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High urinary glucose is associated with improved renal prognosis in patients with diabetes mellitus

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ABSTRACT

Aims/Introduction: The relationship between renal function and urinary glucose is poorly understood in diabetes patients who are not using sodium–glucose cotransporter 2 inhibitors. This study aimed to investigate the association of urinary glucose excretion with renal function prognosis in such patients.

Materials and Methods: This retrospective cohort study included 1,172 patients with type 1 or 2 diabetes mellitus. Patients were recruited and data were collected between 1 January 2007 and 31 December 2011; follow-up data were collected until 30 June 2015. The primary outcome was set as a 30% decline in estimated glomerular filtration rate relative to baseline. The relationship between this outcome and urinary glucose was investigated using Cox proportional hazards model. For analysis, patients were categorized into two groups: urinary glucose <5 g/day or ≥5 g/day. Interaction terms were analyzed.

Results: Multivariate analysis showed that the prognosis of renal function was significantly better in patients with high urinary glucose (≥5 g/day; adjusted hazard ratio 0.58, 95% confidence interval 0.35–0.96; $P = 0.034$). Significant interactions were observed between high urinary glucose and male sex (hazard ratio 0.33, 95% confidence interval 0.14–0.74; $P = 0.007$), and between high urinary glucose and longer duration of diabetes (≥10 years; hazard ratio 0.25, 95% confidence interval 0.11–0.58; $P = 0.001$).

Conclusions: The present study suggests that high urinary glucose is associated with prognosis in diabetes patients not taking sodium–glucose cotransporter 2 inhibitors. Measurement of 24-h urinary glucose excretion might have clinical utility for predicting renal prognosis.

INTRODUCTION

Chronic kidney disease (CKD) leads to end-stage renal disease. Furthermore, the condition is associated with the onset of cardiovascular disease (CVD)[1,2], and the incidence of these three diseases is increasing worldwide. Diabetes mellitus is one of the most important risk factors for renal dysfunction and CVD, and affects health and quality of life through the development of microvascular and macrovascular complications[3–5].

A recent study has generated significant new knowledge regarding sodium–glucose cotransporter (SGLT) 2 inhibitors, which has had a huge impact on the current understanding of diabetes[6]. The therapeutic effects of SGLT2 inhibitors include strong protective effects against CVD and renal function beyond the control of blood glucose levels in patients with type 2 diabetes[7]. A number of potential pathways have been suggested to underly the renoprotective effects of these inhibitors. Although the precise mechanisms remain unclear, it is expected that increased renal glucose excretion is key to the therapeutic effects of SGLT2 inhibitors[8].

Renal glycosuria is defined as the excretion of glucose at abnormally high levels despite blood glucose levels being within the normal range. This occurs when the threshold for glucose

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reabsorption in the renal tubules is decreased. In general, renal glycosuria is thought to be a benign disease for kidney function, but there is a possibility that it has beneficial effects for various other organs[9]. Specifically, the condition has been reported to be associated with improved renal outcomes in CKD patients without diabetes[10]. Among patients with type 2 diabetes, improved effects have been reported in patients with renal glycosuria with respect to risk factors for CVD, including body mass index (BMI) and homeostatic model assessment of insulin resistance score[11].

It is therefore important to reconsider the significance of urinary glucose excretion in patients with diabetes. Urinary glucose excretion increases after the administration of SGLT2 inhibitors; nevertheless, there are few studies on the association of urinary glucose levels with kidney function in the absence of SGLT2 inhibitors. The purpose of the present study was to investigate this association in patients with diabetes who were not using SGLT2 inhibitors.

METHODS

Study design and participants

The prsent study was a retrospective, observational cohort study. Study participants included patients with diabetes who regularly visited the Department of Diabetology and Nephrology, Ogaki Municipal Hospital, Ogaki, Japan. The hospital is a regional core and tertiary referral hospital. We recruited all patients who met the criteria from 1 January 2007 to 31 December 2011, and collected baseline clinical and laboratory data during this period. The baseline data used for statistical analysis were the results of the first and single measurement carried out in the hospital. Follow-up data were collected until 30 June 2015. We enrolled patients who: (i) were diagnosed with type 1 or 2 diabetes at our hospital; (ii) attended regular appointments (every 1–3 months) at the Department of Diabetology and Nephrology for at least 1 year; and (iii) had a baseline estimated glomerular filtration rate (eGFR) of >30 mL/min (1.73 m)^2. The following patients were excluded from the analysis: (i) patients who could not complete a 24-h urinary collection test or who were judged to have creatinine excretion that deviated by ±25% of the predicted value calculated according to age, sex, height and weight[12,13]; (ii) patients with missing laboratory data for parameters, such as urinary albumin or urinary glucose; (iii) patients with missing follow-up data on kidney function from blood tests at Ogaki Municipal Hospital after the baseline laboratory tests; (iv) patients with comorbidities of systemic diseases, such as autoimmune diseases and vasculitis, primary glomerular diseases, neoplasms or liver cirrhosis, at baseline because of the possibility that these diseases and their treatments affect diabetes control and renal function; and (v) patients in whom the onset of diabetes was within 5 years, because renal events within this period are considered atypical in terms of kidney dysfunction.

