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Glomerular hyperfiltration and increased proximal sodium reabsorption in subjects with type 2 diabetes or impaired fasting glucose in a population of the African region

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Abstract

Background. Glomerular hyperfiltration (GHF) is a well-recognized early renal alteration in diabetic patients. As the prevalence of GHF is largely unknown in populations in the African region with respect to normal fasting glucose (NFG), impaired fasting glucose (IFG) and type 2 diabetes [diabetes mellitus (DM)], we conducted a cross-sectional study in the Seychelles islands among families including at least one member with hypertension.

Methods. The glomerular filtration rate (GFR), effective renal plasma flow (ERPF) and proximal tubular sodium reabsorption were measured using inulin, *p*-aminohippurate (PAH) and endogenous lithium clearance, respectively. Twenty-four-hour urine was collected on the preceding day.

Results. Of the 363 participants (mean age 44.7 years), 6.6% had IFG, 9.9% had DM and 63.3% had hypertension. The prevalence of GHF, defined as a GFR >140 ml/min, was 17.2%, 29.2% and 52.8% in NFG, IFG and DM, respectively (*P* trend <0.001). Compared to NFG, the adjusted odds ratio for GHF was 1.99 [95% confidence interval (CI) 0.73–5.44] for IFG and 5.88 (2.39–14.45) for DM. Lithium clearance and fractional excretion of lithium were lower in DM and IFG than NFG (*P* < 0.001).

Conclusion. In this population of African descent, subjects with impaired fasting glucose or type 2 diabetes had a high prevalence of GHF and enhanced proximal sodium reabsorption. These findings provide further insight on the elevated incidence of nephropathy reported among African diabetic individuals.

Keywords: African region; diabetes; glomerular hyperfiltration; inulin clearance; lithium clearance

Introduction

The prevalence of end-stage renal damage (ESRD) is 15–20% in African-American diabetics, which is four times higher than in Caucasian diabetics [1,2]. This may be partly explained by socio-economic factors and genetic differences in renal haemodynamics and sodium handling [3,4]. For example, healthy African-Americans have a 10% lower renal plasma flow (ERPF) than age-matched Caucasians, possibly due to a more activated intrarenal renin–angiotensin system (RAS) in the former than the latter [5]. African-Americans are also more prone to sodium retention and salt-sensitive hypertension than Caucasians [3]. Besides, there is some evidence that glomerular hyperfiltration (GHF) and a disturbed renal autoregulation are more common among hypertensive African-Americans as compared to age-matched hypertensive Caucasians [6].

GHF and enhanced proximal sodium reabsorption are also more frequent in type 2 diabetes [diabetes mellitus (DM)] and in the metabolic syndrome than persons with normal fasting glucose (NFG) [7–9]. According to the tubulocentric view developed recently by Vallon *et al.* and supported by experimental evidence, increased proximal tubular reabsorption of sodium might be one of the trigger mechanisms leading to GHF [8]. Together, GHF and higher proximal reabsorption of sodium may result in accelerated loss of kidney function and hypertension in diabetic persons [10,11].

One may therefore expect that diabetics of African descent have both a high prevalence of GHF and enhanced proximal sodium reabsorption, which may make them more susceptible to kidney function deterioration and hypertension. However, only few studies have examined renal haemodynamics in African subjects, and these studies included mainly African-Americans [12,13]. To our knowledge, no study has used gold standard techniques

Table 1. Participant characteristics by diabetes status

Covariable	Normal fasting glucose	Impaired fasting glucose	Diabetes	<i>P</i> trend
<i>n</i>	303	24	36	
Age (years)	44 (37; 53)	47 (39; 55)	49 (40.5; 62.5)	0.007
Sex (% female)	56	48	42	0.017
BMI (kg/m ²)	27.4 (23.8; 31.1)	28.5 (25.7; 31.7)	28.9 (25.8; 32.4)	0.205
Alcohol (g/day)	0 (0; 7)	0 (0; 13)	0 (0; 16)	0.045
Smoking (%)	13	8	8	0.925
Office MAP (mmHg)	99 (90; 109)	105 (98; 113)	105 (99; 116)	<0.001
Serum potassium (mmol/L)	3.7 (3.6; 3.9)	3.7 (3.5; 4)	3.8 (3.7; 4)	0.139
PRA (ng/ml/hour)	0.34 (0.15; 0.63)	0.44 (0.28; 0.61)	0.40 (0.13; 0.55)	0.740
Plasma aldosterone (pg/ml)	53 (43; 66)	58 (43; 80)	59 (46; 79)	0.159
Urinary sodium (mmol/24 hours)	102 (67; 134)	86 (60; 127)	110 (77; 159)	0.177
Urinary potassium (mmol/24 hours)	41 (31; 51)	42 (30; 55)	51 (39; 72)	0.001
Urine volume (l/24 hours)	1.8 (1.2; 2.3)	2.0 (1.1; 2.7)	1.9 (1.3; 2.7)	0.193

