

Original Article

Plasma uric acid and renal haemodynamics in type 2 diabetes patients

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SUMMARY AT A GLANCE

This paper, which explored the relationship between plasma uric acid (UA) and renal haemodynamics in patients with type 2 diabetes without overt kidney disease showed that higher plasma UA is associated with lower glomerular filtration rate and effective renal plasma flow but higher effective renal vascular resistance, which may contribute to glomerular dysfunction due to impairment in kidney perfusion.

ABSTRACT:

Aim: Increased plasma uric acid (PUA) concentrations are associated with chronic kidney disease in type 2 diabetes (T2D) patients. The mechanisms involved remain unclear. We investigated the relation between PUA and (intra)renal haemodynamics in T2D patients without overt kidney disease.

Methods: Eighty-eight white men and women with T2D were included (age 64 (58–68) years; body mass index 30.9 (28.3–33.6) kg/m²; glycated haemoglobin 7.1 (6.8–7.6)%). Plasma UA and fractional excretion of UA were measured, while glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were assessed by inulin and PAH-clearance techniques, respectively. Effective renal vascular resistance was calculated (ERVR). Renal afferent and efferent arteriolar resistances and glomerular hydrostatic pressure were estimated. Relationships between PUA and fractional excretion of UA and (intra)renal haemodynamic parameters were evaluated by multivariable linear regression analyses.

Results: Plasma UA concentrations were at the higher end of the normal range in most participants: 342 ± 68 μmol/L or 5.7 ± 1.1 mg/dL (mean ± SD). In multivariable analyses, PUA concentrations were negatively associated with GFR ($r = -0.471$; $P = 0.001$), ERPF ($r = -0.436$; $P = 0.003$) and glomerular hydrostatic pressure ($r = -0.427$; $P = 0.003$). In contrast, PUA concentrations had a positive correlation with ERVR ($r = 0.474$; $P = 0.001$), but not with efferent vascular resistance. Fractional excretion of UA was not related to renal haemodynamics.

Conclusion: Plasma UA was negatively associated to GFR, ERPF but positively related to ERVR in T2D patients without overt renal impairment. Plasma UA-related increase in ERVR may be related to increased arterial afferent tone, which may put the kidney at risk for renal damage through ischaemia.

The prevalence of diabetic kidney disease (DKD), characterized by declined glomerular filtration rate and/or urinary protein excretion, is increasing due to the obesity and type 2 diabetes (T2D) pandemic and has become the leading cause of end-stage kidney disease worldwide.¹ The pathophysiology of DKD is complex, multifactorial and not fully elucidated. Diabetic kidney disease results in increased morbidity and mortality as it is also strongly linked to the development of cardiovascular disease. Successful treatment of renal risk factors including

obesity, hyperglycaemia, hypertension (most notably by blocking the renin-angiotensin system) and dyslipidaemia, have improved renal outcomes; however, residual renal risk burden remains.^{1,2} Therefore, studies exploring novel mechanisms that contribute to the development of DKD in T2D patients are being conducted, which may help to formulate new targets to treat or even prevent DKD.

Asymptomatic hyperuricaemia, occurring as a result of increased conversion of purines into uric acid (UA),

