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Relationship between renal capacity to reabsorb glucose and renal status in patients with diabetes

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Abstract

Aims. – Interindividual variability in capacity to reabsorb glucose at the proximal renal tubule could contribute to risk of diabetic kidney disease. Our present study investigated, in patients with diabetes, the association between fractional reabsorption of glucose (FR_{GLU}) and degree of renal disease as assessed by urinary albumin excretion (UAE) and estimated glomerular filtration rate (eGFR).

Methods. – FR_{GLU} [1-(glucose clearance/creatinine clearance)] was assessed in 637 diabetes patients attending our tertiary referral centre, looking for correlations between FR_{GLU} and UAE (normo-, micro-, macroalbuminuria) and Kidney Disease: Improving Global Outcomes (KDIGO) eGFR categories: > 90 (G1); 90–60 (G2); 59–30 (G3); and < 30–16 (G4) mL/min/1.73 m^2. Patients were stratified by admission fasting plasma glucose (FPG) into three groups: low (< 6 mmol/L); intermediate (6–11 mmol/L); and high (> 11 mmol/L).

Results. – Median (interquartile range, IQR) FR_{GLU} levels were blood glucose-dependent: 99.90% (0.05) for low (n = 106); 99.90% (0.41) for intermediate (n = 288); and 96.36% (12.57) for high (n = 243) blood glucose categories ($P < 0.0001$). Also, FR_{GLU} increased with renal disease severity in patients in the high FPG group: normoalbuminuria, 93.50% (17.74) (n = 135); microalbuminuria, 96.56% (5.94) (n = 77); macroalbuminuria, 99.12% (5.44) (n = 31; $P < 0.001$); eGFR G1, 94.13% (16.24) (n = 111); G2, 96.35% (11.94) (n = 72); G3 98.88% (7.59) (n = 46); and G4, 99.11% (2.20) (n = 14; $P < 0.01$). On multiple regression analyses, FR_{GLU} remained significantly and independently associated with UAE and eGFR in patients in the high blood glucose group.

Conclusion. – High glucose reabsorption capacity in renal proximal tubules is associated with high UAE and low eGFR in patients with diabetes and blood glucose levels > 11 mmol/L.

Key words: Diabetic kidney disease; Renal glucose transport; Tubuloglomerular feedback

Abbreviations:

ACR: albumin/creatinine ratio

ARB: angiotensin receptor blockers

CKD: chronic kidney disease

DKD: diabetic kidney disease

eGFR: estimated glomerular filtration rate

FPG: fasting plasma glucose

FR_{GLU}: fractional reabsorption of glucose

IQR: interquartile range

SGLT1: sodium–glucose cotransporter 1

SGLT2: sodium–glucose cotransporter 2

UAE: urinary albumin excretion

Introduction

Hyperglycaemia is associated with alterations in the tubuloglomerular feedback system leading to an increase in glomerular filtration rate (GFR) [1]. Such an effect results from the inappropriate openingof preglomerular vascular resistances, mediated by hyperglycaemia-related changes in the composition of tubular fluid and altered sensing of sodium load by the macula densa [2]. This opening of preglomerular resistances causes hypertension in the glomerular circulation and itsrelated renovascular complications [3].

It has previously been reported that increased renal reabsorption of glucose during hyperglycaemia, coupled with increased reabsorption of sodium in the proximal tubule, is a characteristic of patients with type 1 diabetes (T1D) with glomerular hyperfiltration and/or microalbuminuria, two established risk factors of chronic kidney disease (CKD) [4]. Additional evidence of a possible link between increased renal glucose reabsorption and kidney disease was also suggested by the results of recent clinical trials of sodium–glucose cotransporter 2 (SGLT2) inhibitors. Indeed, these molecules, which decrease glucose and sodium reabsorption in the proximal tubule, have shown beneficial effects on kidney outcomes in high-risk patients with type 2 diabetes (T2D) [5–7].

The risk of kidney disease is highly variable among individuals with diabetes. Allelic variations in components of the renin–angiotensin system [8], notably the I/D polymorphism in the *ACE* gene [9], confer a major increase in risk, although many other genetic markers and biomarkers of diabetic kidney disease (DKD) have been identified [10–18]. The maximum capacity for glucose reabsorption across the proximal tubule, the *primum movens*of impaired tubuloglomerular feedback in diabetes [2, 19], is also a variable trait [20]. Thus, our hypothesis was that interindividual variability in the capacity to reabsorb glucose at the proximal tubule could contribute to risk of DKD. For this reason, our present study

investigated, in patients with diabetes, the association of fractional reabsorption of glucose (FR_{GLU}), a marker of tubular capacity to reabsorb glucose independent of GFR, with degree of renal disease, as assessed by urinary albumin excretion (UAE) and estimated GFR (eGFR).