The present study and its protocols were approved by the ethics committee of Ogaki Municipal Hospital (approval number: 20161222-4) and conformed to the provisions of the Declaration of Helsinki, as revised in Fortaleza, Brazil (October 2013). Having been approved by the ethics committee, we guaranteed patients the opportunity to opt out. The requirement for the acquisition of informed consent from patients was waived owing to the retrospective nature of the study.

Categorization of patients by quantification of urinary glucose

There are currently no clear criteria for the categorization of urinary glucose level. Therefore, we designed a system for categorization and analyzed data using the following procedure: (i) we divided the study cohort using sextiles for the quantification of urinary glucose; and (ii) based on the result, we subsequently divided the patients into two groups: those with urinary glucose >5 g/day and those with urinary glucose <5 g/day.

Clinical outcomes

The primary clinical outcome was a 30% decline in eGFR relative to baseline. Baseline eGFR was taken as the first measurement of eGFR within the study period. Patients were followed up until an event occurred or until 30 June 2015. When diseases that were regarded as exclusion criteria developed during follow up, patients were considered a censored case at the time of diagnosis. We calculated eGFR using the following equation of the Japanese Society of Nephrology: eGFR (mL/min [1.73 m]^2) = 194 × serum creatinine$^{1.094}$ × age$^{-0.287}$ (for men) or 194 × serum creatinine$^{1.094}$ × age$^{-0.287}$ × 0.739 (for women)[14].

Procedure

A diagnosis of type 1 or 2 diabetes was established by a specialist at the Department of Diabetology. Systolic and diastolic blood pressure measurements were carried out in the hospital, and hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or the use of antihypertensive medication. Albuminuria and urinary glucose were measured using a 24-h urine-collection test, and urine volume was self-reported. Use of oral hypoglycemic agents was recorded, defined as all types of medication excluding SGLT2 inhibitors (e.g., biguanide, α-glucosidase inhibitors, thiazolidine derivatives, sulfonylurea, dipeptidyl peptidase four inhibitors, glinide). Use of renin–angiotensin–aldosterone system blockers were also recorded, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and direct renin inhibitors.

For interaction analysis, we categorized some variables into two subgroups. Age was categorized as either ≥65 or <65 years, total cholesterol as ≥220 or <220 mg/dL, duration of diabetes as ≥10 or <10 years, eGFR as ≥76.7 or <76.7 mL/min (1.73 m)^2, albuminuria as ≥30 mg/day or <30 mg/day, BMI as ≥25 or <25 kg/m^2 and glycated hemoglobin (HbA1c) level as either ≥7% or <7%.

Statistical analysis

All statistical analyses were carried out using Stata version 15.0 (StataCorp LLC, College Station, TX, USA). Urinary glucose level, age, duration of diabetes, existence of hypertension, eGFR, total cholesterol, albuminuria, sex, BMI and HbA1c level were used as independent variables for adjustment. There were no missing data. Data are expressed as the number and percentage for categorical variables or as the median/interquartile range for continuous variables. Between-group differences in baseline characteristics were evaluated using unpaired Student's *t*-test for continuous variables, and the unpaired χ^2-test for categorical variables. First, we analyzed the association between 24-h urinary glucose excretion and kidney function. The groups of 24-h urinary glucose excretion were categorized using sextiles, and we analyzed the primary outcome using the Cox proportional hazards model. Second, we carried out the same analysis of urinary glucose excretion after dividing the data into two groups using the threshold of 5 g/day for glucose excretion based on the result of the first analysis. Third, we used the Cox proportional hazards model including the interaction terms between high glycosuria (≥5 g/day) and other variables. Finally, we used multivariable fractional polynomial interaction approach to determine the effects of higher urinary glucose on the renal outcome in patients with different levels of HbA1c[15]. Statistical significance was accepted at $P < 0.05$.

RESULTS

Study population

In total, 4,184 patients were recruited for this study. After the application of inclusion and exclusion criteria, 1,172 patients were finally enrolled (Figure 1). Baseline characteristics of all participants are summarized in Table 1. Patients were divided into six preliminary groups according to urinary glucose levels, and Cox regression analysis was carried out. There was a clearly large difference in the hazard ratio (HR) between the top two sextiles with urinary glucose ≥5.135 g/day and the other four sextiles with urinary glucose <5.135 g/day (Figure 2). The change in HR was not linear, and it seemed that the threshold for urinary glucose excretion was approximately 5 g/day. Therefore, we deemed that it would not be appropriate to determine the effect of urinary glucose on continuous variables, and decided to evaluate the categorical variables by dividing the patients into two groups using a urinary glucose excretion level of 5 g/day. We divided the patients into two groups, because the dividing point approximated 5 g/day. Patients in the ≥5 g/day urinary glucose group were younger; had higher bodyweight, higher BMI and higher eGFR; and were more likely to be men and diagnosed with type 2 diabetes than those in the <5 g/day urinary glucose group. The prevalence of diabetic retinopathy, higher $HbA1c_c$ levels, high blood glucose levels, the rate of insulin use and the proportion of type 1 diabetes were higher in the high urinary glucose group, indicating poor glycemic control in this group (Table 1).