impaired renal UA-excretion or both, is a common phenomenon in patients with chronic kidney disease (CKD), but also in T2D patients with lower eGFR.³ In addition, several prospective studies have demonstrated that hyperuricaemia (or plasma uric acid (PUA) concentrations high in the normal range) represents an independent risk factor for adverse renal outcomes in the general population⁴ and in T2D patients.⁵ Several mechanisms have been put forward as to how increased PUA concentrations may lead to reduced GFR. First, UA has been proposed to cause oxidative stress with increased reactive oxygen species production in the kidney and its vascular system.^{6–8} Second, UA has been proposed to induce an inflammatory response, which may cause tubular damage.⁸ Third, UA has been associated with an activated intrarenal renin-angiotensin system which increases glomerular pressure.^{9,10} In line with this hypothesis, in a hyperuricaemic rodent model, glomerular hypertension was prevented by UA lowering therapies.¹¹ Fourth, increased PUA is associated with enhanced proximal tubular sodium reabsorption, further contributing to enhanced glomerular pressure.¹² Fifth, UA has been shown to impair endothelial function causing a decrease in nitric oxide synthesis, thereby contributing to impaired vasodilation and enhanced renal arteriolar resistance.¹³ Indeed, rodent studies have suggested that UA induces pre-glomerular arteriolar damage characterized by arteriolar wall thickening and hyalinosis promoting ischaemia.^{11,14,15} These results were supported by renal biopsy studies in DKD patients where a positive correlation between PUA and renal arteriopathy was observed.¹⁶ The association between PUA and (intra)renal haemodynamics, including glomerular pressure and afferent and efferent resistances, has not been studied in T2D patients. Thus, in this study we aimed to investigate the association between PUA and renal haemodynamic parameters as derived from gold-standard inulin and para-aminohippurate (PAH) clearance techniques in T2D patients with an eGFR >60 mL/min per 1.73m².

METHODS

Study design and population

This is a cross-sectional analysis including baseline data from 88 patients that participated in two randomized clinical trials: the SAFEGUARD and RENALIS trials. The SAFEGUARD study (NCT01744236)¹⁷ was designed to investigate safety aspects of incretin-based therapies in T2D patients. The RENALIS trial (NCT02106104) investigated the renal haemodynamic effects of linagliptin versus glimepiride in T2D patients. The inclusion criteria of these studies were identical and described in full elsewhere.¹⁸ In short, overweight (body mass index (BMI) of 25–40 kg/m²) Caucasian men and postmenopausal women aged between 35 and 75 years with T2D were recruited by advertisement in local newspapers. Patients were on a stable dose of metformin and/or sulfonylurea for at least 3 months prior to inclusion.

Patients were excluded if they used diuretics which could not be stopped during the study, had a history of malignancy or pancreatic disease, active liver disease, current urinary tract infection or active nephritis, renal impairment (defined as an estimated GFR < 60 mL/min per 1.73m²), a neurogenic bladder or if they had a history of cardiovascular disease in the past 6 months. None of the patients used other glucose-lowering drugs than metformin and/or sulfonylurea. Finally, the use of NSAIDs precluded inclusion. Both studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice. All patients provided written informed consent before any trial related activities.

Study protocol

Patients were admitted at the Clinical Research Unit of the VU University Medical Center in Amsterdam, the Netherlands as previously published. Medical history and medication were recorded. Body weight, height and BMI were obtained. Systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP) and heart rate were measured in triplicate by an automated oscillometric device (Dinamap; GE Healthcare, Little Chalfont, UK) over the brachial artery of the non-dominant arm. Before the renal tests, blood samples were taken to measure glycated haemoglobin (HbA1c), plasma glucose, albumin, creatinine, PUA and renin concentrations. Urine was collected to measure sodium, creatinine, albumin, neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1). Subsequently, a renal function protocol was performed with infusion of inulin and PAH to measure GFR and effective renal plasma flow (ERPF), respectively as described. In short, patients adhered to an average intake of sodium and protein to reduce diet-induced variation in renal physiology for 48 h before the study day. After an overnight fast, participants were asked to drink 500 mL of tap water to stimulate diuresis and to delay all medication until conclusion of the experiments, except for their morning dose of metformin. After an acclimatization period of 90 min, infusion of inulin (Inutest; Fresenius Kabi Austria, Graz, Austria) and PAH sodium (20%, Merck Sharp & Dohme International, Merck, Whitehouse Station, NJ, USA) was primed with 45 and 6 mg/kg body weight, respectively. Thereafter, maintenance infusion was started at 22.5 mg/min for inulin (target plasma concentration 250 mg/L) and 12.7 mg/min for PAH (target plasma concentration 20 mg/L). Following a 90 min equilibration period, urine was collected by spontaneous voiding every 45 min for two periods. Inulin, PAH, sodium and UA were measured in all urine and blood samples.

