal disease. Here we studied causality between the serum uric acid concentration and progression of diabetic nephropathy in 3895 individuals with type 1 diabetes in the FinnDiane Study. The renal status was assessed with the urinary albumin excretion rate and estimated glomerular filtration rate (eGFR) at baseline and at the end of the follow-up. Based on previous genomewide association studies on serum uric acid concentration, 23 single nucleotide polymorphisms (SNPs) with good imputation quality were selected for the SNP score. This score was used to assess the causality between serum uric acid and renal complications using a Mendelian randomization approach. At baseline, the serum uric acid concentration was higher with worsening renal status. In multivariable Cox regression analyses, baseline serum uric acid concentration was not independently associated with progression of diabetic nephropathy over a mean follow-up of 7 years. However, over the same period, baseline serum uric acid was independently associated with the decline in eGFR. In the cross-sectional logistic regression analyses, the SNP score was associated with the serum uric acid concentration. Nevertheless, the Mendelian randomization showed no causality between uric acid and diabetic nephropathy, eGFR categories, or eGFR as a continuous variable. Thus, our results suggest that the serum uric acid concentration is not causally related to diabetic nephropathy but is a downstream marker of kidney damage.

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Diabetic nephropathy is a common complication in type 1 diabetes, affecting approximately one-third of the patients.[1] Characteristic of the condition are persistent urinary albumin excretion and a progressive decline in renal function.[2] Indeed, diabetic nephropathy is a major factor leading to dialysis and renal transplantation. Importantly, however, diabetic nephropathy is also associated with premature death.[3] In order to alleviate the long-term burden related to renal failure, it is important to discover factors associated with its development and progression.

A number of epidemiologic studies have shown a connection between serum uric acid concentration and progression of diabetic nephropathy in type 1 diabetes. Jalal *et al.*,[4] for example, reported that during a 6-year follow-up period, elevated baseline serum uric acid concentrations predicted the development of albuminuria. Similarly, Hovind *et al.*[5] observed that uric acid was associated with subsequent development of macroalbuminuria, but not microalbuminuria, during 18-year follow-up. Moreover, Ficociello *et al.*[6] reported that the baseline uric acid concentration was associated with the development of an early decrease in glomerular filtration rate (GFR) in a 6-year follow-up. In their study, uric acid was not, however, associated with an increase in urinary albumin excretion rate (AER).

In epidemiologic studies, causal inference and confounding pose challenges to the accurate interpretation of the results. In such studies, randomization, as customarily conducted in randomized, controlled trials, may not be applicable due to the study design or ethical reasons. To tackle this shortcoming, mendelian randomization, a form of genetic randomization study has been used to assess causality between an outcome and a given biological variable. This is done by studying the relationship between the outcome and a genetic determinant of the biological variable of interest. The idea behind Mendelian randomization is that the alleles derived from both parents are randomly assigned to gametes during meiosis. Therefore, the process is unaffected by confounding factors. Large-scale meta-analyses of genomewide association studies (GWASs) have revealed multiple genetic risk factors associated with elevated serum uric acid concentrations, with the strongest effect seen at rs12498742 in the *SLC2A9* gene encoding a transporter that mediates urate flux across the renal proximal tubule.[7,8]

Although of the genetic variants, rs734553 in the *SLC2A9* gene (also known as *GLUT9*), was used in the Mendelian randomization setting to show a causal link between serum uric acid and progression of chronic kidney disease (CKD) in the general (mainly nondiabetic) population,[9] another Mendelian randomization study, based on genetic variation in uric acid transporters, reported a possible causal link between increased serum uric acid and improved kidney function in healthy men (i.e., in the opposite direction).[10] Furthermore, in populations not focusing on individuals with diabetes, the observed causal associations between serum uric acid concentration and various vascular outcomes are mixed. Kleber *et al.*[11] reported that high uric acid is causally related to adverse cardiovascular outcomes, especially that of sudden cardiac death. Palmer *et al.*,[12] on the other hand, observed no causality between uric acid and ischemic heart disease or blood pressure.

Mendelian randomization has not previously been used to assess the relationship between the serum uric acid concentration and the development of diabetic nephropathy in type 1 diabetes. In the current study, we therefore aimed to assess the causality between the serum uric acid concentration and the progression of diabetic nephropathy in patients with type 1 diabetes using a Mendelian randomization approach.

RESULTS

At baseline, 2524 participants had normal AER, 540 had microalbuminuria, 536 had macroalbuminuria, and 295 had end-stage renal disease (ESRD) (Table 1, Figure 1). The median (interquartile range) baseline serum uric acid concentrations in the respective groups were 214 μmol/l (182–252), 239 μmol/l (199–276), 323 μmol/l (256–398), and 336 μmol/l (278–400) (correlation coefficient between the renal status and serum uric acid concentration $r = 0.481$, $P < 0.001$) (Figure 2).