Follow-up time and outcome data

The median follow-up duration was 6.6 years (interquartile range 3.7–7.3 years). There were no missing data for any variable of interest, and renal events occurred in 121 patients.

Cox regression analysis for the renal outcome of 30% decline in eGFR from baseline

In the univariate model, no significant associations between urinary glucose excretion and renal outcome were observed. Multivariate analysis using the baseline variables of age, BMI, duration of diabetes, presence of hypertension, eGFR, total cholesterol, albuminuria, urinary glucose, sex and HbA1c level showed that higher age (adjusted HR 1.04, 95% confidence interval [CI] 1.01–1.06; $P = 0.002$), higher albuminuria (adjusted HR 2.82, 95% CI 2.09–3.81; $P < 0.001$), urinary glucose of ≥5 g/day (adjusted HR 0.58, 95% CI 0.35–0.96; $P = 0.034$) and higher HbA1c level (adjusted HR 1.02, 95% CI 1.00–1.04; $P = 0.031$) were significantly associated with reduced risk of renal event (Table 2). When factored into the models, the type of diabetes was not a significant factor, and the point estimates of urinary glucose, the main exposure of interest, showed similar results (data not shown).

Analysis using interaction terms

Cox regression analysis including the interaction terms between high urinary glucose excretion and other renal outcome variables showed a significant interaction between high urinary glucose and male sex (adjusted HR 0.32, 95% CI 0.16–0.66; $P = 0.006$), low BMI (adjusted HR 0.36, 95% CI 0.17–0.77; $P = 0.034$) and duration of diabetes ≥10 years (adjusted HR 0.34, 95% CI 0.17–0.69; $P < 0.001$; Figure 3). Interactions with other factors were not significant.

Multivariate Cox regression analysis, including the interaction terms between high urinary glucose excretion and all three aforementioned factors, showed significant interactions with male sex (adjusted HR 0.33, 95% CI 0.14–0.74; $P = 0.007$) and duration of diabetes ≥10 years (adjusted HR 0.25, 95% CI 0.11–0.58; $P = 0.001$). No interaction was detected with BMI (adjusted HR 0.52, 95% CI 0.23–1.19; $P = 0.126$; Table 3).

Multivariable fractional polynomial interaction approach

The multivariable functional polynomial interaction plots represent the interaction among linear and non-linear variables. In the present study, we examined the association of the interaction between HbA1c and the main exposure (urinary glucose <5 or ≥5 g/day) with the outcome. Therefore, the HRs of the main exposure can be illustrated across levels of HbA1c (Figure 4).

DISCUSSION

In the present retrospective observational study, we observed that in addition to higher age, albuminuria, HbA1c and urinary glucose levels of ≥5 g/day (defined as high urinary glucose)

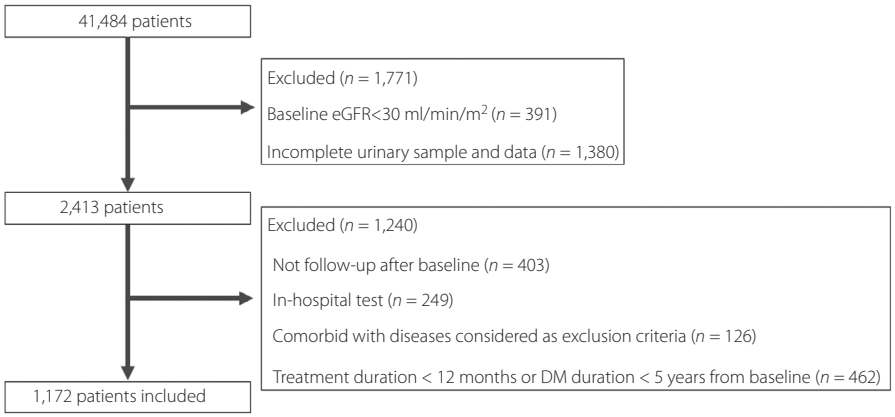

Figure 1 | Flowchart of number of eligible patients after screening. DM, diabetes mellitus; eGFR, estimated glomerular filtration rate.

Table 1 | Baseline characteristics of participants categorized into two groups using urinary glucose level of 5 g/day as the cut-off point