Calculations of intrarenal haemodynamic and tubular functions

GFR and ERPF were calculated from inulin and PAH clearances, respectively, based on timed urine sampling, and the

average of the two consecutive urine collection periods was used for analysis as described.¹⁸ Effective renal blood flow (ERBF) was calculated as $ERPF/(1 - \text{haematocrit})$, filtration fraction as $GFR/ERPF$ and effective renal vascular resistance (ERVR) as $MAP/ERBF$. Intrarenal haemodynamics (glomerular hydrostatic pressure (P_{GLO}), ERVR, flow and afferent (R_A) and efferent (R_E)) resistance was estimated according to equations as described by Gomez.¹⁹ Gomez's model is based on several assumptions. First, intrarenal vascular resistances are divided into (i) afferent resistance, (ii) post glomerular resistance and (iii) efferent resistance. Second, hydrostatic pressures within the renal tubules, venules, Bowman's space and interstitium (P_{BOW}) are in equilibrium of 10 mmHg. Third, the glomerulus is in filtration disequilibrium, and the gross filtration coefficient (K_{FG}) is 0.0867 mL/s per mmHg given normal kidney physiology ($GFR = 130$ mL/min, oncotic pressure (π_G) is 25 mmHg and $P_{GLO} = 60$ mmHg assuming that glomerular pressure is 2/3 of the MAP).²⁰ The following formulas were used: $R_A = [(MAP - P_{GLO})/ERBF] \times 1328$; $R_E = [GFR \times / K_{FG} \times (ERBF - GFR)] \times 1328$; $P_{GLO} = \Delta P_F + P_{BOW} + \pi_G$. Renal haemodynamic variables were corrected for body surface area using the Mosteller formula. We show both corrected and uncorrected data for GRF and ERPF. Fractional sodium and UA excretion (FE_{NA} and FE_{UA} , respectively) was calculated by using inulin as reference substance, as following: $FE [Na \text{ or } UA] = [Na \text{ or } UA]_{urine} \times [\text{inulin}]_{plasma} / [Na \text{ or } UA]_{plasma} \times [\text{inulin}]_{urine}$. Damage markers KIM-1, and NGAL, corrected for urine creatinine concentrations, were measured.

Biochemical measurements

Blood determinations were performed using conventional assay methods by the Department of Clinical Chemistry in the VU University Medical Center as described.²¹ Heparin-plasma and urine samples were used to assess inulin and PAH by colorimetric assay after preparation with p-dimethylamino-benzaldehyde for inulin and trichloroacetic acid and indole-3-acetic acid for PAH.²¹ Urine concentrations of KIM-1 and NGAL were determined by sandwich ELISA according to the manufacturer's specification (R&D Systems, Minneapolis, MN, USA). PUA was measured as urate with an enzymatic colorimetric test (Cobas-C501; Roche Diagnostics, Indianapolis, IN, USA) and urine-pH was buffered to >8.0 with NaOH.

Statistical analyses

Data regarding the demographics were presented as mean \pm SD if normally distributed, and median (IQR) in case of non-normal distribution. Continuous variables such as age, systolic blood pressure, diastolic blood pressure and renal haemodynamic parameters were log-transformed in case of skewed distribution. Correlations between PUA,

