Metabolism Clinical and Experimental 116 (2021) 154465

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Serum uric acid is associated with increased risk of posttransplantation diabetes in kidney transplant recipients: a prospective cohort study

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ARTICLE INFO

Article history:
Received 30 September 2020
Accepted 9 December 2020

Keywords:
Uric acid
Posttransplantation diabetes
Kidney transplantation
Inflammation
Oxidative stress
Metabolic syndrome

ABSTRACT

Background: Serum uric acid (SUA) is associated with fasting glucose in healthy subjects, and prospective epidemiological studies have shown that elevated SUA is associated with increased risk of type 2 diabetes. Whether SUA is independently associated with higher risk of posttransplantation diabetes mellitus (PTDM) in kidney transplant recipients (KTR) remains unknown.

Methods: We performed a longitudinal cohort study of 524 adult KTR with a functioning graft ≥1-year, recruited at a university setting (2008–2011). Multivariable-adjusted Cox proportional-hazards regression analyses were performed to assess the association between time-updated SUA and risk of PTDM (defined according the American Diabetes Association's diagnostic criteria).

Results: Mean (SD) SUA was 0.43 (0.11) mmol/L at baseline. During 5.3 (IQR, 4.1–6.0) years of follow-up, 52 (10%) KTR developed PTDM. In univariate prospective analyses, SUA was associated with increased risk of PTDM (HR 1.75, 95% CI 1.36–2.26 per 1-SD increment; $P < 0.001$). This finding remained materially unchanged after adjustment for components of the metabolic syndrome, lifestyle, estimated glomerular filtration rate, immunosuppressive therapy, cytomegalovirus and hepatitis C virus infection (HR 1.89, 95% CI 1.32–2.70; $P = 0.001$). These findings were consistent in categorical analyses, and robust in sensitivity analyses without outliers.

Conclusions: In KTR, higher SUA levels are strongly and independently associated with increased risk of PTDM. Our findings are in agreement with accumulating evidence supporting SUA as novel independent risk marker for type 2 diabetes, and extend the evidence, for the first time, to the clinical setting of outpatient KTR.

1. Introduction

Kidney transplantation is the preferred treatment for end-stage kidney disease because it offers better survival and quality of life at lower costs than the alternative of dialysis [1,2]. It is, however, not exempt of complications. Posttransplantation diabetes mellitus (PTDM) is one of the main metabolic disorders following kidney transplantation. Its incidence ranges widely between 2—50% [3], progressively increasing after the first year posttransplantation [4]. PTDM associates with a general poor prognosis for kidney transplant recipients (KTR), contributing to increased risk of graft failure, cardiovascular complications and overall mortality [5–8]. Important risk factors for PTDM include maintenance immunosuppressive therapy, obesity, metabolic syndrome and cytomegalovirus and hepatitis C virus infections [9–11].

Similar to type 2 diabetes, PTDM is characterized by insulin resistance and pancreatic β cell dysfunction [10,12]. Also similar to type 2 diabetes, oxidative stress and chronic low-grade inflammation have been proposed to play an important role in pathophysiological mechanisms underlying development of PTDM in KTR [13–15]. Although kidney transplantation aims to restore kidney function, it incompletely abolishes ongoing chronic low-grade inflammation, oxidative stress and impaired metabolic homeostasis [16]. In outpatient KTR, several factors inherent to this clinical setting, including chronic use of calcineurin inhibitors and corticosteroid therapy, and well-documented elevation of serum uric acid (SUA), contribute to perpetuate redox imbalance and low grade of systemic inflammation [16–20], all converging to resemblance of the type 2 diabetes milieu.

Abbreviations: eGFR, estimated Glomerular Filtration Rate; KTR, kidney transplant recipients; PTDM, posttransplantation diabetes mellitus; SUA, serum uric acid.

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https://doi.org/10.1016/j.metabol.2020.154465

Indeed, hyperuricemia (defined as SUA >0.42 mmol/L or >7.0 mg/dL in men and >0.36 mmol/L or >6.0 mg/dL in women) is a common metabolic disorder following kidney transplantation [21]. Interestingly, different metabolic pathways have been proposed between uric acid, insulin resistance and hepatic gluconeogenesis in general population-based studies [22–25]. Additionally, a growing body of evidence, including prospective cohort studies, show that hyperuricemia is associated with the development of type 2 diabetes independently of other risk factors [26–28]. In line, it has recently been shown that decrease in SUA is associated with lower age-related worsening of fasting plasma glucose and systolic blood pressure in a general population-based study [29]. Reduction in SUA has also been associated with pleiotropic effects, including improvement of redox imbalance and endothelial dysfunction [22,30,31]. SUA has been proposed as a new therapeutic target for type 2 diabetes [28], which could also have therapeutic potential in the clinical setting of outpatients KTR.

Since both assessment and treatment of hyperuricemia are widely available and inexpensive, SUA may be an interesting and novel risk factor for PTDM, with foreseeable impact in clinical practice. However, the association of SUA with risk of PTDM in KTR remains unexplored. The current study was initiated to test the extent to which SUA is independently associated with increased risk of PTDM in outpatient KTR.

2. Material and methods

2.1. Study population

Between November 2008 and March 2011, all adult KTR with a functioning allograft ≥1-year, visiting the outpatient clinic of the University Medical Center Groningen (the Netherlands) were invited to participate in the TransplantLines Food and Nutrition Biobank and Cohort Study, as described previously [32]. A total of 707 of 817 (87%) eligible KTR signed informed consent. Patients with diabetes or a history of diabetes at baseline ($n = 183$) were excluded from the current analyses, resulting in 524 KTR, of whom data are hereby presented (a flowchart is shown in Supplemental Fig. 1). The study protocol has been approved by the institutional review board (METc 2008/186) and was conducted in accordance with the Declaration of Helsinki.