Variable	All	Glucose <5 g	Glucose ≥5 g	*P*-value
n	1,172	775	397	
Age (years)	64 (57–70)	65 (58–71)	61 (53–68)	<0.001*
Height (cm)	159 (152–166)	157 (151–164)	162 (155–168)	<0.001*
Weight (kg)	60 (53–68)	59 (52–67)	63 (55–71)	<0.001*
BMI (kg/m^2)	23.9 (21.7–26.5)	23.8 (21.5–26.3)	24.2 (21.9–26.8)	0.035*
Duration of diabetes (years)	10.6 (6.2–17.1)	10.4 (5.8–17.1)	11.2 (6.9–17.0)	0.273
Systolic blood pressure (mmHg)	131 (120.0–143.5)	131 (120–140)	130 (119–142)	0.350
Diastolic blood pressure (mmHg)	72 (64–80)	71 (64–79)	74 (66–82)	<0.001*
Creatinine (mg/mL)	0.7 (0.59–0.83)	0.7 (0.59–0.85)	0.7 (0.58–0.81)	0.003*
eGFR, mL/min (1.73 m^2)	76.7 (65.9–89.9)	74.1 (63.0–85.9)	82.4 (71.2–97.5)	<0.001*
HbA1c (mmol/L)	54 (49–62)	52 (46–57)	63 (56–68)	<0.001*
HbA1c (%)	7.1 (6.6–7.8)	6.9 (6.4–7.4)	7.9 (7.3–8.4)	<0.001*
Total cholesterol (mg/dL)	198 (175–220)	197 (175–221)	200 (176–219)	0.631
Triglycerides (mg/dL)	99 (72–143.5)	99 (71–136)	99 (73–156)	0.001*
HDL cholesterol (mg/dL)	51 (43–62)	51 (43–60)	51 (43–63)	0.090
LDL cholesterol (mg/dL)	120 (100.5–140)	121 (101–142)	117 (99–138)	0.098
Albuminuria (mg/day)	12.3 (6.5–30.4)	11.5 (6.3–27.8)	15.2 (6.9– 35.3)	0.468
Urine volume (L/day)	1.6 (1.4–2.1)	1.6 (1.3–2.0)	1.7 (1.5–2.1)	<0.001*
Glycosuria (g/day)	1.98 (0.30–8.66)	0.58 (0.12–1.92)	14.4 (8.55–25.82)	<0.001*
Male sex	617 (52.65)	355 (45.81)	262 (65.99)	<0.001*
Comorbidities				
Type 2 diabetes	1,057 (90.2)	716 (92.4)	341 (85.89)	<0.001*
Hypertension	742 (63.31)	495 (63.87)	247 (62.22)	0.578
Retinopathy	469 (40.02)	288 (37.16)	181 (45.59)	0.005*
Use of drugs				
Oral hypoglycemic agents	785 (66.98)	513 (66.19)	272 (68.51)	0.424
Insulin	400 (34.13)	238 (30.71)	162 (40.81)	0.001*
Renin–angiotensin–aldosterone system blockers	590 (50.34)	394 (50.84)	196 (49.37)	0.634
Calcium channel blockers	446 (38.05)	308 (39.74)	138 (34.76)	0.096
Diuretic	133 (11.35)	95 (12.26)	38 (9.57)	0.170
Statins	427 (36.43)	293 (37.81)	134 (33.75)	0.172

Continuous data are presented as the median (25th–75th percentile), whereas categorical data are presented as absolute numbers (%). Between-group differences in baseline characteristics were evaluated using unpaired Student's *t*-test for continuous variables, and unpaired χ^2-test for categorical variables. BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein. *Values with $P < 0.05$ were considered to be statistically significant.

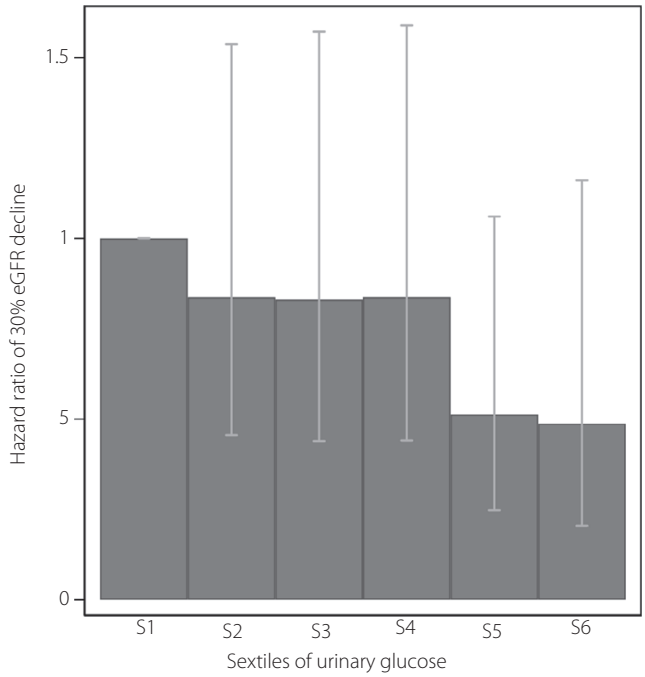

Figure 2 | Hazard ratio of 30% estimated glomerular filtration rate (eGFR) decline from baseline for each group divided into sextiles (S1–S6). Error bar indicates 95% confidence interval of each hazard ratio. The reference group was S1.

were significantly associated with the occurrence of a 30% decline in eGFR relative to the baseline.

Analysis of the association between renal events, as indicated by a <30% decline in eGFR, and baseline variables including interaction terms showed that high urinary glucose levels exhibited better renal outcomes, especially in male patients or those with duration of diabetes ≥10 years.

To the best of our knowledge, this is the first study to investigate the clinical significance of urinary glucose levels in terms of kidney function among patients with diabetes who are not using SGLT2 inhibitors.