Materials and Methods

From September 2017 to January 2018, all patients with diabetes attending the Diabetes Department at the Bichat-Claude Bernard University Medical Centre in Paris, France, for a one-day global assessment of their condition, or for hospitalization in our ward, were asked to participate to the present study. All underwent, as part of their routine evaluation, blood and urine sampling in a fasting state. Plasma, urinary glucose and creatinine, glycated haemoglobin (HbA1c) and urinary albumin were measured, and age, gender, diabetes type and duration, and antidiabetic and other treatments were also recorded. No patients were taking SGLT2 inhibitors, which were not available in France at the time. Glucose and creatinine were measured by enzymatic methods, HbA1c by high-performance liquid chromatography (HPLC) and urinary albumin by nephelometry, all through the use of automated systems (Siemens AG, Munich, Germany). Patients' blood pressure (BP) was taken three times at 2-min intervals with a Dinamap BP monitor (GE Healthcare, Princeton, NJ, USA) in a sitting position, and the median value recorded.

All patients gave their informed consent to participate, and the investigation was carried out in accordance with the principles of the Declaration of Helsinki (as revised in 2008).

FR_{GLU} was calculated as 1 minus fractional glucose clearance, which was defined as urinary glucose clearance divided by GFR. Urinary glucose clearance was defined as urinary glucose concentration multiplied by urine volume divided by plasma glucose. Creatinine clearance was used as an estimate of GFR: this was defined as the urinary creatinine concentration

multiplied by urine volume divided by plasma creatinine. Thus, fractional glucose clearance was calculated as (urinary glucose × plasma creatinine)/(urinary creatinine × plasma glucose) and the FR_{GLU} expressed as a percentage.

Because the FR_{GLU} is primarily dependent on the prevailing blood glucose level, participants were stratified according to their admission fasting plasma glucose (FPG) levels as low (< 6 mmol/L), intermediate (6–11 mmol/L) and high (> 11 mmol/L). These glycaemic thresholds were chosen because 11 mmol/L is widely recognized to be the maximum threshold for glycosuria to arise [20], while < 6 mmol/L defines the upper limit of normal glucose tolerance based on FPG. The 6–11 mmol/L FPG is a zone of uncertainty for glycosuria. Patients using a flash continuous glucose monitoring system (FreeStyle Libre, Abbott Laboratories, Abbott Park, IL, USA) were asked to report their average blood glucose during the 8 h preceding blood sampling. This allowed confirmation of the representativeness of the blood glucose levels—the average blood glucose during the hours prior to urine collection—used to calculate the FR_{GLU}.

Classification of CKD was based on the UAE and expressed as the albumin/creatinine ratio (ACR), while eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [21]. UAE was categorized as normoalbuminuria (ACR < 30 mg/g), microalbuminuria (ACR 30–300 mg/g) and macroalbuminuria (ACR > 300 mg/g); eGFR was categorized according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification [22] as G1 (> 90 mL/min/1.73 m^2), G2 (90–60 mL/min/1.73 m^2), G3 (59–30 mL/min/1.73 m^2) and G4 (< 30–16 mL/min/1.73 m^2). Patients with eGFR ≤ 15 mL/min/1.73 m^2 (G5) were excluded from the study.

UAE and eGFR contribute independently and additively to risk for end-stage kidney disease in diabetes [23]. Thus, for a sensitivity analysis, a score of kidney disease severity (ranked 0

to 5) was calculated for each participant by summing UAE and eGFR scores: normoalbuminuria (0), microalbuminuria (1) and macroalbuminuria (2), and G1 (0), G2 (1), G3 (2) and G4 (3), respectively.

Data are presented as means (standard deviation, SD) and medians (interquartile range, IQR), and as means (standard error of mean, SEM) for analysis of covariance (ANCOVA) results. As FR_{GLU} values were not normally distributed but significantly skewed towards the higher end of the distribution, these values were ranked and the ranking order used for all statistical analyses. Comparisons of FR_{GLU} ranking between groups were made by Kruskal–Wallis tests, and Cochran–Mantel–Haenszel tests were used to assess group interactions. Correlations between FR_{GLU} ranking and kidney disease severity scores were assessed by Spearman's rank correlation coefficient (rho). Comparisons of other traits between groups were made by ANCOVA, Kruskal–Wallis or Pearson's chi-squared tests. Assessments of the covariates associated with UAE and eGFR were made using multiple regression analyses. Statistical analyses were performed with JMP software (SAS Institute Inc., Cary, NC, USA), and $P \leq 0.05$ was considered significant.

Results

The present study analyzed data from 637 of the 651 participants after excluding patients who had eGFRs ≤ 15 mL/min/1.73 m^2. Thus, the study population consisted of 62 patients with T1D, 482 with T2D and 93 with some other type of diabetes (62 had diabetes and pancreatic disease, 31 had monogenic diabetes). Clinical characteristics of participants stratified by FPG group at admission are presented in Table I, and treatment data are shown in Table S1 (see supplementary materials associated with this material online). Among the 213 participants using flash glucose monitoring devices, admission FPG correlated well with the average

blood glucose recorded by their devices during the 8 h preceding blood samplings ($r^2 = 0.642$, $P < 0.0001$). Patients in the high FPG group compared with the other groups more frequently had T1D, higher HbA1c levels and lower FR_{GLU} values, whereas eGFR did not differ by FPG group (Table I).