Table 1 Population characteristics

	Type 2 diabetes patients (n = 88)
Clinical characteristics	
Age (years)	64.0 (58.0–68.0)
Male, n (%)	71 (80.7%)
Weight (kg)	99.5 \pm 15.4
Height (m)	177.9 \pm 9.2
Body mass index (kg/m ²)	30.9 (28.3–33.6)
RAAS inhibitor use, n (%)	50 (56.8%)
Metformin use, n (%)	85 (96.6%)
Systemic haemodynamic function	
Heart rate (beats/min)	65.4 \pm 9.4
Systolic blood pressure (mmHg)	135.8 \pm 14.1
Diastolic blood pressure (mmHg)	78.1 \pm 7.7
Mean arterial pressure (mmHg)	98.7 \pm 9.1
Plasma analyses	
HbA1c (%)	7.1 (6.8–7.6)
HbA1c (mmol/mol)	54.0 (51.3–60.0)
Albumin (g/L)	36.0 (35.0–38.0)
Creatinine (umol/L)	75.0 \pm 13.4
Plasma glucose (mmol/l)	7.9 (7.2–9.1)
Plasma uric acid (umol/L)	342 \pm 68
Plasma uric acid (mg/dL)	5.7 \pm 1.1
Fractional uric acid excretion (%)	8.0 (7.1–9.9)
Fractional Na ⁺ excretion (%)	0.59 (0.45–0.76)
RAAS	
Renin (μ U/mL)	10.57 (4.9–18.9)
Renal haemodynamic function	
Glomerular filtration rate (mL/min)†	104.9 (87.8–118.6)
Effective renal plasma flow (mL/min)†	438.4 (357.3–522.4)
Glomerular filtration rate (mL/min per 1.73m ²)	79.5 (70.4–93.2)
Effective renal plasma flow (mL/min per 1.73m ²)	323 (292–407)
Filtration fraction (no dimension)	0.24 (0.22–0.27)
Effective renal blood flow (mL/min per 1.73m ²)	5801 (487–733)
Effective renal vascular resistance (mmHg/L per min)	0.17 (0.14–0.22)
Intraglomerular haemodynamic parameters	
P_{GLO} (mmHg)	60 (56–64)
R_A (dyn.s/cm ⁵)	5331 (3837–7449)
R_E (dyn.s/cm ⁵)	4020 (3378–4449)
Tubular injury markers (urine)	
KIM-1 (ng/mmol))	0.09 (0.06–0.14)
NGAL (ng/mmol)	1.18 (0.72–2.0)

Values are mean (\pm SD) or median (interquartile range). †uncorrected for body surface area. HbA1c, glycated haemoglobin; KIM-1, Kidney Injury Molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; P_{GLO} , glomerular pressure; R_A , afferent resistance; RAAS; renin-angiotensin-aldosterone system; R_E , efferent resistance.

FE_{UA} and renal haemodynamic parameters were assessed using univariate linear regression analyses. Variables that correlated with PUA were included in a multivariable linear regression to adjust for putative confounders. All analyses were performed using SPSS version 22.0 and statistical significance was defined at a two-tailed P -value <0.05.