In patients with diabetes, glycosuria generally develops when urinary glucose concentration exceeds the renal tubular reabsorption capacity (which is ~10 mmol/L). Increased glycosuria is commonly an indicator of poor glycemic control[16]; however, the threshold differs between individuals[17], and has been reported to be higher in women and older patients[18]. Glycosuria can also occur in individuals without diabetes. This is referred to as renal glycosuria, a condition in which urinary glucose excretion occurs even when blood glucose levels are within the normal range. This is an effect of compromised renal tubule function and has been suggested to be induced by genetic mutation or variation[19]. For these reasons, the level of glycosuria can indicate glycemic control, as well as renal tubule impairment.

A recent report showed beneficial effects of SGLT2 inhibitors on all-cause mortality, CVD and kidney function in patients with type 2 diabetes[20]. Several mechanisms of the renoprotective effects of these drugs have been proposed, including enhanced sodium excretion, increased efficiency of energy utilization in tubular cells and ketone production[8]. It was not until recently, however, that researchers started to show interest in glycosuria. Hung *et al.*[10] reported that the presence of glycosuria or renal glycosuria is associated with favorable renal outcomes in stage 5 CKD patients without diabetes. Although this suggests the beneficial effects of glycosuria, the authors did not investigate the effects of glycosuria in patients with diabetes. Gong *et al.*[11] showed that, among patients with type 2 diabetes, glycosuria is independently associated with a lower risk of

Table 2 | Association of baseline variables with 30% decline in estimated glomerular filtration rate from baseline

Variable	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P*-value
Age (years)	1.05 (1.02–1.07)	<0.001	1.04 (1.01–1.06)	0.002*
BMI (kg/m^2)	1.06 (1.01–1.11)	0.013	1.04 (0.99–1.10)	0.111
Duration of diabetes (years)	1.03 (1.01–1.05)	0.006	1.01 (0.98–1.03)	0.539
Hypertension	2.28 (1.48–3.52)	<0.001	1.24 (0.78–1.98)	0.354
Baseline eGFR, mL/min (1.73 m^2)	0.98 (0.98–0.99)	0.010	1.01 (0.99–1.02)	0.374
Total cholesterol (10 mg/dL)	1.01 (0.96–1.07)	0.592	1.03 (0.98–1.08)	0.294
Albuminuria (mg/day)	3.09 (2.33–4.10)	<0.001	2.82 (2.09–3.81)	<0.001*
Urinary glucose level ≥5 g/day	0.75 (0.50–1.11)	0.156	0.58 (0.35–0.96)	0.034*
Female sex	1.41 (0.99–2.04)	0.056	1.15 (0.78–1.73)	0.471
HbA1c (%)	1.02 (0.99–1.03)	0.051	1.02 (1.00–1.04)	0.031*

The univariate and multivariate Cox proportional hazards models were carried out after adjustment for baseline variables of age, body mass index (BMI), duration of diabetes, presence of hypertension, , estimated glomerular filtration rate (eGFR), total cholesterol, albuminuria, urinary glucose level, sex and glycated hemoglobin (HbA1c) level. CI, confidence interval; HR, hazard ratio. *Values with $P < 0.05$ were considered to be statistically significant.