Characteristics of our study patients stratified by UAE categories are presented in Table II, and FR_{GLU} by UAE categories in the three FPG groups are shown in Fig. 1. There was a significant interaction between UAE category and FPG group in the FR_{GLU} distribution ($P < 0.0001$). Whereas FR_{GLU} was not affected by UAE category in either the low FPG ($P = 0.14$) or intermediate FPG ($P = 0.16$) groups, in the high FPG group, median (IQR) FR_{GLU} values increased from 93.50% (17.74) in patients with normoalbuminuria (n = 135) to 96.56% (5.94) in those with microalbuminuria (n = 77) and to 99.12% (5.44) in those with macroalbuminuria (n = 31; $P = 0.002$). Fig. 3A shows glycosuria plotted by FR_{GLU} rank in participants with high FPG stratified by UAE category: glycosuria was 137 ± 8 mmol/L, 114 ± 10 mmol/L and 65 ± 16 mmol/L in patients with normoalbuminuria, microalbuminuria and macroalbuminuria, respectively (presented as means ± SEM; $P < 0.0001$; ANCOVA adjusted for FR_{GLU} rank and FPG).

Characteristics of patients stratified by eGFR category are presented in Table III: HbA1c and FPG (or FPG groups) did not differ by eGFR category. FR_{GLU} by eGFR category in the three FPG classes are shown in Fig. 2. There was a significant interaction between eGFR category and FPG group on FR_{GLU} distribution ($P < 0.0001$): FR_{GLU} increased across eGFR categories in those with high FPG: median (IQR) FR_{GLU} values were 94.13% (16.24) for G1 (n = 111), 96.35% (11.94) for G2 (n = 72), 98.88% (7.59) for G3 (n = 46) and 99.11% (2.18) for G4 (n = 14; $P = 0.002$). Fig. 3B shows glycosuria plotted by FR_{GLU} rank in participants with high FPG stratified by eGFR category: glycosuria means ± SEM were 154 ± 8 mmol/L, 109 ± 10

mmol/L, 79 ± 13 mmol/L and 40 ± 23 mmol/L in G1, G2, G3 and G4 patients, respectively ($P < 0.0001$; ANCOVA adjusted for FR_{GLU} rank and FPG).

The results of multiple regression analysis of covariates associated with UAE and eGFR in those with high FPG are shown in Table IV. FR_{GLU} was independently associated with UAE ($P = 0.003$) and eGFR ($P = 0.04$) in a regression model including age, gender, duration and type of diabetes, systolic BP, HbA1c and use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Type of diabetes was not significantly associated with either UAE or eGFR in these analyses.

Sensitivity analyses were performed with renal disease scores that took into account both UAE and eGFR categories. The results revealed a significant correlation between renal disease score and FR_{GLU}: Spearman's rho = 0.08 ($P = 0.04$) for FPG groups combined; and rho = 0.29 ($P < 0.0001$) for the high FPG group on its own.

Discussion

In this cross-sectional study of patients with diabetes, their renal capacity to reabsorb glucose (FR_{GLU}) during hyperglycaemia (FPG > 11 mmol/L) was indeed associated with kidney disease. In fact, FR_{GLU} was higher in patients with more severely impaired kidney function in terms of UAE, eGFR or a kidney disease score of these two markers combined. On the other hand, glycosuria was lower in patients with more severely impaired kidney function. These results were unexpected, as tubules are reportedly anatomically damaged in kidney biopsies of patients with established diabetic nephropathy [24]. Thus, intuitively, it would be expected that a reduction in glucose reabsorption, a tubular function, would be observed in those with reduced kidney function. One possible explanation is that the tubular capacity to transport glucose from the urine back to the capillary bloodstream was not saturared in those with low

and intermediate FPG, not even in participants with reduced kidney function. Also, hyperglycaemia stimulates tubular reabsorption capacity to reabsorb glucose [25]. As the most consistent associations between UAE and eGFR with FR_{GLU} were observed in the group of patients with high FPG (> 11 mmol/L), this suggests that maximum glucose reabsorption activity had been reached in those patients.

The major limitation of our present study was that it was a cross-sectional single-centre investigation and a reverse causation relationship cannot be excluded. Therefore, our study can only bring first-level evidence to our hypothesis, and further investigations are now required for confirmation of our findings. In addition, as the distribution of FR_{GLU} was far from normal, only non-parametric tests were used in this study, and whether the statistical significance levels reported here are clinically meaningful or not still needs to be ascertained. Thus, it is important to design follow-up studies to investigate the renal outcomes of patients selected according to their baseline glycaemic control.

The major strength of our study was that it evaluated a large sample of patients with several types of diabetes, and variable degrees of diabetes control and duration.

The pathophysiological mechanisms related to renal capacity to reabsorb glucose and risk for kidney disease have yet to be clearly determined. They could be related, at least in part, to changes in sodium concentrations in tubular fluid. Tubular reabsorption of glucose by SGLT1 and SGLT2 is coupled with sodium reabsorption, and increased tubular reabsorption of sodium leads to low tubular lumen concentrations of NaCl and reduced NaCl uptake at the macula densa, thereby triggering the complex mechanisms of tubuloglomerular feedback leading to increased renin release and activation of the renin–angiotensin system.