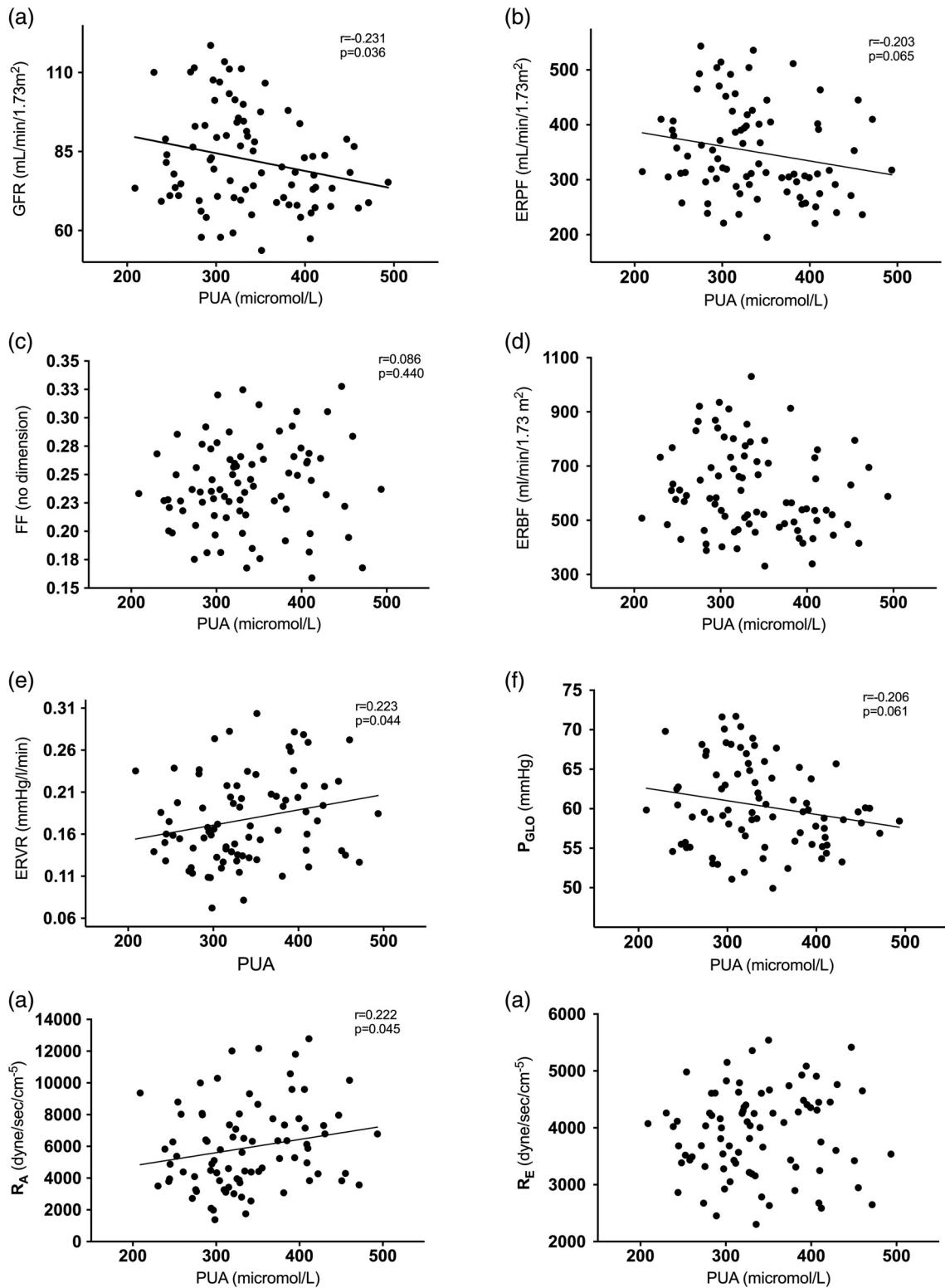


Fig. 1 Correlation analysis of plasma uric acid with GFR (A), ERPF (B), FF (C), ERBF (D), ERVR (E), P_{GLO} (F), R_A (G) and R_E (H) in T2DM ($n = 88$). ERBP, effective renal blood flow; ERPF, effective renal plasma flow; FF, filtration fraction; GFR, glomerular filtration rate; P_{GLO}, glomerular pressure; R_A, afferent resistance; R_E, efferent resistance; RVR, renal vascular resistance.

RESULTS

Population characteristics

In total, 88 subjects were included in this analysis. In general, subjects were male, overweight, well-controlled T2D with normal kidney function. All characteristics are provided in detail in Table 1.

Relation between PUA and renal haemodynamics

The PUA concentrations of the total population were at the higher end of the normal range in most participants: 342 ± 68 $\mu\text{mol/L}$ or 5.7 ± 1.1 mg/dL (Table 1) and were significantly higher in men (350.3 ± 67.9) as compared to women (304.6 ± 56.0) $\mu\text{mol/L}$; $P = 0.012$. FE_{UA} was 8.1 (7.1 – 9.9)%. We examined the association between PUA and (intra)renal haemodynamic parameters using univariate analysis. Potential effect modification was assessed but not

observed. Therefore, all analyses are reported for the whole group. PUA was negatively associated with GFR ($r = -0.231$; $P = 0.036$) and FE_{UA} ($r = -0.609$; $P < 0.001$) and positively correlated with ERVR ($r = 0.223$; $P = 0.044$) and R_A ($r = 0.222$; $P = 0.045$) (Fig. 1; Table 2; model 1). Correlations between PUA and clinical characteristics are reported in Table 3. PUA increased significantly with male sex ($r = 0.267$; $P = 0.012$) and BMI ($r = 0.282$; $P = 0.008$), while PUA was negatively associated to HbA1c ($r = -0.315$; $P = 0.003$). None of the other clinical characteristics showed an association with PUA concentrations.