2.2. Posttransplantation diabetes mellitus

The primary end-point of this study was PTDM, which was diagnosed according to the American Diabetes Association criteria, when at least one of the following criteria was met: 1) symptoms of diabetes (*e.g.*, polyuria, polydipsia, unexplained weight loss) plus a nonfasting plasma glucose concentration ≥ 11.1 mmol/L (200 mg/dL), 2) fasting plasma glucose (FPG) ≥7.0 mmol/L (126 mg/dL), 3) start of antidiabetes medication, or 4) plasma HbA1c ≥6.5% (48 mmol/mol) [33,34]. KTR were censored for PTDM at the time of graft failure (*i.e.*, they returned to dialysis or received another transplantation, $n = 54$) or death ($n = 62$). The surveillance system of the outpatient program at our university hospital ensures updated information on patient status and events. Within this system, patients visited the outpatient clinic with declining frequency, in accordance with the guidelines of the American Society of Transplantation [35]. The end-point was recorded until September 2015. General practitioners or referring nephrologists were contacted in case the status of a patient was unknown. No patients were lost to follow-up.

2.3. Data collection and definitions

Medical and transplantation history as well as medication use were extracted from electronic patient records. According to a strict protocol, all patients were asked to collect a 24 h urine specimen during the day before to their visit at the outpatient clinic. Blood was drawn in the morning after completion of the 24 h urine collection. The measurement of clinical and laboratory parameters has been described in detail [36]. Serum concentrations of uric acid were measured with the Merck Mega clinical chemistry analyzer with the uricase PAP (peroxidase-aminophenazone) method, with an intra- and interassay coefficient of variation of 1.1% and 1.3%, respectively. Information on alcohol consumption and smoking behavior was obtained by questionnaire [37]. History of diabetes was defined as the use of antidiabetic medication or a fasting blood glucose ≥7.0 mmol/L. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [38].

2.4. Statistical analyses

Data analyses were performed by using SPSS 27.0 for Windows (IBM, Chicago, Illinois, USA), GraphPad Prism 7.02 software (GraphPad Software Inc., San Diego, CA, USA), and R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). Baseline characteristics of study subjects are described overall the study population and by subgroup of patients according to tertiles and sex-specific tertiles of SUA distribution. Normally distributed variables are described as mean (SD), and skewed variables as median (IQR). Categorical variables are expressed as *n* (number) with percentage (%). Differences were studied with the chi-squared test for categorical variables and by means of linear regression analyses for continuous variables. A two-sided *P* value <0.05 was considered significant.

2.5. Prospective analyses

In prospective analyses of the primary end-point PTDM, a Kaplan-Meier curve and a log-rank test were performed to study whether the distribution of events was significantly different by subgroups of KTR according to tertiles of SUA concentration. The association of SUA with risk of PTDM was further examined by means of Cox proportional-hazards regression analyses, in which SUA was standardized to estimate regression coefficients per 1-SD relative increment. In these analyses, the competing risk of death was taken into account by performing analyses according to the proportional cause-specific hazards model approach, which allows estimation of regression parameters that directly quantify hazard ratios among those individuals who are actually at risk of developing the event of interest [39–41], which needs to be distinguished from the sub-distribution hazards model approach (proposed by Fine and Gray) [42], in which subjects who experience a competing event (*e.g.*, death) remain in the risk set, although they are in fact no longer at risk of the event of interest (*i.e.*, posttransplant diabetes). For these analyses, we used baseline and time-updated measurements of SUA as available during follow-up visits to the outpatient clinic. Thus, to calculate of the regression coefficients in time-updated analyses, each time we used the most recent SUA measurement, as available previous to the event, censoring or end of follow-up, *i.e.*, at a median of 3.0 (interquartile range, 2.1—3.7) years after enrollment. Associations are shown with SUA as a continuous variable and according to tertiles and sex-specific tertiles of the SUA distribution. Schoenfeld residuals were calculated to assess whether proportionality assumptions were satisfied. We entered the quadratic and cubic terms of SUA with the linear term to assess the presence of nonlinear relationships. To illustrate the association of SUA with risk of PTDM, data were fitted using median SUA concentration as reference value.

To study the effect of potential confounders, several Cox regression models were fitted to the data. We performed adjustment for age, sex, body mass index, high-sensitivity C-reactive protein, and gout medication in model 1. Subsequently, additive adjustments were performed for components of the metabolic syndrome (waist circumference, fasting plasma glucose, glycated hemoglobin, blood pressure, triglycerides, and high-density lipoprotein cholesterol) in model 2; lifestyle (smoking status, alcohol consumption, physical activity, total energy intake, and fruit and vegetable consumption) in model 3; dialysis vintage,

transplant vintage, eGFR, and proteinuria, in model 4; cytomegalovirus infection, hepatitis C virus infection, and immunosuppressive therapy, in model 5.

2.6. Effect-modification analyses

In adherence with international recommendations for analyses and reporting of observationsl studies, in secondary analyses, potential effect-modification on risk of PTDM by age, sex, body mass index, eGFR, fasting glucose, and immunosuppressive therapy were tested by fitting models containing both main effects and their cross product terms [43,44]. $P_{interaction} < 0.05$ was considered to indicate significant effect-modification. We then performed correction for multiple testing by means of the Bonferroni method. Because we have investigated potential effect-modification for 6 variables, the corrected threshold based on the false discovery rate level of 0.05 was $0.05/6 = 0.008$. This Bonferroni-adjusted significance threshold ($P_{interaction} < 0.008$) was considered to justify stratified analyses.

