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Original Paper

Renal Dysfunction in the Presence of Normoalbuminuria in Type 2 Diabetes: Results from the DEMAND Study

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Key Words
Albuminuria · Chronic kidney disease · Diabetes · Diabetic nephropathy · Normoalbuminuria · Proteinuria

Abstract
Background/Aims: Microalbuminuria is associated with diabetes and is an independent risk factor for developing diabetic nephropathy. We have previously reported the overall prevalence of normoalbuminuria, microalbuminuria, and macroalbuminuria to be 51, 39, and 9.8%, respectively, in an unselected population of patients with type 2 diabetes. Renal dysfunction was present in a large proportion of these patients without proteinuria, assessed by a single random albumin-to-creatinine ratio (ACR) . We therefore undertook to characterize the nature of this association of non-proteinuric renal dysfunction in type 2 diabetes. ***Methods:*** In the DEMAND (Developing Education on Microalbuminuria for Awareness of Renal and Cardiovascular Risk in Diabetes) study, a global, cross-sectional study which described the prevalence and risk factors for albuminuria in a clinic-based cohort, kidney function was assessed in 11,573 pa-

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tients; ACR was measured using the Bayer reagent strip Multistix® 10SG. Normoalbuminuria was defined as ACR <30 mg/g, microalbuminuria as 30–299 mg/g, and macroalbuminuria as >300 mg/g. ***Results:*** Among the patients with estimated kidney function determined, chronic kidney disease was noted in 17% of those with normoalbuminuria (stage 3–5), and significant kidney dysfunction was found in 27% of those with microalbuminuria and 31% of those with overt proteinuria. CrCl was <60 ml/min in 20.5% of normoalbuminurics, 30.7% of microalbuminurics, and 35.0% of macroalbuminurics ($p < 0.0001$). ***Conclusion:*** A large proportion of diabetic patients with completely normal urinary albumin excretion or microalbuminuria presented with significant kidney dysfunction. Therefore, further investigation is warranted.

Introduction

It has been long recognized that microalbuminuria [urinary albumin excretion (UAE) between 30 and 300 mg/24 h] is associated with diabetes [1] and is an independent risk factor for both developing diabetic nephropathy and the occurrence of adverse cardiovascular events [2–4]. We have previously reported that in a global cohort of type 2 diabetes patients without known kidney disease, the overall prevalence of normoalbuminuria, microalbuminuria, and macroalbuminuria was 51, 39, and 9.8%, respectively [5]. Renal dysfunction was present in a large proportion of these subjects without proteinuria [assessed by albumin-to-creatinine ratio (ACR)]. We therefore aimed to characterize the nature of this association of non-proteinuric renal dysfunction in type 2 diabetes.

Patients and Methods

The DEMAND (Developing Education on Microalbuminuria for Awareness of Renal and Cardiovascular Risk in Diabetes) study design, methods, and principal results have been published previously [5]. Patients were included from North America, Europe, Africa, and Asia (see Appendix). Eligible patients were males and females aged 18–80 years with or without hypertension, type 2 diabetes mellitus (according to World Health Organization criteria) without a known history of proteinuria and/or diabetic kidney disease. A total of 32,208 subjects were evaluated, and after applying exclusion criteria (a history of kidney disease and/or proteinuria, invalid urine collections, absent nationality or region data, or absence of a single random ACR determination), 24,151 subjects were available for the study.

All participating general practitioners, physicians and nurses received the complete study protocol and were instructed to perform urinary ACR tests and blood pressure (BP) measurements with a sphygmomanometer after approximately 10 min of rest in the sitting position (single recording). Furthermore, demographics (age, gender, ethnicity, and region), clinical characteristics [height, body mass index (BMI), duration of diabetes, and hemoglobin A_{1c} (HbA_{1c}), and serum creatinine (sCr) levels], medical history [family history of diabetes, hypertension, any cardiovascular disease (CVD); retinopathy; diabetic foot lesion; smoking, and hyperlipidemia], and concomitant treatments (glucose lowering, antihypertensive, lipid-lowering, and antiplatelet/anticoagulant treatment) were recorded on a single-page clinical report form for each patient. Data on the presence of CVD [coronary artery disease (CAD), myocardial infarction (MI), left ventricular hypertrophy (LVH), congestive heart failure (CHF), stroke, transient ischemic attack, or peripheral vascular disease (PVD)] were retrieved from medical records and information obtained during the interview. The presence of hyperlipidemia was based on objective measurements, as stated in the medical records. Arterial hypertension was considered present in patients receiving BP-lowering therapy. A single random urinary ACR was obtained using the semiquantitative reagent strip Multistix 10SG (Bayer AG, Leverkusen, Germany). According to this strip test, normoalbuminuria is defined as ACR <30 mg/g, microalbuminuria as 30–299 mg/g, and macroalbuminuria as ≥300 mg/g. According to the manufacturer, this test strip has a sensitivity of 84% and a specificity of 91% for ACR. Urine samples with creatinine concentrations ≤10 mg/dl were discarded as too dilute, as prespecified in the protocol.