Multivariable analyses

Because male sex, BMI, HbA1c and FE_{UA} were associated to PUA, these variables were additionally included in multivariable analyses (Table 2, model 2–4). After correcting for these factors, PUA was negatively correlated with GFR, ERPF and P_{GLO} and positively correlated with ERVR and R_A

Table 2 Multivariable association of PUA- and BSA-corrected and uncorrected renal haemodynamic parameters

	Model 1	Model 2 Model 1 + sex	Model 3 Model 2 + BMI + HbA1c	Model 4 Model 3 + FE_{UA}
BSA-corrected renal haemodynamic parameters				
GFR, mL/min per 1.73m ²	-0.950 ± 0.445 (P = 0.036)	-1.052 ± 0.430 (P = 0.017)	-1.182 ± 0.400 (P = 0.004)	-1.203 ± 0.354 (P = 0.001)
ERPF, mL/min per 1.73m ²	-0.154 ± 0.082 (P = 0.065)	-0.144 ± 0.080 (P = 0.078)	-0.156 ± 0.075 (P = 0.042)	-0.208 ± 0.067 (P = 0.003)
FF	141.592 ± 182.591 (P = 0.440)	51.630 ± 182.440 (P = 0.778)	39.463 ± 171.711 (P = 0.819)	158.363 ± 159.857 (P = 0.325)
ERBF, mL/min per 1.73m ²	-0.069 ± 0.044 (P = 0.119)	-0.075 ± 0.042 (P = 0.079)	-0.081 ± 0.040 (P = 0.045)	-0.111 ± 0.036 (P = 0.003)
ERVR, mmHg/L per min	272.668 ± 133.442 (P = 0.044)	267.827 ± 130.167 (P = 0.043)	300.725 ± 120.560 (P = 0.015)	352.398 ± 105.285 (P = 0.001)
P_{GLO} , mmHg	-2.449 ± 1.291 (P = 0.061)	-2.750 ± 1.251 (P = 0.031)	-3.283 ± 1.166 (P = 0.006)	-3.139 ± 1.028 (P = 0.003)
R_A , dyn. s/cm ⁵	0.005 ± 0.003 (P = 0.045)	0.005 ± 0.003 (P = 0.044)	0.006 ± 0.002 (P = 0.012)	0.007 ± 0.002 (P = 0.001)
R_E , dyn. s/cm ⁵	0.004 ± 0.009 (P = 0.637)	0.003 ± 0.009 (P = 0.705)	0.003 ± 0.009 (P = 0.708)	0.009 ± 0.008 (P = 0.240)
BSA-uncorrected renal haemodynamic parameters				
GFR, mL/min	-0.228 ± 0.313 (P = 0.468)	-0.509 ± 0.316 (P = 0.112)	-0.783 ± 0.301 (P = 0.011)	-0.780 ± 0.265 (P = 0.004)
ERPF, mL/min	-0.046 ± 0.062 (P = 0.461)	-0.071 ± 0.061 (P = 0.250)	-0.105 ± 0.058 (P = 0.073)	-0.141 ± 0.052 (P = 0.008)
ERBF, mL/min	-0.018 ± 0.033 (P = 0.576)	-0.039 ± 0.032 (P = 0.236)	-0.055 ± 0.031 (P = 0.077)	-0.075 ± 0.028 (P = 0.009)
ERVR, mmHg/L per min	41.413 ± 119.435 (P = 0.730)	127.593 ± 120.041 (P = 0.291)	186.304 ± 113.566 (P = 0.105)	254.671 ± 102.044 (P = 0.015)
P_{GLO} , mmHg	-0.835 ± 1.250 (P = 0.506)	-1.856 ± 1.258 (P = 0.144)	-2.964 ± 1.192 (P = 0.015)	-2.794 ± 1.048 (P = 0.009)
R_A , dyn. s/cm ⁵	0.000 ± 0.002 (P = 0.849)	0.002 ± 0.002 (P = 0.323)	0.003 ± 0.002 (P = 0.118)	0.004 ± 0.002 (P = 0.023)
R_E , dyn. s/cm ⁵	0.006 ± 0.012 (P = 0.648)	0.004 ± 0.012 (P = 0.773)	0.003 ± 0.011 (P = 0.788)	0.011 ± 0.011 (P = 0.292)