Progression of albuminuria

Of the 3600 participants without ESRD at baseline, prospective data on renal status were available for a total of 3384 individuals (94%). At the end of the mean follow-up period of 7 ± 4 years, kidney disease had progressed in 521 of these participants (15.4%) (Table 2). Compared with those whose renal status remained unchanged during the follow-up, those whose renal status declined had longer diabetes duration, higher body mass index, higher systolic blood pressure, higher diastolic blood pressure, higher serum uric acid concentration, lower estimated glomerular filtration rate (eGFR), higher HbA_{1c}, higher total cholesterol, lower high-density lipoprotein cholesterol, and higher triglyceride concentration at baseline. Moreover, the progressors were more frequently men.

Of those with normal AER at baseline, the renal status of a total of 202 individuals (8.6%) deteriorated to microalbuminuria or worse during the follow-up period (Figure 1). The renal status progressed in 95 individuals (19.5%) and 224 individuals (41.9%) with microalbuminuria and macroalbuminuria at baseline, respectively. In the unadjusted Cox regression analyses, baseline serum uric acid concentration was associated with the progression from normal AER to microalbuminuria ($P = 0.047$), from microalbuminuria to macroalbuminuria ($P = 0.031$), and from macroalbuminuria to ESRD ($P < 0.001$) (Table 3). After adjusting for confounding factors (normal AER to microalbuminuria: triglyceride concentration, HbA_{1c}, sex, and diastolic blood pressure; microalbuminuria to macroalbuminuria: triglyceride concentration, HbA_{1c}, and sex; macroalbuminuria to ESRD: HbA_{1c}, diastolic blood pressure, and eGFR), baseline serum uric acid concentration was, however, no longer associated with the progression (respective P values: $P = 0.648$, $P = 0.133$, and $P = 0.054$).

Decrease in eGFR

Of the 2455 participants with baseline eGFR stages 1 and 2, the renal status of a total of 139 individuals (5.7%) deteriorated to stages 3 to 5 during the follow-up period. In the multivariable Cox regression analysis, the serum uric acid

Table 1 | Baseline characteristics of study subjects categorized by renal status at baseline

	Normal AER $N = 2524$ (64.8%)	Microalbuminuria $N = 540$ (13.9%)	Macroalbuminuria $N = 536$ (13.7%)	ESRD $N = 295$ (7.6%)	All $N = 3895$	P value[a]
Men (%)	48.1	59.4	58.2	60.0	52.0	<0.001
Age (yr)	37 (27–47)	39 (30–49)	41 (34–50)	46 (41–52)	39 (30–48)	<0.001
Diabetes duration (yr)	17 (9–27)	25 (17–33)	28 (22–34)	34 (29–40)	22 (13–31)	<0.001
BMI (kg/m^2)	24.6 (22.6–26.6)	25.5 (23.1–28.0)	25.6 (23.3–28.6)	23.6 (21.1–26.4)	25.0 (23.0–27.0)	<0.001
Systolic blood pressure (mm Hg)	129 (119–140)	135 (124–148)	142 (130–157)	150 (136–167)	132 (121–145)	<0.001
Diastolic blood pressure (mm Hg)	79 (71–85)	80 (74–88)	82 (77–90)	84 (73–91)	80 (72–86)	<0.001
Insulin dose (units/kg per day)	0.67 (0.53–0.82)	0.70 (0.56–0.90)	0.65 (0.53–0.79)	0.67 (0.51–0.83)	0.67 (0.53–0.83)	<0.001
Serum uric acid (μmol/l)	214 (182–252)	239 (199–276)	323 (256–398)	336 (278–400)	233 (192–281)	<0.001
eGFR (ml/min per 1.73 m^2)	94 (82–107)	89 (75–105)	58 (36–77)	NA	90 (75–105)[b]	<0.001
HbA_{1c} (mmol/mol)	65.0 (56.3–74.9)	71.6 (61.7–80.3)	72.7 (63.9–85.8)	67.2 (56.3–77.0)	67.2 (57.4–77.0)	<0.001
HbA_{1c} (%)	8.1 (7.3–9.0)	8.7 (7.8–9.5)	8.8 (8.0–10.0)	8.3 (7.3–9.2)	8.3 (7.4–9.2)	<0.001
Total cholesterol (mmol/l)	4.8 (4.2–5.4)	5.0 (4.4–5.6)	5.2 (4.6–5.9)	4.9 (4.1–5.7)	4.9 (4.3–5.5)	<0.001
HDL cholesterol (mmol/l)	1.33 (1.11–1.58)	1.28 (1.06–1.53)	1.19 (0.95–1.42)	1.22 (0.93–1.53)	1.30 (1.08–1.56)	<0.001
Triglycerides (mmol/l)	0.94 (0.72–1.28)	1.08 (0.82–1.56)	1.41 (1.03–2.04)	1.40 (0.98–1.90)	1.03 (0.77–1.46)	<0.001

AER, albumin excretion rate; BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; NA, not available.
Data are presented as frequency (%) for categorical variables and median (interquartile range) for continuous nonnormally distributed variables.
[a]*P* value represents the difference among the 4 groups of renal status.
[b]Values represent median (interquartile range) values of participants with normal AER, microalbuminuria, and macroalbuminuria.