2.7. Sensitivity analyses

We identified SUA outliers by using Turkey's fences [45], according to the formula: [$Q_1 - k$ (IQR), $Q_3 + k$ (IQR)]; in which k is 1.5 for all outliers, Q_1 is the lower quartile and Q_3 is the upper quartile. For prospective analyses without outliers, we used Cox regression models analogous to the overall prospective analyses. Estimates are shown for patients pertaining to tertile 3 of SUA distribution in relation to patients pertaining to tertile 1 (reference group).

3. Results

3.1. Baseline characteristics

We included 524 KTR (52 ± 13 years-old, 57% male). Mean eGFR was 52 ± 23 mL/min/1.73 m^2. Mean (SD) SUA was 0.43 (0.11) mmol/L. Detailed description of baseline characteristics by tertiles and sex-specific tertiles of SUA distribution is presented in Table 1 and Supplemental Table 1, respectively. Significant differences across tertiles of SUA were observed with a positive trend over increasing tertiles for male sex, body mass index, proteinuria, diastolic blood pressure, use of antihypertensive medication, high-sensitivity C reactive protein, fasting plasma glucose, total cholesterol, low-density lipoprotein cholesterol, triglycerides, and use of cyclosporine. A negative trend over increasing tertiles of SUA were observed for eGFR, high-density lipoprotein cholesterol, and living donation.

3.2. Serum uric acid and risk of PTDM

During a median follow-up of 5.3 (IQR, 4.1–6.0) years, 52 KTR (10%) were diagnosed with PTDM, with a significantly different distribution across increasing tertiles of SUA ($P = 0.02$). A Kaplan-Meier curve for PTDM according to tertiles of SUA distribution is shown in Fig. 1, and according to sex-specific tertiles of SUA in Supplemental Fig. 2. In Cox regression analyses, among those patients who did not (yet) experience the event of interest or a competing event, unadjusted baseline SUA was associated with risk of PTDM (HR 1.47, 95% CI 1.13–1.90 per 1-SD increment; $P = 0.004$), and we consistently found that patients in the highest tertile of baseline SUA were at higher risk of PTDM (HR 2.55, 95% CI 1.24–5.26) compared to patients in the lowest tertile (Supplemental Table 2). These findings remained consistent in analyses of sex-specific tertiles of SUA (Supplemental Table 3). In analyses with time-updated SUA, we observed that the association of SUA with PTDM was of higher magnitude compared to analyses using baseline SUA (Table 2). These findings remained consistent in analyses of time-updated sex-specific tertiles of SUA (Supplemental Table 4). In each of these approaches, we found that the association of SUA with PTDM remained materially unchanged after accounting for components of the metabolic syndrome, lifestyle, eGFR, and transplant-related factors, including cytomegalovirus and hepatitis C virus infection, and immunosuppressive therapy. The multivariable-adjusted association of SUA with risk of PTDM (A) in the overall study population and (B) after exclusion of 3 outliers, using Cox regression analyses with median SUA (0.42 mmol/L) as reference, and in relation to the histogram of SUA is visualized in Fig. 2.

3.3. Effect-modification analyses

We observed no effect-modification on PTDM by age, sex, body mass index, eGFR, fasting glucose, and immunosuppressive therapy ($P_{interaction} > 0.05$ for all).

3.4. Sensitivity analyses

In sensitivity analyses with exclusion of all outliers ($n = 3$, SUA >0.73 mmol/L) from the third tertile, SUA remained significantly associated with risk of PTDM (HR 2.98, 95% CI 1.46–6.07). This finding remained materially unchanged in further multivariable-adjusted analyses (Table 2; Fig. 2).

4. Discussion

Our results consistently show that higher SUA concentrations are associated with increased risk of PTDM, independently of components of the metabolic syndrome, lifestyle, eGFR, and transplant-related variables including immunosuppressive therapy, cytomegalovirus and hepatitis C virus infections. The association was particularly strong in time-updated SUA analyses and robust in analyses with exclusion of outliers. These results suggest that SUA is an independent risk marker for PTDM in KTR, pointing toward the need for further evaluating potential underlying mechanisms linking uric acid with increased risk of PTDM. These findings may pave the way toward a novel therapeutic strategy for PTDM potentially based on timely management of SUA elevations in outpatient KTR.

Our findings are consistent with previous studies in the general population reporting that relatively high SUA is associated with increased risk of type 2 diabetes [26,27]. In the Rotterdam Study, van der Schaft et al. reported that SUA was positively associated with incidence of prediabetes in individuals with normoglycemia [46]. Two previous meta-analyses showed that every 1 mg/dL (0.0595 mmol/L) increase in SUA results in an increased risk of 6% to 11% for type 2 diabetes [27,47]. Moreover, hyperuricemia was reported to be a strong predictor of incident type 2 diabetes during 5-years of follow-up in an Asian population [48]. Previous studies have reported that higher SUA and use of antigout medication —which may be representative of higher SUA— are associated with PTDM [11,49]. Chakkera et al. found that, among 37 individuals who used gout medication before transplantation, 43% developed PTDM during the first year posttransplantation [49]. The authors emphasized that SUA and gout medication have been identified as risk factors for type 2 diabetes but have not been reported as risk factors for PTDM. Our study is in line with previous findings on the association of SUA with type 2 diabetes, and extends those findings for the first time to the clinical setting of outpatient KTR.

Although kidney transplantation aims to recover kidney function, it incompletely mitigates mechanisms of disease such as inflammation, oxidative stress and impaired metabolic homeostasis [16]. In the current study, we found that most patients had hyperuricemia, which is in line with previous studies [21,50]. On the basis that about 70% of SUA is eliminated by the kidneys, these data may indicate that intestinal secretion of uric acid is not sufficient to compensate excess SUA in KTR [51]. It has also been proposed that beyond impaired kidney function, hyperuricemia may be related to maintenance use of immunosuppressive agents [52,53]. Calcineurin inhibitors, specifically, have been associated

Table 1
Baseline characteristics of 524 KTR, overall and by tertiles of serum uric acid.