Previously, increased reabsorption of both glucose and sodium at the proximal tubule level, and increased GFR following the transition from near-normal glycaemia to hyperglycaemia,

have been reported during intravenous glucose infusion in patients with T1D and glomerular hyperfiltration and/or microalbuminuria [4]. These effects were largely attenuated in patients with normal GFR and UAE. Over the 20-year follow-up, a high renal capacity to reabsorb glucose and sodium contributed independently to other known risk factors for the development of kidney disease [4]. Moreover, clinical trials of SGLT2 inhibitors, which decrease tubular reabsorption of glucose, have shown beneficial effects on kidney outcomes in both T1D and T2D patients [5–7, 19], including correction of glomerular hyperfiltration during hyperglycaemia in those with recent-onset T1D [19]. Our present findings are consistent with the results of those investigations [4–7, 19].

The basis for interindividual variability in renal glucose reabsorption capacity is heterogeneous and probably includes variations in the genes implicated in tubular glucose handling, including its energy demands. Mutations in *SLC5A2*, the gene encoding SGLT2, result in familial renal glycosuria [26]. Mutations in transcription factor HNF-1α, a protein that binds to the *SLC5A2* promoter and regulates SGLT2 expression, decrease tubular glucose reabsorption and lead to renal glycosuria [27]. *SLC5A2* and *HNF1A* gene polymorphisms are frequent in the general population, yet their impact on glucose transport, renal function and kidney outcomes still needs to be established. Proximal tubules reabsorb 80% of the filtrate that passes through the glomerulus, and their reabsorption capacity depends on the efficiency of oxidative phosphorylation to produce adenosine triphosphate (ATP), which drives the active transport of glucose, ions and nutrients. As such, these tubules contain more mitochondria than any other structure in the kidney [28]. Renal mitochondria are sensitive to oxidative stress, and mitochondrial fragmentation and changes in mitochondrial energetics have been observed in proximal tubules in the early stages of diabetes [29]. Indeed, there have been reports of the association of allelic variations in genes implicated in oxidative stress or in antioxidant mechanisms with the development and progression of DKD in T1D [10, 12, 30–

33]. Nevertheless, the impact of these frequent variants on tubular function also needs to be established.

In conclusion, the present study suggests that maximum glucose reabsorption capacity can influence the risk of kidney disease in patients with diabetes and that interindividual heterogeneity of this function is a determinant of heterogeneity in the risk for diabetic kidney disease. However, further studies are now required to explore this hypothesis, as they are likely to contribute some interesting data towards the creation of personalized treatment strategies to protect diabetes patients against kidney disease.

Highlights

- Susceptibility to kidney disease is heterogeneous in patients with diabetes;
- Assessment of fractional renal glucose reabsorption in patients with diabetes revealed a strong association between glucose reabsorption capacity and renal status severity;
- High renal glucose reabsorption might be contributing to diabetic kidney disease.

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Data availability

The dataset analyzed during the present study is not publicly available due to hospital records policy.

Contribution statement

OM and MM designed the study, researched data and drafted the manuscript. GV researched data and drafted the manuscript. YA and MHF researched data, contributed to the discussion and reviewed/edited the manuscript. LP, FF, SH and RR contributed to the discussion and reviewed/edited the manuscript. MM is the guarantor of this work and, as such, had full access to all study data, and takes full responsibility for the integrity of the data and accuracy of the data analysis. All authors approved the submitted version of the manuscript.