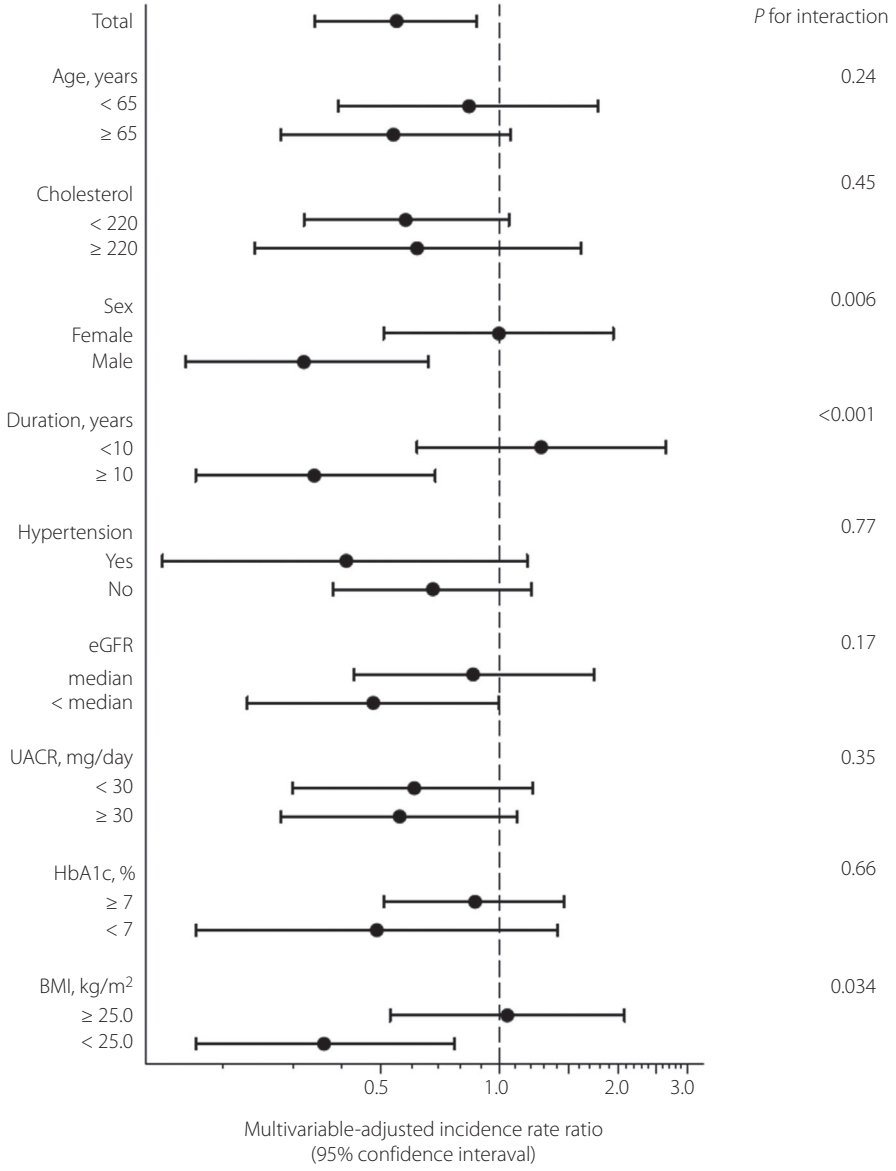

Figure 3 | Forest plot with subgroups representing hazard ratio for estimated glomerular filtration rate (eGFR) decline on the *y*-axis, and 95% confidence interval on the *x*-axis. Comparisons between the subgroups were carried out by the Cox proportional hazards model adjusted for baseline variables of age, body mass index (BMI), duration of diabetes, presence of hypertension, estimated glomerular filtration rate (eGFR), total cholesterol, albuminuria, urinary glucose, sex and glycated hemoglobin (HbA1c) level. UACR, urine albumin-to-creatinine ratio.

CVD, as indicated by features that include lower homeostatic model assessment of insulin resistance, lower BMI, lower blood pressure and lower fasting blood glucose. Their study showed the beneficial effects of glycosuria in patients with diabetes; nevertheless, it was a cross-sectional study that did not analyze kidney function.

In the present study, patients were divided into sextiles, and multivariate Cox hazards analysis was carried out. We found that patients in the top two sextiles with urinary glucose ≥5.135 g/day showed a lower risk of eGFR decline than those in the other four sextiles. We subsequently divided patients into two groups using the threshold of 5 g/day for urinary glucose, and performed a longitudinal analysis. The result showed that, among patients with similar blood glucose control who were not using SGLT2 inhibitors, urinary glucose excretion of >5 g/day was significantly associated with better kidney function compared with that of <5 g/day. Together with the results of previous studies, this suggests that excretion of high urinary glucose levels leads to better prognosis for kidney function. Several hypotheses have been suggested to explain the mechanism

Table 3 | Association between baseline variables, including interaction terms between higher urinary glucose levels and body mass index <25, male sex, and duration of diabetes ≥10 years, with 30% decline in estimated glomerular filtration rate from baseline

Variable	HR (95% CI)	*P*-value
Age (years)	1.04 (1.02–1.07)	<0.001*
Hypertension	1.31 (0.82–2.10)	0.243
Baseline eGFR, mL/min (1.73 m^2)	1.00 (0.99–1.01)	0.443
Total cholesterol (10 mg/dL)	1.00 (0.99–1.01)	0.279
Albuminuria (mg/day)	3.00 (2.21–4.07)	<0.001*
Urinary glucose level ≥5 g/day	3.28 (1.44–7.45)	0.005*
Male (sex)	1.18 (0.75–1.86)	0.451
Interaction term between urinary glucose level ≥5 g/day and male sex	0.33 (0.14–0.74)	0.007*
BMI <25 kg/m^2	0.84 (0.55–1.31)	0.454
Interaction term between urinary glucose level ≥5 g/day and BMI <25 kg/m^2	0.52 (0.23–1.19)	0.126
Duration of diabetes ≥10 years	1.47 (0.90–2.37)	0.116
Interaction term between urinary glucose level ≥5 g/day and duration of diabetes ≥10 years	0.25 (0.11–0.58)	0.001*
HbA1c (%)	1.02 (0.99–1.04)	0.056

The multivariate Cox proportional hazards model was carried out after adjustment for baseline variables of age, body mass index (BMI), duration of diabetes, presence of hypertension, estimated glomerular filtration rate (eGFR), total cholesterol, albuminuria, urinary glucose, sex, glycated hemoglobin (HbA1c) level, and the interaction terms between high glycosuria (≥5 g/day) and sex, BMI, and duration of diabetes. CI, confidence interval; HR, hazard ratio. *Values with $P < 0.05$ were considered to be statistically significant.