Data are medians (interquartile range), unless otherwise specified. Data are unadjusted. PRA, plasma renin activity.

such as inulin, *p*-aminohippurate (PAH) and endogenous lithium clearances to assess the renal function and renal sodium handling in type 2 DM in the African region so far. Therefore, the purpose of this analysis was to compare renal haemodynamic parameters, renal sodium handling and the prevalence of GHF between NFG, impaired glucose tolerance (IGT) and DM categories in the Seychelles, a rapidly developing country in the African region, taking into account possible confounding effects of parameters such as age, sex, obesity and estimated sodium intake.

Materials and methods

This study was conducted on a sample of families collected prospectively for the primary purpose of a candidate gene study of hypertension [14,15]. The study took place in the Seychelles islands (Indian Ocean), which lie ~1000 km east of Kenya and 1000 km north of Madagascar and Mauritius. The majority of the population is of African descent. We enrolled 494 subjects of East African descent from 76 families enriched in hypertensive individuals between August 1999 and January 2002. The detailed family selection process has been described previously [4]. The study was approved by the Ethical Committees of the Ministry of Health in the Seychelles and of the University of Lausanne (Switzerland). All participants provided written informed consent. Of the 363 participants with data on inulin clearance, 343 had available valid data on PAH clearance and 329 valid data on endogenous lithium clearance.

Antihypertensive therapy, if any, was stopped 2 weeks before conducting clearance protocols. Clearance studies were performed after an overnight fast, as reported previously [16]. In brief, two intravenous catheters were inserted into antecubital veins, one for the infusion of inulin and PAH, and a second into the contra lateral arm for blood drawing. After an oral water load of 8 ml/kg and a 2-hour equilibration period, two 1-hour inulin and PAH clearances were obtained to measure GFR and ERPF, respectively. The inulin, PAH and endogenous lithium clearances (C_x) were calculated with the formula $C_x = (U_x \times V) / P_x$, where U_x and P_x are urinary and plasma concentrations of the x solute, and V is the urine flow rate in millilitre per minute. Renal blood flow (RBF) was calculated as $ERPF / [1 - (\text{haematocrit} / 100)]$ and renal vascular resistance (RVR) as $(\text{mean arterial blood pressure}) / \text{RBF}$. Fractional excretions of endogenous lithium (FELi) and sodium (FENa) were calculated by the standard formula $FE_x = (U_x \times P_{\text{creat}}) / (P_x \times U_{\text{creat}})$. Fractional sodium reabsorption in the post-proximal tubule (FDRNa) was estimated as $[(\text{FELi} - \text{FENa}) / \text{FELi}] / 100$. Filtration fraction (FF) was calculated as GFR divided by ERPF. Creatinine concentration was measured by the picric acid method (Cobas-Mira, Roche, Basel, Switzerland). Mean arterial blood pressure (MAP) was calculated as one-third of systolic blood pressure plus two-thirds of diastolic blood pressure from the mean of six measurements taken with a mercury sphygmomanometer (three on the day preceding

clearances and three on the morning of the clearances). GHF was defined as a GFR >140 ml/min/1.73 m² [13]. On the day preceding clearance studies, participants collected their urine for 24 hours to assess sodium intake. Urinary and plasma sodium and potassium concentrations were measured by flame photometry (IL-943, Instrumentation Laboratory, Milan, Italy). Endogenous trace lithium was measured by atomic absorption spectrophotometry [17]. Plasma renin activity (PRA) was measured using the antibody-trapping principle [18,19]. Aldosterone was measured by a direct radioimmunoassay using a very sensitive and specific antiserum raised in a New Zealand white rabbit [20]. The coefficients of variation for within- and among-assay precision were 0.04 to 0.13 for the PRA and aldosterone assays [18,20].