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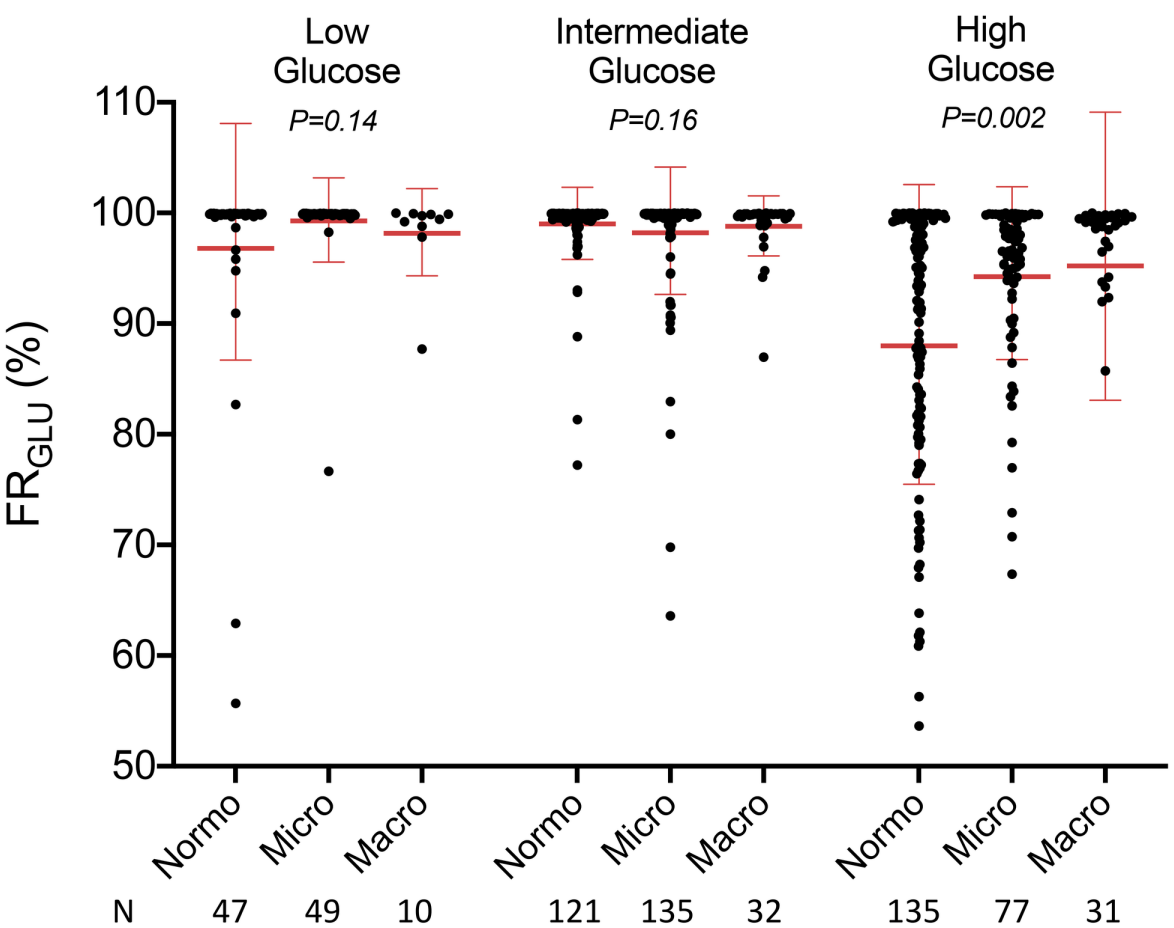
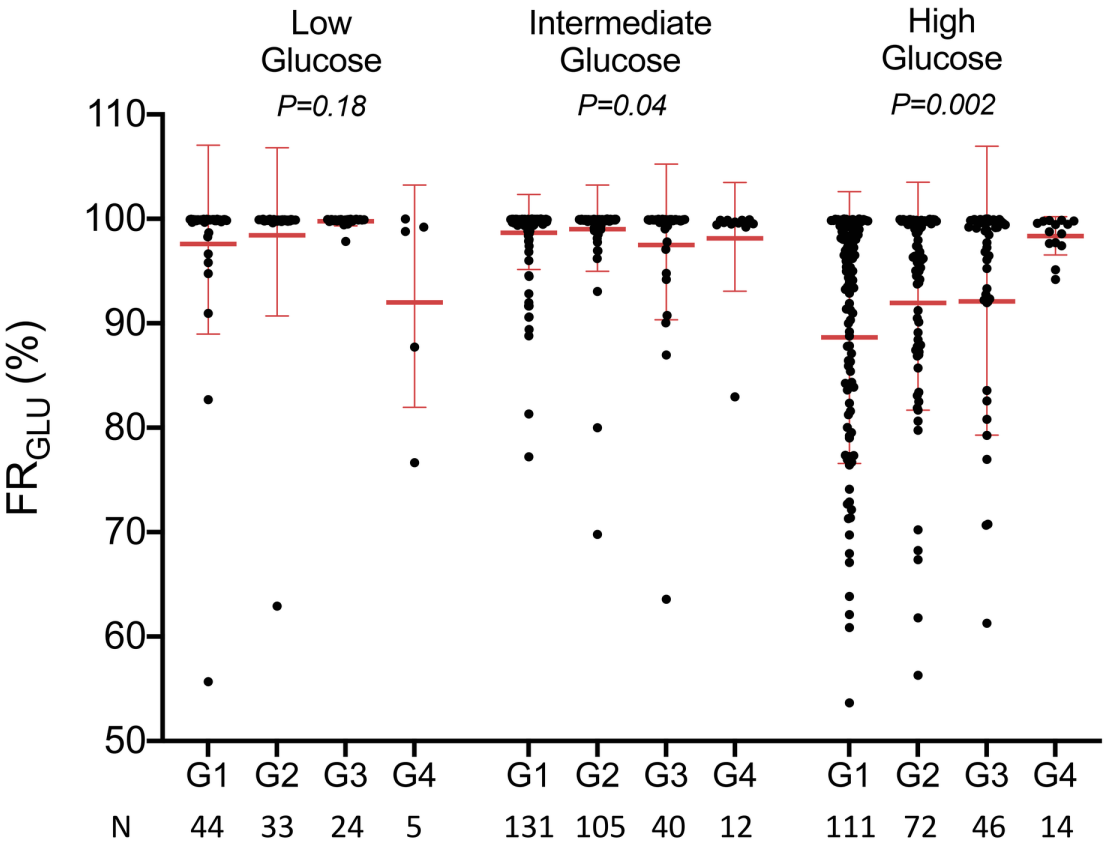
Legends for figures

Fig. 1. Fractional reabsorption of glucose (FR_{GLU}) by urinary albumin excretion (UAE) category in participants with low (< 6 mmol/L), intermediate (6–11 mmol/L) and high (> 11 mmol/L) fasting plasma glucose (FPG) at admission. Normo/Micro/Macro: normoalbuminuria/microalbuminuria/macroalbuminuria; N: number of participants in each category. Bars represent geometric means ± SD. $P < 0.0001$ for normo- and microalbuminuria, and $P = 0.005$ for macroalbuminuria (by Kruskal–Wallis test); $P < 0.0001$ for interaction between UAE category and FPG group (by Cochran–Mantel–Haenszel interaction test).