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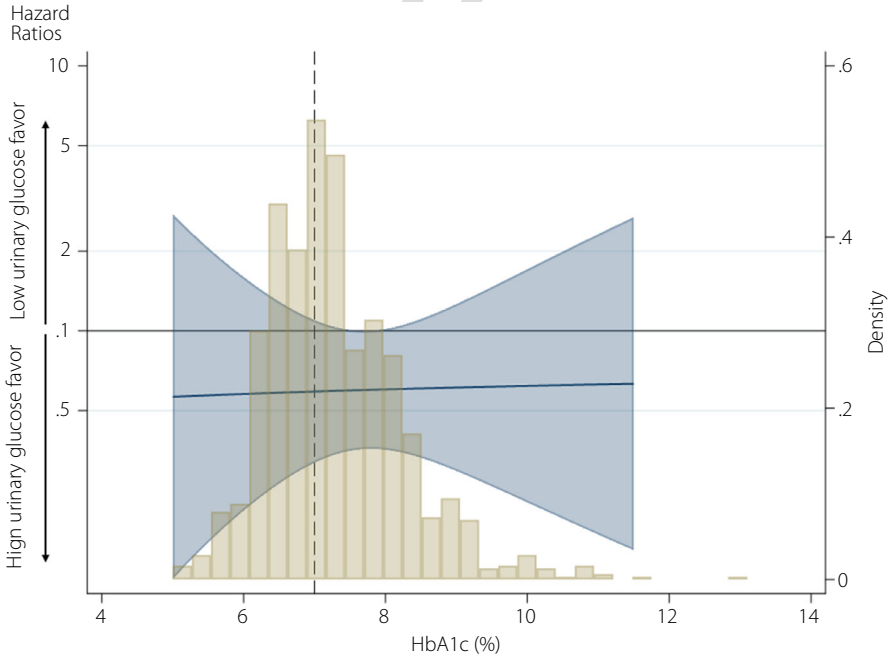

Figure 4 | The vertical dashed line represents the commonly used cut-off value of glycated hemoglobin (HbA1c; 7%). The horizontal line at the hazard ratio of 1 denotes the equivalence of the effect of urinary glucose levels; thus, an effect function parallel to the horizontal line indicates no interaction. For the outcome, values of HbA1c where the hazard ratios are beneath this line indicate that lower levels of urinary glucose are more beneficial. The multivariable Cox proportional hazards model was adjusted for age, sex, body mass index, duration of diabetes, estimated glomerular filtration rate, total cholesterol, log-transformed urinary albumin and hypertension.

of this effect. First, individuals with high urinary glucose levels will experience benefits similar to those observed in individuals using SGLT2 inhibitors, and might show higher sodium excretion and suppressed glomerular hyperfiltration due to tubuloglomerular feedback. Furthermore, high urinary glucose might limit oxygen consumption in the tubules, leading to

improved oxygenation in the kidneys[8]. Animal studies have shown that genetic knockout of SGLT2 leads to a reduction in blood glucose levels and prevents glomerular hyperfiltration in a diabetic mouse model[21]. Second, individuals with high urinary glucose levels might show lower sympathetic nerve activation[22]. Chhabra *et al.*[23,24] reported that glycemic conditions are regulated by a hypothalamic–sympathetic nervous system–renal axis, which controls glucose reabsorption in the proximal renal tubule. Using an animal model, the authors showed that mice with hypothalamic proopiomelanocortin deficiencies showed lower sympathetic nerve activation, resulting in reduced glucose transporter 2 expression and higher glycosuria. In human studies, mutation of the melanocortin 3 receptor – which is found on hypothalamic proopiomelanocortin neurons – resulted in improved glycemic control despite obesity and insulin resistance[22,25]. Furthermore, renal sympathetic denervation has been shown to improve blood glucose levels in patients with hypertension[26].

In the present study, multivariate Cox analysis including interaction terms showed that a statistically significant effect of high glycosuria was only seen in three types of patients: those with the duration of diabetes ≥10 years, men and those with low BMI (BMI <25 kg/m^2). However, when all these interaction terms were analyzed in one model, low BMI was no longer statistically significant. These results suggest that patients with a longer history of diabetes, as well as male patients with high urinary glucose levels, had better renal prognoses. It might take a long time for the benefits of high glycosuria to be realized. Many studies have investigated the influence of sex on renal function, but the results have not been consistent[27–29]. Some studies from the USA have shown that the prevalence of CKD is higher among men, whereas others have reported the opposite[27,30]. In the Japanese population, men have been found to be at a higher risk of CKD[31]. Similarly, among patients with diabetes, sex does not necessarily affect the prevalence or rate of CKD progression[32,33]. Multivariate analysis in the present study failed to show a significant association between sex and renal prognosis. However, it did show that high glycosuria had beneficial effects in men, but not in women. An animal model study has also shown that male hormones exert a deleterious effect on the kidney by increasing oxidative stress, activating the renin–angiotensin system, and enhancing the fibrotic process[34]. In patients with high glycosuria, however, the presence of male hormones might have had beneficial effects. Further studies are required to clarify the reasons for this discrepancy.

The strength of the present study was the measurement of 24-h urinary glucose excretion. In the above-mentioned previous studies, only spot urine tests were used to assess glycosuria[10,11]. The process of 24-h urinary collection might be difficult for some patients, especially the elderly. However, analysis of urinary glycose by spot urine tests is susceptible to error compared with that of 24-h urinary collection. In this context, the present results should be more reliable than those of the previous studies. Of note, the proportion of patients with type 1 diabetes mellitus in the present study was 10.8%, which is higher than that in the general population. As the study facility was a regional core hospital with multiple diabetes specialists, patients with type 1 diabetes mellitus tended to be referred and retained as outpatients there. Our analyses showed that the type of diabetes was not influential in this study.