Participants on antidiabetic treatment during the preceding month, or with fasting blood glucose ≥ 7.0 mmol/l (measured on venous whole blood in duplicate using a Glycotronic® C reflectometer, Macherey-Nagel, Düren, Germany), were considered as having diabetes (DM). Impaired fasting glucose tolerance (IFG) was defined as fasting glucose ≥ 5.6 mmol/l and < 7 mmol/l and normal fasting glucose (NFG) as fasting glucose < 5.6 mmol/l [21]. Body surface area (BSA) was calculated using the Dubois formula [22]. Body mass index (BMI) was calculated as weight (kilogram) divided by squared height (square metre).

All analyses were conducted with Stata 10 (StataCorp, College Station, Texas, USA). We used generalized estimating equations with an exchangeable correlation structure to account for familial correlation. A Gaussian link was used for continuous phenotypes (e.g. GFR and ERPF) and a binomial link for dichotomous phenotypes (e.g. GHF). To better approximate a normal distribution of the residuals, GFR was log-transformed, and FELi and FF were square-root transformed, whereas ERPF was not transformed. For fully adjusted models, we used as predictors the age, sex, BMI, 24-hour urinary sodium and potassium excretion, MAP, alcohol consumption, smoking and being taken off antihypertensive treatment. We conducted stratified analyses in untreated and treated participants, as well as sensitivity analyses after excluding participants taking diuretics before the treatment was stopped.

Results

Participant characteristics are presented in Table 1. IFG or DM was associated with age and male sex. Plasma renin activity and plasma aldosterone levels were similar across the three blood glucose categories. The mean urinary creatinine excretion was 0.16 mmol/kg/24 hours in women and 0.20 mmol/kg/24 hours in men, which suggests good completeness of urine collections. The median urinary sodium excretion was similar across diabetes categories, and also in hypertensive (96 mmol/24 hours) and non-hypertensive (104 mmol/24 hours) individuals ($P = 0.36$). Urinary excretion of potassium was greater in DM than

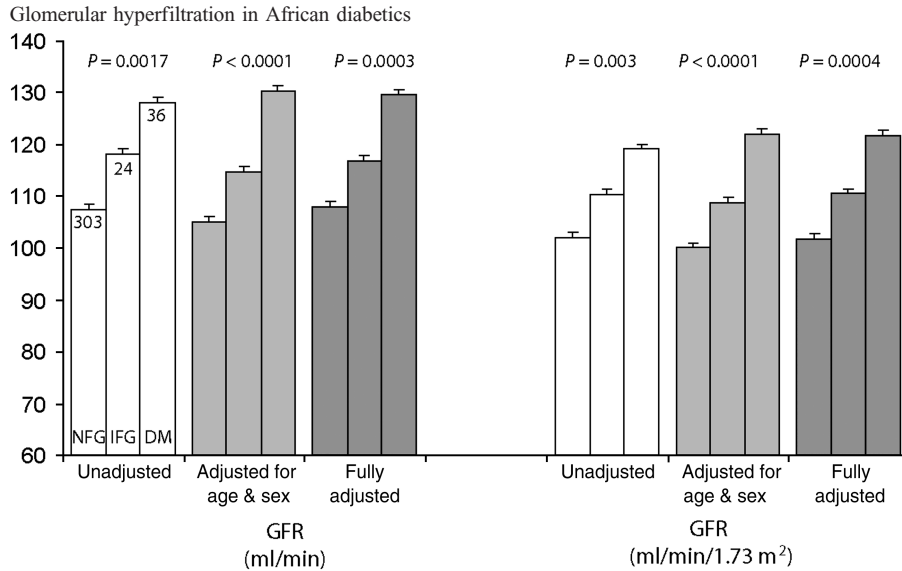


Fig. 1. Glomerular filtration rate and effective renal plasma flow by diabetes status. Bars are means, and whiskers are standard errors. NFG, normal fasting glucose. IFG, impaired fasting glucose ($5.6 \leq FG < 7.0$ mmol/L). DM, diabetes mellitus. GFR was estimated using inulin clearance. Inulin clearance data were log-transformed to conducted linear regression analyses (generalized estimating equations) and then back-transformed to provide untransformed adjusted data. Fully adjusted models included age, sex, body mass index, alcohol consumption, smoking status, 24-hour urinary sodium and potassium excretion, mean arterial blood pressure and a dummy variable to indicate whether or not the participant was taken off antihypertensive treatment. *P*-values are from a likelihood ratio test (2 df) comparing a model with and without categorical diabetes status [i.e. normal glucose (reference category), impaired glucose tolerance and diabetes mellitus].