Bold values indicate clinical significance.

ERBF, effective renal blood flow; ERPF, effective renal plasma flow; ERVR, effective renal vascular resistance; FE_{UA} , fractional excretion of uric acid; GFR, glomerular filtration rate; P_{GLO} , glomerular pressure; R_A , afferent resistance; R_E , efferent resistance.

Table 3 Association PUA with population characteristics

Variables	R	P
Age	-0.12	0.914
Male sex	0.267	0.012
BMI	0.282	0.008
RAAS inhibitor use	0.014	0.895
Systolic blood pressure (mmHg)	0.015	0.886
Diastolic blood pressure (mmHg)	0.168	0.118
MAP (mmHg)	0.094	0.384
HbA1c	-0.315	0.003
Plasma glucose (mg/dL)	-0.197	0.065
Fractional uric acid extraction (%)	-0.609	0.001

Data show the Pearson correlation coefficient. Bold values indicate statistically significant correlations. BMI, body mass index; HbA1c, glycated haemoglobin; MAP, mean arterial pressure; RAAS, renin aldosterone angiotensin system.

(Table 2). Also, when assessing associations between PUA and uncorrected renal haemodynamic parameters, PUA was negatively correlated with GFR, ERPF and P_{GLO} , and positively correlated with ERVR and R_A (Table 2). In contrast, FE_{UA} was not related to any (intra)renal haemodynamic parameters (correlations with GFR $r = -0.059$; $P = 0.6$; with ERPF $r = -0.125$; $P = 0.2$; with filtration fraction $r = 0.74$; $P = 0.5$ and with ERVR $r = 0.103$; $P = 0.4$).

DISCUSSION

Renal complications of T2D are associated with significant morbidity and mortality despite current treatment strategies, while the underlying mechanisms driving DKD remain incompletely understood. Since increased PUA concentrations have been consistently associated with declined eGFR and DKD development in T2D patients, it is important to understand the mechanisms that are involved. In the current report, we are the first to describe the association between PUA and measured GFR in T2D patients as well as the relations between PUA and (intra)renal haemodynamic parameters in this population, measured by gold-standard inulin and PAH clearance techniques. We observed an inverse relation between PUA and GFR and ERPF, and a positive association with renal vascular resistance (ERVR). In contrast, no effect of PUA on renal efferent arteriolar resistance was observed, nor was FE_{UA} associated with (intra)renal haemodynamics. This could suggest that effects of PUA particularly related to the afferent arterioles of the kidney. Our results are in line with experimental studies where increased PUA concentrations were related to arteriopathy of the pre-glomerular vasculature though medial thickening and hyalinosis. In addition, hyperuricaemia impaired endothelial function, which increased resistance of the afferent arteriole.^{11,13,15,22} Notably, this was prevented by UA lowering by allopurinol treatment.¹¹ Furthermore, in humans with CKD but without diabetes, Kohagura *et al.*¹⁶ reported that high concentrations of UA

were significantly associated with renal arteriolar wall thickening and hyalinosis using renal biopsy samples. The presence of these histological abnormalities in the afferent arteriole may predispose the kidney to damage through ischaemia.