The present study had some limitations that should be acknowledged. First, it was an observational, retrospective, cohort study carried out in a single center. Even when adjustments are made, some bias effects might have remained. Furthermore, this is an exploratory study for obtaining hypotheses. Future research using different cohorts will be necessary. Second, we showed the association between 24-h urinary glucose levels and kidney function, but we did not directly measure the threshold for glucose reabsorption in the renal proximal tubules. Third, we did not analyze mutations in causative genes, such as solute carrier family 5 member 2, which is one of the most well-known genes associated with familial renal glycosuria, or proopiomelanocortin, whose deficiency causes severe obesity.

In conclusion, the present results show that high 24-h urinary glucose excretion is associated with better renal prognosis in terms of a 30% decline in eGFR compared with baseline among patients with diabetes who are not using SGLT2 inhibitors, particularly men or patients with a duration of diabetes ≥10 years. Quantification of urinary glucose by 24-h urinary collection test might, therefore, have clinical utility for identifying patients with better renal prognoses. The present results showed that high urinary glucose excretion might be associated with better renal function in a similar manner to SGLT2 inhibitors, providing better insight into the pathogenesis of diabetic kidney disease. Further studies are necessary to confirm the significance of glycosuria with respect to renal function.

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DISCLOSURE

The authors declare no conflict of interest.

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Graphical Abstract

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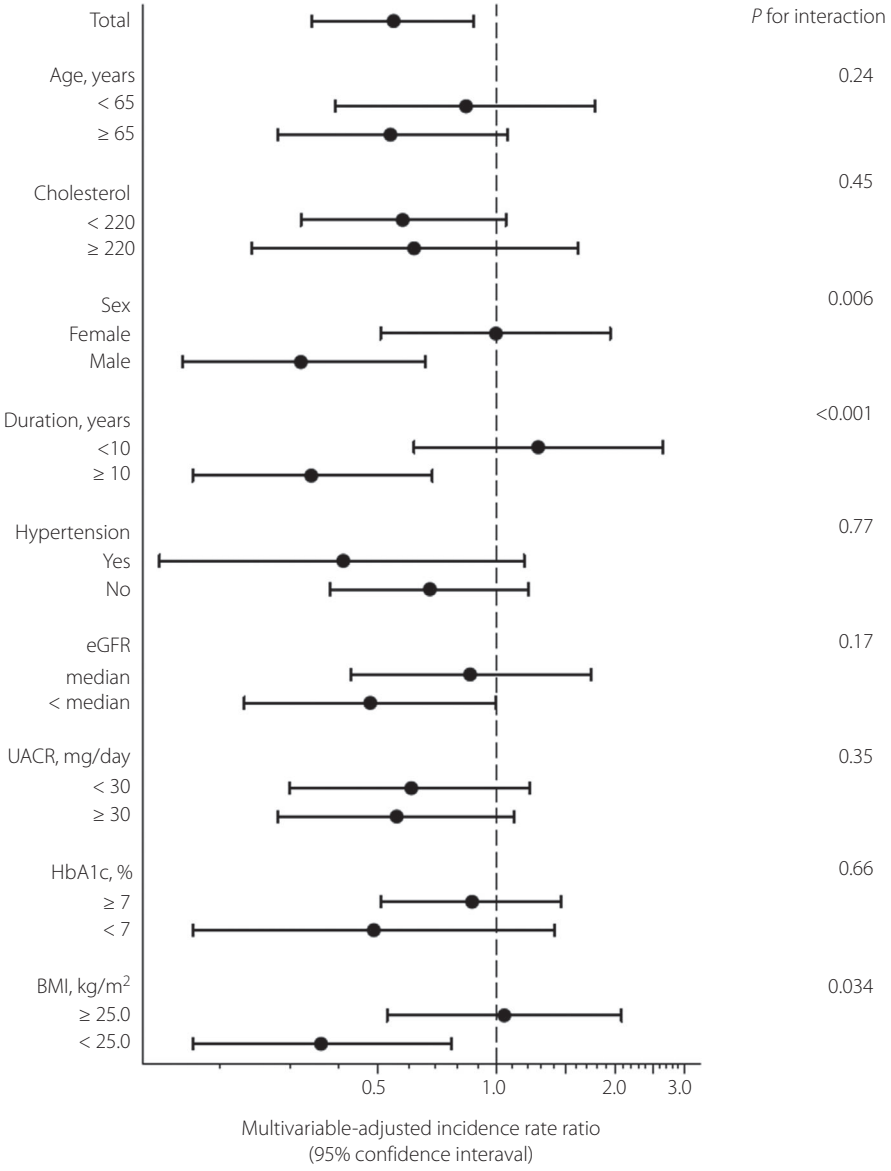

Urinary glucose excretion of ≥5 g/day is significantly related to a lower risk of a 30% decline in estimated glomerular filtration rate relative to baseline.