Table 2. Risk of hyperfiltration by diabetes status

	Impaired fasting glucose	Diabetes	Impaired fasting glucose + diabetes	<i>P</i> difference ^a
<i>n</i>	24	36	60	
Hyperfiltration (ml/min)				
Unadjusted	1.88 (0.77–4.65)	4.73 (2.34–9.56)***	3.32 (1.84–6.01)***	0.08
Age- and sex-adjusted	1.98 (0.78–4.98)	6.57 (3.01–14.45)***	3.95 (2.09–7.48)***	0.03
Fully adjusted	1.99 (0.73–5.44)	5.88 (2.39–14.45)***	3.63 (1.79–7.38)***	0.08
Hyperfiltration (ml/min/1.73 m ²)				
Unadjusted	2.75 (0.99–7.63)	3.22 (1.39–7.46)**	3.02 (1.49–6.12)**	0.80
Age and sex-adjusted	2.75 (0.97–7.75)	3.58 (1.48–8.67)**	3.20 (1.53–6.70)**	0.67
Fully adjusted	2.63 (0.91–7.57)	2.52 (0.97–6.55)	2.57 (1.18–5.58)*	0.95

Data are odds ratio (OR) (95% CI) for hyperfiltration. Hyperfiltration cutoff: 140 ml/min (high part of the table) or 140 ml/min/1.73 m² (lower part of the table). Reference category is normal fasting glucose (*n* = 303). Full models include age, sex, body mass index, urinary sodium and potassium excretion, alcohol consumption, smoking, mean arterial pressure and being taken off antihypertensive treatment. * $0.01 \geq P < 0.05$, ** $0.001 \geq P < 0.01$, *** $P < 0.001$.

^a*P* for the difference in odds ratio between impaired fasting glucose and diabetes mellitus.

NFG categories. This was not due to a higher use of diuretics (17% in diabetics vs 22% in non-diabetics).

The prevalence of hypertension, defined as having office blood pressure $\geq 140/90$ mmHg and/or being on antihypertensive treatment, was 63.3%, and the prevalence tended to be higher in DM and IFG categories than in NFG participants. Among the 230 hypertensive participants, 68% were on antihypertensive treatment, which was stopped in all individuals for a median of 15 days before clearance studies. The following treatment types were stopped: angiotensin-converting enzyme (ACE) inhibitors in 30%, calcium channel blockers in 44%, diuretics (mainly hydrochlorothiazide) in 49%, beta-blockers in 28%. Median (range) diabetes duration was 3 (0–21) years, and six participants had newly diagnosed type 2 diabetes mellitus.

Compared to NFG, GFR was higher in the presence of DM, and intermediate values were found for IFG, regardless of the adjustment procedure used (Figure 1) and irrespective of BSA.

The prevalence of hyperfiltration (defined as GFR >140 ml/min) was 17.2%, 29.2% and 52.8% in NFG, IFG and DM categories, respectively (*P* trend <0.001). When corrected for body surface area, the corresponding prevalence of hyperfiltration (defined as GFR >140 ml/min) was 9.9%, 25.0% and 27.8%, respectively (*P* trend = 0.001). The odds ratios of having GHF are illustrated in Table 2 after adjustment for different covariate combinations. Participants with IFG and DM had an ~2- to 3-fold increased risk of GHF when compared to NFG.