Fig. 2. Fractional reabsorption of glucose (FR_{GLU}) by estimated glomerular filtration rate (eGFR: G1–G4) in participants with low (< 6 mmol/L), intermediate (6–11 mmol/L) and high (> 11 mmol/L) fasting plasma glucose (FPG) at admission. N: number of participants in each category. Bars represent geometric means ± SD. $P < 0.0001$ for G1, G2 and G3, and $P = 0.15$ for G4 (by Kruskal–Wallis test); $P < 0.0001$ for interaction between eGFR and FPG groups (by Cochran–Mantel–Haenszel interaction test).

Fig. 3. Glycosuria by fractional reabsorption of glucose ranking in participants with high fasting plasma glucose (FPG) stratified by (A) urinary albumin excretion and (B) estimated glomerular filtration rate categories (G1–G4). N: normoalbuminuria; μ: microalbuminuria; M: macroalbuminuria. Curves are log-fitted by analysis of covariance (ANCOVA).


Low Glucose
Intermediate Glucose
High Glucose
P=0.14
P=0.16
P=0.002
FR_GLU (%)
110
100
90
80
70
60
50
Normo
Micro
Macro
Normo
Micro
Macro
Normo
Micro
Macro
N
47
49
10
121
135
32
135
77
31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P=0.18
Intermediate Glucose
P=0.04
High Glucose
P=0.002
FRGLU (%)
110
100
90
80
70
60
50
G1 G2 G3 G4
G1 G2 G3 G4
G1 G2 G3 G4
N 44 33 24 5
131 105 40 12
111 72 46 14

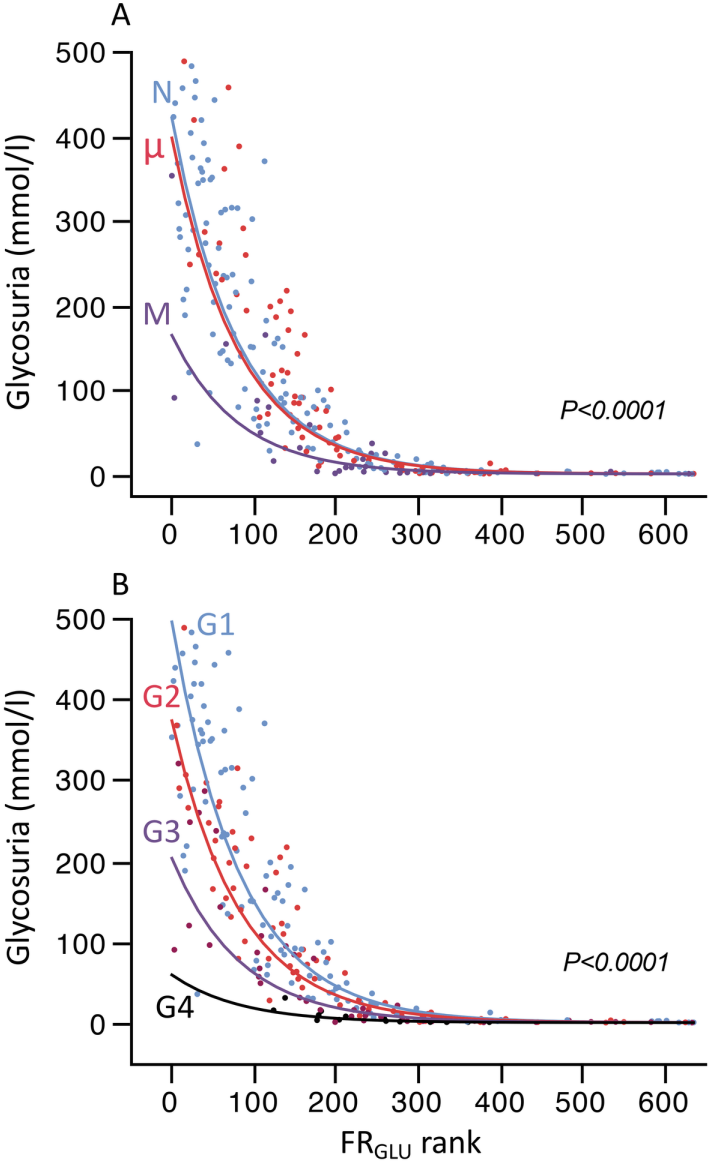
A
Glycosuria (mmol/l)
500
400
300
200
100
0
N
μ
M
P<0.0001
0
100
200
300
400
500
600
B
Glycosuria (mmol/l)
500
400
300
200
100
0
G1
G2
G3
G4
P<0.0001
0
100
200
300
400
500
600
FR$_{GLU}$ rank

Table I
Characteristics of participants by fasting plasma glucose (FPG) group at admission