Baseline characteristics	Overall		Tertiles of serum uric acid						*P* value
			Tertile 1		Tertile 2		Tertile 3		
Uric acid, mmol/L	0.43	(0.11)	0.31	(0.05)	0.42	(0.03)	0.55	(0.07)	–
Gout medication use, *n* (%)	46	(9)	13	(7)	16	(9)	17	(10)	0.70
Demographics and allograft function									
Age, years	52	(13)	51	(14)	51	(13)	52	(13)	0.41
Sex (male), *n* (%)	299	(57)	77	(44)	114	(64)	108	(64)	<0.001
Ethnicity (Caucasian), *n* (%)	521	(99)	173	(99)	179	(100)	169	(99)	0.36
Body mass index, kg/m^2	26.0	(4.4)	25.2	(4.1)	26.0	(4.3)	26.7	(4.6)	<0.001
Waist circumference, cms	96.4	(14.0)	93.0	(14.0)	97.3	(14.8)	99.0	(12.5)	<0.001
eGFR, mL/min/1.73 m^2	52	(23)	69	(22)	48	(20)	38	(16)	<0.001
Proteinuria, ≥0.5 g/24 h, *n* (%)	110	(21)	21	(12)	45	(25)	44	(26)	0.002
Cardiovascular history and lifestyle									
Systolic blood pressure, mmHg	135	(17)	134	(16)	134	(17)	137	(18)	0.10
Diastolic blood pressure, mmHg	83	(11)	81	(11)	82	(11)	84	(11)	0.02
Use of antihypertensive medication, *n* (%)	454	(87)	134	(77)	159	(89)	161	(95)	<0.001
Current smoker, *n* (%)	67	(13)	15	(9)	25	(14)	27	(16)	0.14
Alcohol consumption									0.58
0–10 g/day, *n* (%)	340	(65)	120	(69)	113	(63)	107	(63)	
10–30 g/day, *n* (%)	109	(21)	34	(19)	37	(21)	38	(22)	
≥30 g/day, *n* (%)	25	(5)	5	(3)	10	(6)	10	(6)	
Physical activity, time * intensity, median (IQR)	5520	(2585−8513)	5160	(2760−7140)	5800	(3150−9240)	5685	(1800−9255)	0.99
Energy intake, kcal/day	2188	(618)	2186	(582)	2218	(684)	2158	(582)	0.83
Fruit consumption, g/day, median (IQR)	123	(58–232)	132	(77–239)	109	(49–227)	120	(66–232)	0.36
Vegetable consumption, g/day, median (IQR)	90	(52–132)	91	(59–122)	82	(47–135)	91	(52–135)	0.91
Inflammation, glucose and lipids									
hs-CRP, mg/L, median (IQR)	1.4	(0.6–3.8)	1.2	(0.5–3.5)	1.4	(0.7–3.9)	1.6	(0.7–4.6)	0.03
Fasting plasma glucose, mmol/L	5.2	(0.6)	5.1	(0.6)	5.2	(0.6)	5.3	(0.7)	0.02
HbA1c, %	5.7	(0.4)	5.7	(0.3)	5.7	(0.4)	5.7	(0.4)	0.92
Total cholesterol, mmol/L	5.1	(1.1)	5.0	(1.0)	5.1	(1.1)	5.2	(1.2)	0.05
HDL cholesterol, mmol/L, median (IQR)	1.3	(1.1–1.7)	1.4	(1.2–1.8)	1.3	(1.1–1.6)	1.2	(1.0–1.6)	<0.001
LDL cholesterol, mmol/L	3.0	(0.9)	2.9	(0.9)	3.1	(1.0)	3.1	(0.9)	0.02
Triglycerides, mmol/L, median (IQR)	1.6	(1.2–2.2)	1.4	(1.3–2.2)	1.7	(1.3–2.2)	1.8	(1.4–2.5)	<0.001
Lipid-lowering drugs									
Use of statins, *n* (%)	259	(49)	88	(50)	81	(45)	90	(53)	0.34
Use of cholestyramine, *n* (%)	6	(1)	1	(1)	3	(2)	2	(1)	0.62
Other, *n* (%)	16	(3)	2	(1)	6	(3)	2	(1)	0.14
Transplantation and immunosuppressive therapy									
Dialysis vintage, months, median (IQR)	25	(7–50)	21	(3–47)	25	(9–47)	31	(9–59)	0.16
Transplant vintage, years, median (IQR)	5.3	(2.1–12.2)	5.1	(2.3–10.5)	5.2	(1.6–11.9)	5.6	(1.8–13.9)	0.53
Living donor, *n* (%)	191	(37)	79	(45)	64	(36)	48	(28)	0.01
Cytomegalovirus infection, *n* (%)	131	(25)	39	(22)	47	(26)	45	(27)	0.67
Hepatitis C virus infection, *n* (%)	6	(1)	1	(1)	2	(1)	3	(2)	0.34
Cyclosporine, *n* (%)	197	(38)	47	(27)	62	(35)	88	(52)	<0.001
Tacrolimus, *n* (%)	90	(17)	20	(11)	35	(20)	35	(21)	0.05
Sirolimus, *n* (%)	6	(1)	3	(2)	1	(1)	2	(1)	0.58
Azathioprine, *n* (%)	97	(19)	36	(21)	26	(15)	35	(21)	0.24
Mycophenolic acid, *n* (%)	342	(65)	119	(69)	124	(69)	99	(58)	0.06
Prednisolone use, *n* (%)	519	(99)	175	(100)	178	(99)	166	(98)	0.06
Prednisolone dose, mg/day, median (IQR)	10.0	(7.5–10.0)	10.0	(7.5–10.0)	10.0	(7.5–10.0)	10.0	(7.5–10.0)	0.59