How UA alters afferent arteriolar morphology and function at the molecular level is unclear, but it has proposed to be secondary to changes in renin concentrations/activity, cyclooxygenase-2 or nitric oxide synthase-1 activities. We did not observe an association between PUA and plasma renin concentrations, nor did renin concentrations modulate the associations between PUA and renal haemodynamics. UA may also induce renal damage via other mechanisms, for example, by inducing inflammation or through deposition of toxic UA crystals that cause tubular obstruction. Although we did not measure plasma markers of inflammation, we did not observe an association between PUA and tubular damage markers such as NGAL or KIM-1. In the Olivetti Heart Study,¹² increased PUA concentrations were associated with enhanced proximal tubular resorption of UA and of sodium. Especially the latter, has been strongly linked to increased glomerular pressure. Although FE_{UA} was negatively associated with PUA in our analyses, there were no associations between FE_{UA} and FE_{NA} and (intra)renal haemodynamic parameters, making a primary tubular mechanism relating PUA and ERVR unlikely.

Interestingly, previous studies showed that also in the general population (e.g. without the presence of T2D), PUA was shown to be a risk factor for CKD,^{4,23} as well as in type 1 diabetes (T1D) patients.²⁴ And in line with our data, similar renal haemodynamic responses have been linked to PUA in these populations. Uedono *et al.* showed the association between PUA and a decrease in GFR and ERPF in healthy subjects, with concomitant increase in R_A , while in T1D patients similar observations were published by Lytvyn *et al.*^{20,25} Since the pathophysiology of CKD in T2D patients, due to a combination of factors including hyperglycaemia, hypertension and atherosclerosis, is markedly different from T1DM patients as well as normoglycaemic CKD, our study provides relevant new information.

This study has a few limitations. First, due to study design, we could only study associations and not causality. Second, we included white participants only. Hence, our study may not be extrapolated to other ethnicities. Third, we could not measure all renal haemodynamic parameters directly since this is impossible in humans. Therefore, we used Gomez-derived formulas to estimate intrarenal haemodynamic parameters. Fourth, UA concentrations vary within individuals depending on dietary intake. Hence, differences in diet could influence UA concentrations between subjects; although this might not influence observed associations. Fifth, we did not measure stable nitric oxide metabolites (nitrite and nitrate) to determine if increased vascular resistances are the result of UA-dependent nitric oxide depletion, but it should be noted that these metabolites are also influenced by dietary nitrite

and nitrate intake.²⁶ Additionally, NO depletion is not specific to the afferent arteriole.

Intervention studies are necessary to study the effect of PUA lowering therapy on renal haemodynamic function and on long-term renal outcome. A few smaller studies have investigated the effects of UA lowering on renal function. In hyperfiltering T1D patients, but not healthy controls, febuxostat reduced GFR without affecting afferent resistance.²⁷ In another small study in T2D patients with asymptomatic hyperuricaemia, it was observed that allopurinol, after 3 years of treatment, reduced urinary albumin excretion and preserved eGFR compared to placebo.²⁸ Furthermore, Goicoechea *et al.*²⁹ reported that treatment with allopurinol slowed down the progression of renal disease in CKD patients. Similar effects were observed in hyperuricaemic CKD patients (eGFR <60 mL/min) 30–40% of whom were diagnosed with T2D, where allopurinol treatment over 24 months slowed eGFR decline compared to usual care. These data suggest the potential of allopurinol to reduce CKD progression, a hypothesis which requires confirmation in a large T2D DKD outcome trial. Currently, a clinical trial, the PERL study, is investigating the 3-year effect of allopurinol *versus* placebo on the progression of DKD in T1D.³⁰ Studies assessing the effects of PUA lowering on renal haemodynamics will further contribute to our knowledge regarding the potential nephroprotective properties of these agents.

In conclusion, the findings of the present study indicate that higher PUA concentrations in T2D patients are associated with lower GFR and ERPF as measured by gold-standard inulin and PAH clearance techniques. The observed increase in ERVR may contribute to glomerular dysfunction due to impairment in kidney perfusion. Intervention studies are needed to fully grasp the potential renoprotective effects of PUA lowering therapies in T2D patients.

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DISCLOSURE

We have no conflict of interest to report.

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