	FPG group			*P*
	Low (< 6 mmol/L)	**Intermediate (6–11 mmol/L)**	**High (> 11 mmol/L)**	
Number of patients	106	288	243	
Age, years	59 (14)	60(14)	59(15)	0.88
Male gender, n (%)	65 (61.3)	156 (54.2)	149 (61.3)	0.19
Diabetes type: Type 1, n (%)	12 (11.3)	18 (6.2)	32 (13.2)	< 0.0001
Type 2, n (%)	64 (60.4)	232 (83.0)	179 (73.6)	
Other, n (%)	30 (28.3)	31 (10.8)	32 (13.2)	
Diabetes duration, years*	12 (14)	12 (14)	15 (16)	0.08
FPG, mmol/L	4.7 (1.0)	8.3 (1.4)	16.7 (5.0)	< 0.0001
HbA1c, mmol/mol	60 (16)	67 (14)	89 (20)	< 0.001
HbA1c, %	7.6 (1.9)	8.3 (1.6)	10.3 (2.3)	< 0.0001
Body mass index, kg/m^2	28.6 (6.3)	29.5 (6.1)	29.0 (6.7)	0.23
Systolic blood pressure, mmHg	126 (16)	129 (18)	132 (20)	0.07
Diastolic blood pressure, mmHg	72 (12)	72 (12)	73 (13)	0.76
Urinary albumin excretion (UAE), mg/g*	24 (43)	25 (55)	16 (50)	0.15
UAE category: Normoalbuminuria, n (%)	47 (44.3)	121 (42.0)	135 (55.5)	0.006
Microalbuminuria, n (%)	49 (46.2)	135 (46.9)	77 (31.7)	
Macroalbuminuria, n (%)	10 (9.5)	32 (11.1)	31 (12.8)	
Estimated glomerular filtration rate (eGFR), mL/min/1.73 m^2	81 (30)	84 (28)	83 (31)	0.56
eGFR category: G1 (> 90), n (%)	44 (41.5)	131 (45.5)	111 (45.7)	0.31
G2 (90–60), n (%)	33 (31.1)	105 (36.4)	72 (29.6)	
G3 (59–30), n (%)	24 (22.7)	40 (3.9)	46 (18.9)	
G4 (< 30–16), n (%)	5 (4.7)	12 (4.2)	14 (5.8)	
Urinary glucose, mmol/L*	0.9 (1.2)	1.5 (3.8)	69.9 (197.8)	< 0.0001
FR_{GLU}, %*	99.90 (0.15)	99.90 (0.41)	96.36 (12.57)	< 0.0001

Quantitative data expressed as means (SD) or *medians (IQR); analysis of covariance (ANCOVA) by *Kruskal–Wallis or Pearson's chi-squared test (qualitative data); $P \leq 0.05$ considered significant;
FR_{GLU}: fractional reabsorption of glucose

Table II
Characteristics of participants by urinary albumin excretion (UAE) category

	UAE category			
	Normoalbuminuria	**Microalbuminuria**	**Macroalbuminuria**	***P***
Number of patients	303	261	73	
Age, years	57 (15)	63 (14)	62 (14)	< 0.0001
Male gender, n (%)	166 (54.8)	148 (56.7)	56 (76.7)	0.002
Diabetes type: Type 1, n (%)	36 (11.9)	20 (7.7)	6 (8.2)	0.17
Type 2, n (%)	217 (71.6)	205 (78.5)	60 (82.2)	
Other, n (%)	50 (16.5)	36 (13.8)	7 (9.6)	
Diabetes duration, years*	11 (15)	13 (13)	18 (12)	< 0.0001
Fasting plasma glucose (FPG), mmol/L	11.5 (6.1)	10.1 (5.3)	11.1 (5.4)	0.01
FPG group: Low (< 6), n (%)	47 (15.5)	49 (18.8)	10 (13.7)	0.006
Intermediate (6–11), n (%)	121 (39.9)	135 (51.7)	32 (43.8)	
High (> 11), n (%)	135 (44.6)	77 (29.5)	31 (42.5)	
HbA1c, mmol/mol	78 (21)	72 (17)	70 (15)	0.007
HbA1c, %	9.3 (2.5)	8.7 (2.0)	8.6 (1.7)	0.007
Body mass index, kg/m^2	28.6 (6.3)	29.4 (6.2)	31.0 (6.5)	0.02
Systolic blood pressure, mmHg	127 (18)	132 (18)	137 (20)	< 0.0001
Diastolic blood pressure, mmHg	71 (12)	74 (12)	73 (11)	0.02
Urinary albumin excretion, mg/g*	9 (7)	42 (50)	580 (917)	< 0.0001
Estimated glomerular filtration rate (eGFR), mL/min/1.73 m^2	91 (27)	81 (27)	57 (31)	< 0.0001
eGFR category: G1 (> 90), n (%)	166 (54.8)	108 (41.4)	12 (16.4)	< 0.0001
G2 (90–60), n (%)	99 (32.7)	93 (35.6)	18 (24.7)	
G3 (59–30), n (%)	33 (10.9)	50 (19.2)	27 (37.0)	
G4 (< 30–16), n (%)	5 (1.6)	10 (3.8)	16 (21.9)	
Urinary glucose, mmol/L*	5.5 (86.1)	1.8 (32.8)	2.2 (17.1)	0.04
FR_{GLU}, %*	99.64 (6.53)	99.86 (1.97)	99.47 (1.74)	0.002