Values presented as mean (SD) unless stated otherwise. Differences among tertiles of serum uric acid (tertile 1, $n = 175$: ≤0.37 mmol/L; tertile 2, $n = 179$: 0.37–0.47 mmol/L; tertile 3, $n = 170$: ≥0.47 mmol/L) were studied by means of analysis of variance or the linear regression test for continuous variables and by means of the chi-squared test for categorical variables. Abbreviations: eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein cholesterol.

with both higher uric acid levels and risk of PTDM, independently [52,53]. In line with our findings, cyclosporine has been more associated to hyperuricemia than tacrolimus in KTR [54]. Yet, we found that the association between SUA and PTDM was independent of immunosuppressive treatment, which may be indicative of additional mechanisms. It has also been shown that uric acid amplifies immunossupressive agents-derived toxicity, which may ultimately lead to increased pancreatic toxicity and diabetogenic mechanisms related with pancreatic β cell impairment and insulin resistance [10,55]. Although we did not find signs of an effect-modification of immunosuppression agents on the association between SUA and risk of PTDM, further studies are needed to evaluate whether this proposed mechanism may contribute to increased risk of PTDM by relatively high SUA.

SUA contributes to insulin resistance by altering glucose uptake, inhibiting nitric oxide synthase, inducing oxidative stress and TNF-α production, and inducing endothelial dysfunction [23,24,56,57]. Intracellular UA has been shown to increase hepatic gluconeogenesis by stimulating adenosine monophosphate dehydrogenase and inhibiting adenosine monophosphate protein kinase [25]. Indeed, hyperuricemia has been strongly associated with insulin resistance in healthy subjects [22]. An association between higher SUA and impaired β cell function, both in patients with and without diabetes, has been reported in previous studies [30,48,58]. In patients without type 2 diabetes, SUA has been positively associated with homeostasis model assessment of insulin resistance and negatively with quantitative insulin sensitivity check index [30,48]. The aforementioned mechanisms and clinical studies may causally explain and support our findings on the prospective association between SUA and risk of PTDM in outpatient KTR [25].

The aforementioned studies about potential mechanisms underlying the observed associations between uric acid and risk of type 2 diabetes

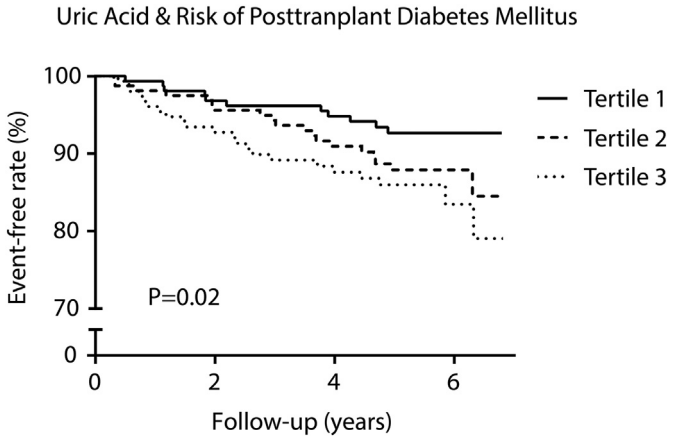

Fig. 1. Kaplan-Meier curve for posttransplant diabetes mellitus according to tertiles of serum uric acid (tertile 1, $n = 175$: ≤0.37 mmol/L; tertile 2, $n = 179$: 0.37–0.47 mmol/L; tertile 3, $n = 170$: ≥0.47 mmol/L). Event-free rate was significantly different across increasing tertiles of serum uric acid ($P = 0.02$). *P* value was calculated by log-rank test.

mellitus underscore a need for further studies to substantiate the therapeutic potential of uric acid-targeted strategies. It should be realized that previous studies on the therapeutic potential of allopurinol —a xanthine oxidase inhibitor— in chronic kidney disease patients have focused on decline of eGFR as outcome of interest. Lack of a beneficial effect of allopurinol on progression of chronic kidney disease in a recent randomized clinical trial has been suggested to be indicative of absence of a cause-effect relationship between uric acid and progression of chronic kidney disease [59]. Other studies have, however, shown a beneficial effect of lowering SUA by allopurinol in the context of type 2 diabetes [56]. Takir et al. reported that lowering SUA with allopurinol improved insulin resistance and systematic inflammation after 3 months [30]. Interestingly, allopurinol was recently shown to improve recurrent cardiovascular disease in patients with stable ischemic coronary artery disease [60]. On the basis that SUA contributes to systemic inflammation, persistent oxidative stress, endothelial dysfunction and insulin resistance [15,18,57,61], an interventional strategy aimed at lowering SUA may offer interesting opportunities in the post-kidney transplant setting [28,30,31].

Table 2
Prospective association of time-updated serum uric acid with posttransplant diabetes.