IFG and DM were not associated with ERPF or renal vascular resistance levels except for a non-significant trend

Table 3. Effective renal plasma flow, filtration fraction and renal vascular resistance, by diabetes status

Covariable	Normal fasting glucose	Impaired fasting glucose	Diabetes	<i>P</i> trend
<i>n</i>	296	23	24	
ERPF (ml/min)	441 (357; 551)	485 (394; 541)	406 (347; 503)	0.675
ERPF (ml/min/1.73 m ²)	426 (336; 506)	427 (358; 515)	358 (325; 464)	0.184
Renal vascular resistance (mmHg/ml/min)	0.14 (0.1; 0.18)	0.13 (0.12; 0.16)	0.15 (0.13; 0.17)	0.172
Renal vascular resistance (mmHg/ml/min/1.73m ²)	0.13 (0.09; 0.18)	0.11 (0.1; 0.15)	0.14 (0.11; 0.17)	0.577
Filtration fraction	0.24 (0.22; 0.27)	0.27 (0.24; 0.28)	0.30 (0.26; 0.34)	<0.001

Data are unadjusted medians (interquartile range). ERPF, effective renal plasma flow, measured using PAH clearance.

towards lower ERPF in DM (Table 3). Hence, the higher FF observed in DM resulted essentially from differences in GFR. Filtration fraction was higher in DM than NFG even after using the fully adjusted models (data not shown).

IFG or DM was associated with lower FELi compared to NFG, indicating increased reabsorption of sodium in proximal segments of the nephron in IFG and DM (Figure 2). As FELi did not differ between IFG and DM, analyses were conducted with both groups combined. Similar results were obtained when using lithium clearance instead of FELi as the dependent variable. In these latter models, GFR was included as a covariate in all analyses. The fractional distal reabsorption of sodium (FDRNa) was not associated with DM or IFG [data not shown, *P* = not significant (NS)].

Sensitivity analyses conducted in untreated participants (*n* = 186) showed similar results. FELi across diabetes categories was 18%, 15% and 13% for unadjusted analyses (*P* = 0.02), 18%, 16% and 13% for age- and sex-adjusted analyses (*P* = 0.02) and 18%, 15% and 13% for fully adjusted analyses (*P* = 0.07), respectively. Sensitivity analyses conducted in participants not taking diuretics (*n* = 255) clearly confirmed our results (*P* < 0.02 for all analyses).

Discussion

This study in a population in the African region shows that subjects with DM and IFG have, compared to subjects with NFG, a higher prevalence of glomerular hyperfiltration and greater proximal tubular sodium reabsorption, as measured by FELi, independently of several potentially confounding variables.

GHF is a well-recognized early renal alteration in DM. Today, only few studies have reported data on GFR in DM in individuals in the African region, and data were obtained on small samples (48–162 subjects) [23–25]. Moreover, to our knowledge, none of these studies has used radio-isotopic methods or the ‘gold standard’ inulin clearance to measure GFR, and none has reported values on renal plasma flow. Instead, serum creatinine was used as the standard for assessing renal function [23–25].

Comparing our data on GHF with studies performed in Caucasians, Asians and African-Americans is difficult for several reasons. Firstly, different methods were used to measure GFR and ERPF between studies (mostly 125 I-labelled iothalamate or iothexol for GFR and 131 I-labelled

hippuran for ERPF). Secondly, there is no generally accepted definition for GHF: cutoff values vary between 125 and 160 ml/min, some but not all being corrected for body surface area. Furthermore, some authors have argued against the use of a fixed cutoff value and recommended the use of >1.96 standard deviations (SD) above the mean GFR as the definition for GHF [26]. Nonetheless, studies that have used GFR >140 ml/min/1.73 m² found a prevalence of GHF ranging between 6% and 29% in type 2 diabetic Caucasians [27–29], and between 25% and 36% in type 2 diabetic African-Americans [13,30], as compared to 27.8% in our study. In our multivariate analysis, we used GFR >140 ml/min to define GHF in order to be able to examine the relationship between GFR and BMI. Adjusting to BSA would have obscured this relationship, since BMI itself is highly correlated with BSA. Studies that used this same cutoff value found a prevalence of GHF in 16% of Caucasians [7], but no data are available in African-Americans. In our population, the prevalence of GHF, when uncorrected for BSA, reached 53% in DM and 29% in IFG. These data suggest that the prevalence of GHF was rather high in Seychelles compared to other populations, but probably similar to the prevalence found in African-Americans.