Quantitative data expressed as means (SD) or *medians (IQR); analysis of covariance (ANCOVA) by *Kruskal–Wallis or Pearson's chi-squared test (qualitative data); $P \leq 0.05$ considered significant;
FR_{GLU}: fractional reabsorption of glucose

Table III
Characteristics of participants by category of estimated glomerular filtration rate (eGFR)

	eGFR category (mL/min/1.73 m^2)				
	G1 (> 90)	**G2 (90–60)**	**G3 (59–30)**	**G4 (30–16)**	***P***
Number of patients	286	210	110	31	
Age, years	51 (14)	65 (10)	70 (11)	66 (10)	< 0.0001
Male gender, n (%)	153 (53.5)	135 (64.3)	60 (54.6)	22 (71.0)	0.04
Diabetes type: Type 1, n (%)	44 (15.4)	11 (5.2)	5 (4.5)	2 (6.4)	< 0.0001
Type 2, n (%)	192 (67.1)	178 (84.8)	86 (78.2)	26 (88.9)	
Other, n (%)	50 (17.5)	21 (10.0)	19 (17.3)	3 (9.7)	
Diabetes duration, years*	10 (13)	14 (14)	18 (17)	19 (15–27)	< 0.0001
Fasting plasma glucose (FPG), mmol/L	10.9 (5.5)	10.6 (5.6)	11.2 (6.7)	11.1 (5.2)	0.74
FPG group: Low (< 6), n (%)	44 (15.4)	33 (15.7)	24 (21.8)	5 (16.1)	0.32
Intermediate (6–11), n (%)	131 (45.8)	105 (50.0)	40 (36.4)	12 (38.7)	
High (> 11), n (%)	111 (38.8)	72 (34.3)	46 (41.8)	14 (45.2)	
HbA1c, mmol/mol	76 (21)	73 (18)	73 (19)	73 (12)	0.36
HbA1c, %	9.1 (2.4)	8.8 (2.1)	8.8 (2.2)	8.5 (1.4)	0.36
Body mass index, kg/m^2	28.2 (6.2)	29.9 (6.5)	29.5 (5.6)	32.3 (7.4)	0.001
Systolic blood pressure, mmHg	126 (17)	133 (19)	132 (18)	141 (20)	< 0.0001
Diastolic blood pressure, mmHg	74 (12)	73 (12)	69 (12)	71 (12)	0.02
Urinary albumin excretion (UAE), mg/g*	14 (28)	21 (42)	50 (176)	228 (505)	< 0.0001
UAE category: Normoalbuminuria, n (%)	166 (58.0)	99 (47.1)	33 (30.0)	5 (16.1)	< 0.0001
Microalbuminuria, n (%)	108 37.8)	93 (44.3)	50 (45.4)	10 (32.3)	
Macroalbuminuria, n (%)	12 (4.2)	18 (8.6)	27 (24.6)	16 (51.6)	
eGFR, mL/min/1.73 m^2	109 (16)	76 (9)	47 (8)	23 (4)	< 0.0001
Urinary glucose, mmol/L*	5.2 (89.7)	2.3 (37.1)	1.5 (0.6-17.8)	1.8 (7.0)	< 0.0001
FR_{GLU}, %*	99.68 (5.38)	99.83 (1.99)	99.80 (2.32)	99.47 (2.10)	0.26

Quantitative data expressed as means (SD) or *medians (IQR); analysis of covariance (ANCOVA) by *Kruskal–Wallis or Pearson's chi-squared test (qualitative data); $P \leq 0.05$ considered significant;
FR_{GLU}: fractional reabsorption of glucose

Table IV

Covariates associated with urinary albumin excretion (UAE) and estimated glomerular filtration rate (eGFR) according to multivariate regression analyses in participants with high fasting plasma glucose (FPG) levels

	UAE			**eGFR**		
	β estimate	**SEM**	***P***	**β estimate**	**SEM**	***P***
Age	-0.4204	0.3927	0.29	-0.6774	0.1114	< 0.0001
Male gender	0.2046	0.0935	0.03	-0.0577	0.0265	0.03
Type 1 diabetes	-0.1875	0.2193	0.39	0.0025	0.0622	0.97
Type 2 diabetes	-0.0883	0.1721	0.61	0.0317	0.0488	0.52
Diabetes duration	0.2964	0.1106	0.008	-0.0197	0.0314	0.53
HbA1c	0.3060	0.5042	0.54	0.1749	0.1431	0.22
Systolic blood pressure	1.8001	0.6725	0.008	-0.2385	0.1908	0.21
Body mass index	0.8807	0.4693	0.06	-0.3419	0.1332	0.01
Use of ACE inhibitors or ARBs	0.1810	0.1133	0.11	0.0465	0.0321	0.15
FR_{GLU}	0.0048	0.0016	0.003	-0.0009	0.0004	0.04

Fractional reabsorption of glucose (FR_{GLU}) ranking order used for computations; other quantitative data log-transformed (ln); $P \leq 0.05$ considered significant;

ACE: angiotensin-converting enzyme; ARBs: angiotensin receptor blockers