Models	Continuous		Tertiles of serum uric acid			
	per 1 − SD increment		Tertile 1	Tertile 2	Tertile 3	Tertile 3[a]
	HR (95% CI)	*P* value	Ref.	HR (95% CI)	HR (95% CI)	HR (95% CI)
Crude	1.75 (1.36–2.26)	<0.001	1.00	1.41 (0.65–3.08)	3.06 (1.51–6.21)	2.98 (1.46–6.07)
Model 1	1.78 (1.35–2.36)	<0.001	1.00	1.62 (0.67–3.91)	3.29 (1.44–7.48)	3.19 (1.40–7.30)
Model 2	1.82 (1.35–2.45)	<0.001	1.00	1.52 (0.62–3.73)	3.33 (1.43–7.77)	3.01 (1.29–7.06)
Model 3	1.81 (1.34–2.44)	<0.001	1.00	1.57 (0.65–3.84)	3.09 (1.34–7.12)	3.01 (1.30–6.97)
Model 4	2.10 (1.45–3.04)	<0.001	1.00	2.05 (0.67–6.29)	5.32 (1.76–16.1)	5.11 (1.68–15.5)
Model 5	1.89 (1.32–2.70)	<0.001	1.00	2.71 (0.84–8.74)	4.69 (1.45–15.1)	4.48 (1.38–14.5)

Cox proportional-hazards regression analyses were performed to assess the association of serum uric acid concentration with posttraplant diabetes ($n_{events} = 52$). Associations are shown with uric acid concentration as a continuous variable and according to tertiles of the uric acid distribution (tertile 1, $n = 175$: ≤0.37 mmol/L; tertile 2, $n = 179$: 0.37–0.47 mmol/L; tertile 3, $n = 170$: ≥0.47 mmol/L).

[a] All ($n = 3$) outliers were excluded. Multivariable model 1 was adjusted for age, sex, body mass index, high-sensitivity C-reactive protein, and gout medication. Subsequently, additive adjustments were performed for components of the metabolic syndrome (waist circumference, fasting plasma glucose, glycated hemoglobin, triglycerides, high-density lipoprotein cholesterol, and blood pressure) in model 2; lifestyle (smoking status, alcohol consumption, physical activity, total energy intake, and fruit and vegetable consumption) in model 3; dialysis vintage, transplant vintage, eGFR, and proteinuria, in model 4; cytomegalovirus infection, hepatitis C virus infection, and immunosuppressive therapy, in model 5.

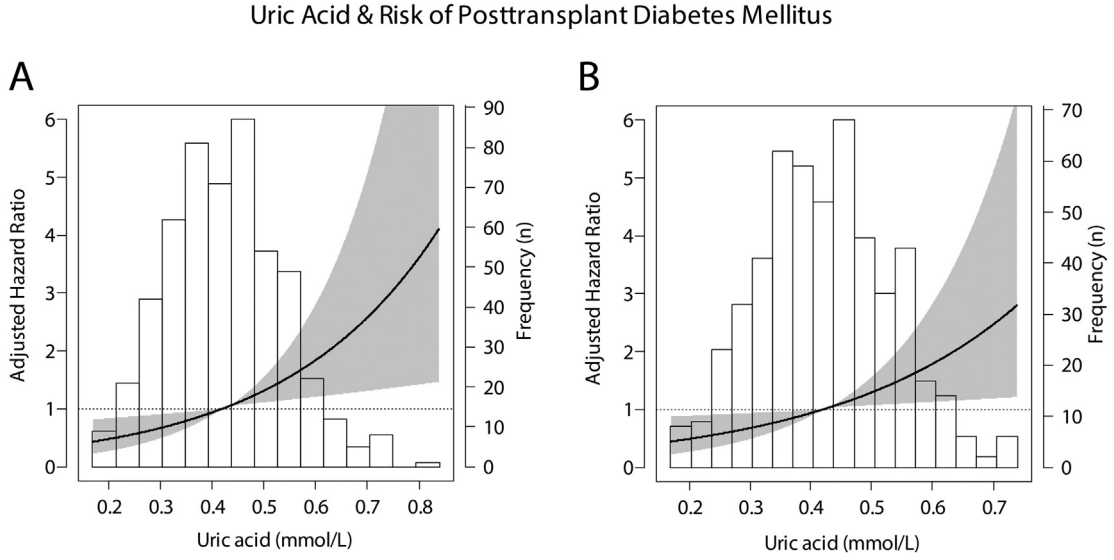

Fig. 2. Associations of serum uric acid (SUA) with risk of posttransplant diabetes mellitus (PTDM) in kidney transplant recipients, within the (A) whole study population and (B) after exclusion of outliers of the distribution of SUA ($n = 3$). X-axis represents SUA concentration and y-axis the estimated hazard ratios using median SUA (0.42 mmol/L) as reference value. Data were fitted by multivariable-adjusted (analogous to model 1 of the primary prospective analyses) Cox proportional-hazards regression. The black line represents the hazard ratio and the gray area represents the 95% confidence interval. The histogram of SUA is provided in the background. Patients with SUA lower and higher than median SUA were, respectively, at lower and higher risk of PTDM.

We performed a prospective cohort study in a large sample of stable KTR, who were closely monitored during a considerable follow-up period by regular check-up in the outpatient clinic, granting complete endpoint evaluation without loss to follow-up. Furthermore, we included outpatient KTR with a functioning graft for >1 year, enabling exclusion of KTR with transient posttransplantation hyperglycemia in the diagnose of PTDM. The primary endpoint PTDM was diagnosed based on American Diabetes Association criteria. On the other side, we acknowledge that the majority of the study population was Caucasian, which calls for prudence to extrapolating our findings to other ethnicities, particularly taking into account that previous studies showed that the association between SUA and type 2 diabetes is stronger in Western compared to Asian countries [27]. As with any observational study, residual confounding may occur despite adjustment for potential confounders. Finally, due to its observational nature, we acknowledge that the current study does not allow for conclusions on causality.

5. Conclusions

In conclusion, elevated SUA is associated with an increased risk of developing PTDM in KTR, independently of the established risk factors for PTDM such metabolic syndrome, lifestyle, immunosuppressive therapy, cytomegalovirus and hepatitis C virus infection. Whether timely management of SUA may be a target to decrease the risk of developing PTDM among outpatient KTR needs to be further studied.