The mechanisms leading to the development of GHF in IFG and DM are still only partially understood, and several hypotheses have been proposed. Some animal studies have suggested that diabetic animals present intraglomerular hypertension because of an inappropriate dilatation of afferent arterioles, leading to raised ERPF and GHF [31]. Studies in humans have also found higher values for GFR and ERPF in Caucasian patients with newly diagnosed type 2 DM as compared to non-diabetic subjects, which also points to afferent vasodilatation [32]. Why afferent vasodilatation occurs is less clear, but elevated levels of insulin, insulin-like growth factor-1 (IGF-1), atrial natriuretic peptide (ANP) and advanced glycosylation end-products (AGE) have been postulated [33–35]. In our study, ERPF was not elevated in IFG and/or DM. On the contrary, ERPF was relatively low in IFG and DM, which argues against afferent vasodilatation as a primary mechanism for GHF in subjects of African descent, unless the former was accompanied by efferent vasoconstriction. However, in line with previous studies, PRA and aldosterone levels were rather low in all groups [36,37]. More stringent efferent vasoconstriction in IGT and DM as compared to NFG could thus only be present in case of a more activated intrarenal renin–angiotensin system or higher

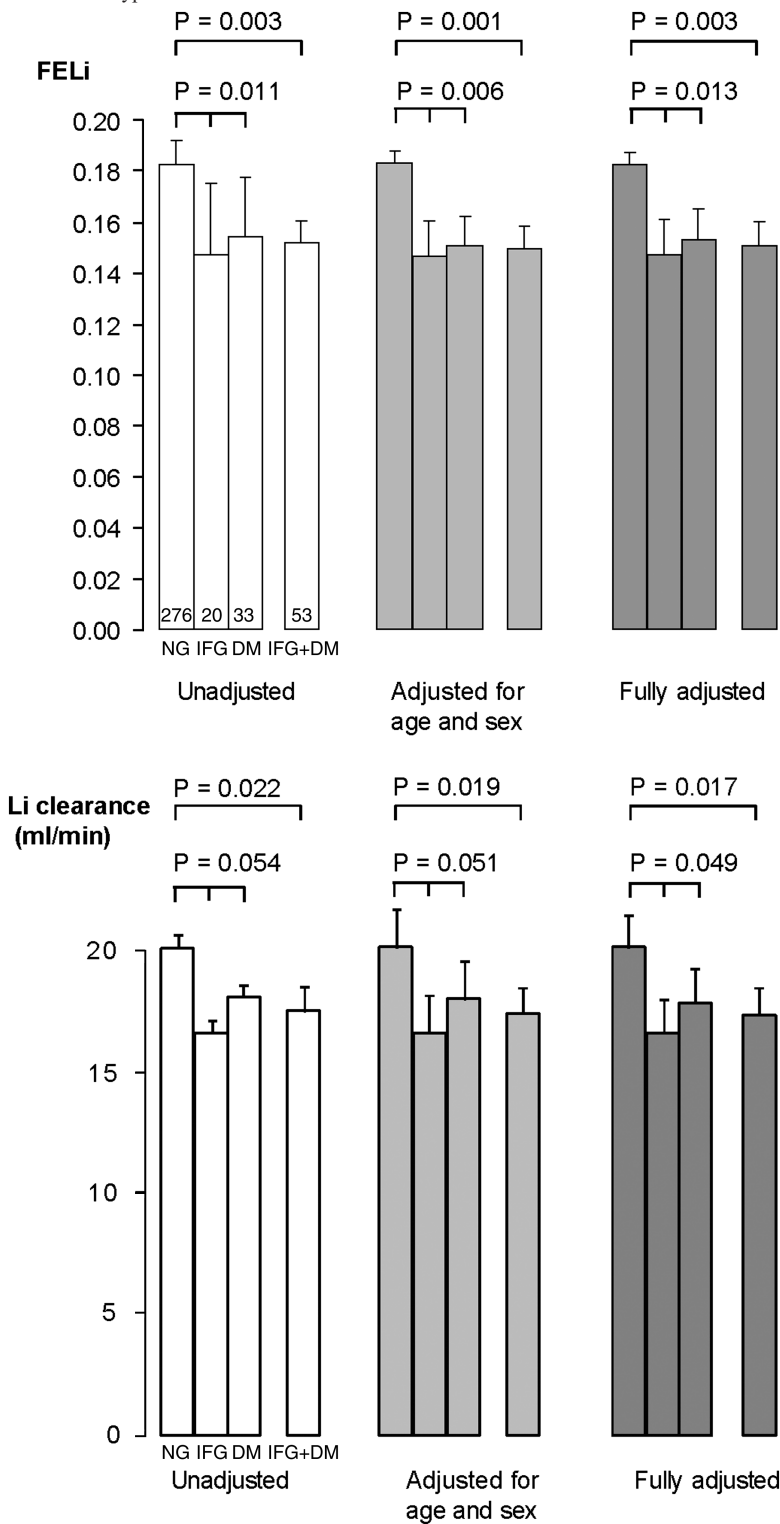


Fig. 2. Fractional excretion of lithium by diabetes status. See Figure 1 legend. *P*-values are either from (i) a likelihood ratio test (2 df) comparing a model with and without categorical diabetes status [i.e. normal glucose (reference category), impaired glucose tolerance and diabetes mellitus] for the three-group comparisons or from (ii) a Wald test (1 df) for the two-group (NFG vs DM + IFG) comparisons.

sympathetic nervous system activity [5]. Since neither of the two were measured, this remains hypothetical.

Another explanation might be the role of (intermittent) high blood glucose levels in DM, which would stimulate

sodium–glucose co-transport in the proximal tubules, thus leading to enhanced proximal sodium reabsorption and diminished distal sodium delivery. Alternatively, or in addition, tubular growth has been proposed to increase

proximal sodium reabsorption in early DM [8]. Reduced distal sodium delivery, via the tubuloglomerular feedback mechanism, leads in turn to dilatation of the afferent arterioles and GHF [8]. This ‘tubulocentric view’ is supported by animal models and might be mediated by adenosine. Indeed, in the streptozotocin-induced diabetic mice model, adenosine knockout mice, which lack a tubuloglomerular feedback response, also lack GHF [38]. Again, our finding of a diminished ERPF in DM and IFG compared to NFG does not fully support such a mechanism in this population, although the participants with IFG and/or DM did have raised proximal sodium reabsorption, as shown by their diminished lithium clearance.