Funding

This study was based on the TransplantLines Food and Nutrition Biobank and Cohort Study (TxL-FN), which was funded by the Top Institute Food and Nutrition of the Netherlands (grant A-1003). Dr. Sotomayor was supported by a doctorate studies grant from Comisión Nacional de Investigación Científica y Tecnológica (F 72190118). The study is registered at clinicaltrials.gov under number NCT02811835.

CRediT authorship contribution statement

C.G.S. wrote the manuscript and analyzed data. S.S.O. and N.I.B. wrote the manuscript and interpreted the data. I.M.N., A.W.G.-N., M.E., J.G.G., S.P.B., G.J.N., and R.R. interpreted data and revised the manuscript. S.J.L.B. designed the cohort, acquired data, and revised the manuscript. R.P.F.D. interpreted data, revised and adapted the manuscript. S.J.L.B. and R.P.F.D. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

Declaration of competing interest

No potential conflicts of interest relevant to this article were reported.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2020.154465.

References

[1] Tonelli M, Wiebe N, Knoll G, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. Am J Transplant. 2011;11:2093–109.
[2] Laupacis A, Keown P, Pus N, et al. A study of the quality of life and cost-utility of renal transplantation. Kidney Int. 1996;50:235–42.
[3] Montori VM, Basu A, Erwin PJ, et al. Posttransplantation diabetes: a systematic review of the literature. Diabetes Care. 2002;25:583–92.
[4] Cosio FG, Pesavento TE, Osei K, et al. Post-transplant diabetes mellitus: increasing incidence in renal allograft recipients transplanted in recent years. Kidney Int. 2001;59:732–7.
[5] Cosio FG, Pesavento TE, Kim S, et al. Patient survival after renal transplantation: IV. Impact of post-transplant diabetes. Kidney Int. 2002;62:1440–6.
[6] Eide IA, Halden TAS, Hartmann A, et al. Associations between posttransplantation diabetes mellitus and renal graft survival. Transplantation. 2017;101:1282–9.
[7] Kasiske BL, Snyder JJ, Gilbertson D, et al. Diabetes mellitus after kidney transplantation in the United States. Am J Transplant. 2003;3:178–85.
[8] Hjelmesæth J, Hartmann A, Leivestad T, et al. The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. Kidney Int. 2006;69:588–95.
[9] Rodrigo E, Fernández-Fresnedo G, Valero R, et al. New-onset diabetes after kidney transplantation: risk factors. J Am Soc Nephrol. 2006;17:291–5.
[10] Chakkera HA, Weil EJ, Pham P-T, et al. Can new-onset diabetes after kidney transplant be prevented? Diabetes Care. 2013;36:1406–12.
[11] Sharif A, Cohney S. Post-transplantation diabetes-state of the art. Lancet Diabetes Endocrinol. 2016;4:337–49.
[12] Zelle DM, Corpeleijn E, Deinum J, et al. Pancreatic-cell dysfunction and risk of new-onset diabetes after kidney transplantation. Diabetes Care. 2013;36:1926–32.
[13] Heldal TF, Ueland T, Jenssen T, et al. Inflammatory and related biomarkers are associated with post-transplant diabetes mellitus in kidney recipients: a retrospective study. Transpl Int. 2018;31:510–9.
[14] Dutkiewicz G, Domanski L, Pawlik A, et al. Polymorphisms of superoxide dismutase, glutathione peroxidase and catalase genes in patients with post-transplant diabetes mellitus. Arch Med Res. 2010;41:350–5.
[15] Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. Int J Physiol Pathophysiol Pharmacol. 2019;11:45–63.
[16] Sotomayor CG, Velde-Keyzer te CA, de Borst MH, et al. Lifestyle, inflammation, and vascular calcification in kidney transplant recipients: perspectives on long-term outcomes. J Clin Med. 2020;9:1911.
[17] Vostálová J, Galandáková A, Svobodová AR, et al. Stabilization of oxidative stress 1 year after kidney transplantation: effect of calcineurin immunosuppressives. Ren Fail. 2012;34:952–9.
[18] Karbowska A, Boratynska M, Kusztal M, et al. Hyperuricemia is a mediator of endothelial dysfunction and inflammation in renal allograft recipients. Transplant Proc. 2009;41:3052–5.
[19] Bandukwala F, Huang M, Zaltzman JS, et al. Association of uric acid with inflammation, progressive renal allograft dysfunction and post-transplant cardiovascular risk. Am J Cardiol. 2009;103:867–71.
[20] Haririan A, Metireddy M, Cangro C, et al. Association of serum uric acid with graft survival after kidney transplantation: a time-varying analysis. Am J Transplant. 2011;11:1943–50.
[21] Clive DM. Renal transplant-associated hyperuricemia and gout. J Am Soc Nephrol. 2000;11:974–9.
[22] Roy D, Perreault M, Marette A. Insulin stimulation of glucose uptake in skeletal muscles and adipose tissues in vivo is NO dependent. Am J Physiol Metab. 1998;274:E692–9.
[23] Facchini F, Chen YD, Hollenbeck CB, et al. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA. 1991;266:3008–11.
[24] Nakagawa T, Tuttle KR, Short RA, et al. Hypothesis: fructose-induced hyperuricemia as a causal mechanism for the epidemic of the metabolic syndrome. Nat Clin Pract Nephrol. 2005;1:80–6.
[25] Cicerchi C, Li N, Kratzer J, et al. Uric acid-dependent inhibition of AMP kinase induces hepatic glucose production in diabetes and starvation: evolutionary implications of the uricase loss in hominids. FASEB J. 2014;28:3339–50.
[26] Dehghan A, van Hoek M, Sijbrands EJG, et al. High serum uric acid as a novel risk factor for type 2 diabetes. Diabetes Care. 2008;31:361–2.
[27] Lv Q, Meng X-F, He F-F, et al. High serum uric acid and increased risk of type 2 diabetes: a systemic review and meta-analysis of prospective cohort studies. PLoS One. 2013;8:e56864.
[28] Lytvyn Y, Perkins BA, Cherney DZI. Uric acid as a biomarker and a therapeutic target in diabetes. Can J Diabetes. 2015;39:239–46.
[29] Cicero AFG, Rosticci M, Bove M, et al. Serum uric acid change and modification of blood pressure and fasting plasma glucose in an overall healthy population sample: data from the Brisighella heart study. Ann Med. 2017;49:275–82.
[30] Takir M, Kostek O, Ozkok A, et al. Lowering uric acid with allopurinol improves insulin resistance and systemic inflammation in asymptomatic hyperuricemia. J Invest Med. 2015;63:924–9.
[31] Simão ANC, Lozovoy MAB, Dichi I. The uric acid metabolism pathway as a therapeutic target in hyperuricemia related to metabolic syndrome. Expert Opin Ther Targets. 2012;16:1175–87.
[32] van den Berg E, Pasch A, Westendorp WH, et al. Urinary sulfur metabolites associate with a favorable cardiovascular risk profile and survival benefit in renal transplant recipients. J Am Soc Nephrol. 2014;25:1303–12.
[33] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37:S81–90.
[34] Sharif A, Hecking M, De Vries APJ, et al. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. Am J Transplant. 2014;14:1992–2000.
[35] Kasiske BL, Vazquez MA, Harmon WE, et al. Recommendations for the outpatient surveillance of renal transplant recipients. American Society of Transplantation J Am Soc Nephrol. 2000;11:S1–86.
[36] van den Berg E, Engberink MF, Brink EJ, et al. Dietary acid load and metabolic acidosis in renal transplant recipients. Cl J Am Soc Nephrol. 2012;7:1811–8.

[37] Feunekes GI, Van Staveren WA, De Vries JH, et al. Relative and biomarker-based validity of a food-frequency questionnaire estimating intake of fats and cholesterol. Am J Clin Nutr. 1993;58:489–96.
[38] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–12.
[39] Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. Am J Epidemiol. 2009;170:244–56.
[40] Andersen PK, Geskus RB, De witte T, et al.. Competing risks in epidemiology: possibilities and pitfalls. Int J Epidemiol. 2012;41:861–70.
[41] Noordzij M, Leffondre K, van Stralen KJ, et al. When do we need competing risks methods for survival analysis in nephrology? Nephrol Dial Transplant. 2013;28:2670–7.
[42] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94:496–509.
[43] von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453–7.
[44] Abraira V, Muriel A, Emparanza JI, et al. Reporting quality of survival analyses in medical journals still needs improvement. A minimal requirements proposal. J Clin Epidemiol. 2013;66:1340–6.
[45] Tukey JW. Exploratory data analysis. Data analysis and regression: a second course in statistics. Reading, Mass: Addison-Wesley; 1977.
[46] van der Schaft N, Brahimaj A, Wen K, et al. The association between serum uric acid and the incidence of prediabetes and type 2 diabetes mellitus: the Rotterdam study. PLoS One. 2017;12:e0179482.
[47] Kodama S, Saito K, Yachi Y, et al. Association between serum uric acid and development of type 2 diabetes. Diabetes Care. 2009;32:1737–42.
[48] Choi BG, Kim DJ, Baek MJ, et al. Hyperuricaemia and development of type 2 diabetes mellitus in Asian population. Clin Exp Pharmacol Physiol. 2018;45:499–506.
[49] Chakkera HA, Weil EJ, Swanson CM, et al. Pretransplant risk score for new-onset diabetes after kidney transplantation. Diabetes Care. 2011;34:2141–5.
[50] Mazzali M. Uric acid and transplantation. Semin Nephrol. 2005;25:50–5.
[51] Maiuolo J, Oppedisano F, Gratteri S, et al. Regulation of uric acid metabolism and excretion. Int J Cardiol. 2016;213:8–14.
[52] Heisel O, Heisel R, Balshaw R, et al. New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. Am J Transplant. 2004;4:583–95.
[53] Eyupoglu S, Eyupoglu D, Kendi-Celebi Z, et al. Risk factors of hyperuricemia after renal transplantation and its long-term effects on graft functions. Transplant Proc. 2017;49:505–8.
[54] Marcen R, Gallego N, Gamez C, et al. Hyperuricemia after kidney transplantation in patients treated with cyclosporine. Am J Med. 1992;93:354–5.
[55] Mazzali M, Kim Y-G, Suga S, et al. Hyperuricemia exacerbates chronic cyclosporine nephropathy. Transplantation. 2001;71:900–5.
[56] Butler R, Morris AD, Belch JJF, et al. Allopurinol normalizes endothelial dysfunction in type 2 diabetics with mild hypertension. Hypertension. 2000;35:746–51.
[57] Puddu P, Puddu GM, Cravero E, et al. The relationships among hyperuricemia, endothelial dysfunction, and cardiovascular diseases: molecular mechanisms and clinical implications. J Cardiol. 2012;59:235–42.
[58] Tang W, Fu Q, Zhang Q, et al. The association between serum uric acid and residual β-cell function in type 2 diabetes. J Diabetes Res. 2014;2014:1–9.
[59] Badve SV, Pascoe EM, Tiku A, et al. Effects of allopurinol on the progression of chronic kidney disease. N Engl J Med. 2020;382:2504–13.
[60] Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in patients with chronic coronary disease. N Engl J Med. 2020;383:1838–47.
[61] Avogaro A, Albiero M, Menegazzo L, et al. Endothelial dysfunction in diabetes: the role of reparatory mechanisms. Diabetes Care. 2011;34:S285–90.