Enhanced proximal sodium reabsorption has been reported previously in DM type 2 [39], and this might be one of the mechanisms responsible for diabetes-associated hypertension [40]. Interestingly, higher renal sodium reabsorption is found more often in subjects of African than Caucasian descent [41,42], although it remains uncertain in which part of the nephron this reabsorption takes place [43]. Increased activity of the Na–K–2Cl channel has been observed in the thick ascending limb in young normotensive African-Americans, while enhanced reabsorption in the distal [44] or proximal segments of the nephron [45] have been advocated as well. Our data also support enhanced sodium reabsorption in the early tubular segments of the nephron (proximal tubule and thick ascending limb), since both the fractional excretion of lithium and lithium clearance were reduced in DM and IFG as compared to NFG, but FDRNa was not. The present observation is in accordance with a recent finding of our group evaluating another African population, which showed that Black individuals in South Africa had enhanced proximal sodium reabsorption compared to Caucasians, regardless of dietary salt intake [46]. Of note, the estimated 24-hour sodium intake was rather low in our study at around 5.8 g of salt (2.3 g of sodium) per day and similar between the three groups. Indeed, diet in the Seychelles is low in salt and potassium as it consists mainly of unsalted rice and fish. The increased proximal sodium reabsorption seen repeatedly in subjects of African descent may further explain why African diabetics are more often hypertensive than Caucasian diabetics [47].

Our study has some limitations. Firstly, our data rely on a sample of families enriched in hypertensive persons, which may limit generalization of our findings. However, the same tendency of enhanced proximal sodium reabsorption in diabetics was found in normotensive individuals and untreated hypertensive individuals. Secondly, microalbuminuria (MAU) and glycated haemoglobin (HbA1c) levels were not available, and we have limited information regarding the degree of kidney damage and diabetes control in our subjects. Finally, the cross-sectional nature of our data limits causal inferences.

In summary, we found a high prevalence of glomerular hyperfiltration and increased proximal sodium reabsorption in individuals in the African region with IFG or DM as compared to normoglycaemic individuals, independently of several potentially confounding variables. Our findings are consistent with the view that the high prevalence of glomerular hyperfiltration and enhanced proximal sodi-

um reabsorption might contribute to the higher incidence of hypertension and diabetic nephropathy in diabetics of African descent.

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Conflict of interest statement. Information in this article was not presented previously.

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Association of *ADIPOQ* genetic variants and plasma adiponectin isoforms with the risk of incident renal events in type 2 diabetes

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