Table 1. Baseline characteristics of the patients according to the presence or absence of sCr measurement

Characteristics	sCr available (n = 11,833)	No sCr (n = 12,318)	p value
Age, years	62.5 (11.3)	60.2 (11.8)	<0.001
Males, n (%)	5,954 (50.3)	5,850 (47.5)	<0.001
Weight, kg	77.2 (17.3)	72.7 (16.6)	<0.001
Blood pressure, mm Hg			
Systolic	135.0 (17.1)	134.6 (18.4)	0.12
Diastolic	79.9 (9.5)	80.0 (10.2)	<0.001
Race/ethnicity, n (%)			
Caucasians	5,799 (49.0)	3,642 (29.6)	<0.001
Africans	215 (1.8)	275 (2.2)	<0.001
Asians	3,210 (27.1)	5,901 (47.9)	<0.001
Hispanics	506 (4.3)	683 (5.5)	<0.001
Other	420 (3.5)	241 (2.0)	<0.001
HbA_{1c}, %	7.48	7.55	0.008
Duration of diabetes, years	7.8 (6.3)	7.4 (6.1)	<0.001
Hypertension, n (%)	7,618 (64.4)	4,215 (34.2)	<0.001
Duration, years	8.9 (6.8)	8.6 (7.0)	0.001
Hyperlipidemia, n (%)	5,832 (49.3)	4,581 (37.2)	<0.001
Retinopathy, n (%)	1,362 (11.5)	1,581 (12.8)	0.002
Smoking history, n (%)	3,375 (28.5)	2,903 (23.6)	<0.001

Patients without data for a specified parameter were excluded. Means (SD) and numbers (%) are shown.

We used both the MDRD 4-variable formula [6] and the Cockcroft-Gault (CG) equation [7] to estimate kidney function [estimated glomerular filtration rate (eGFR) and estimated creatinine clearance (eCrCl), respectively]. The stages of chronic kidney disease (CKD) were defined according to the guidelines of the National Kidney Foundation (NKF) [8].

Statistical Analysis

Univariate comparisons of the impact of independent variables on the average levels of continuous and categorical dependent variables were made using one-way analysis of variance and the χ^2 test, respectively. Data are presented as proportions for categorical variables and means ± SD for continuous variables. Multivariable models predicting eCrCl, eCrCl <60 ml/min, and any history of CVD were created using the generalized linear model function [glm()] of S. All the variables adjusted in the models are prespecified, including age, BMI, race/ethnicity, region, sex, duration of diabetes, HbA_{1c} levels, smoking history, and duration of hypertension. Residuals from the linear regression model were assessed graphically for normality, and transformation on the dependent variable was done to correct non-normal residuals if needed.

Data analyses were performed using SAS for Windows (version 9.0; SAS Institute, Cary, N.C., USA) and S-Plus version 6.2 for Windows (Insightful Corp., Seattle, Wash., USA). A two-sided $p < 0.05$ was required to reject the null hypothesis.

Results

In a total of 11,833 patients, sCr was available. Table 1 summarizes the patient characteristics with respect to the sCr measurement: 11,573 patients had complete data with which to estimate kidney function. Of these, CKD was noted in 1,044 of 6,072 patients with normoalbuminuria (17%; stage 3, 4, or 5 according to the NKF criteria); in 1,207 of 4,409 with

Table 2. CKD stage and level of albuminuria (A)

CKD	n	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
Total	24,151 (100%)	51%	39%	10%
Stage 1	3,132 (13%)	56%	36%	8.4%
Stage 2	5,855 (24%)	56%	36%	8.5%
Stage 3	2,428 (10%)	41%	47%	12%
Stage 4	141 (0.6%)	26%	48%	26%
Stage 5	17 (0.07%)	29%	47%	24%
Unknown	12,578 (58%)	51%	39%	10%

CKD stage was classified according to MDRD and NKF criteria. Total includes even those patients in whom measures of kidney function were not obtained (categorized as Unknown). In a total of 11,573 patients, data to calculate kidney function were available.

Table 3. Renal and cardiovascular variables versus level of albuminuria (A)

Variable	n	Normoalbuminuria	Microalbuminuria	Macroalbuminuria	p value
Renal					
CG eCrCl <60 ml/min, %	11,315	20.5	30.7	35.0	<0.0001
Mean sCr, mg/dl	11,843	0.96	1.04	1.06	<0.0001
CVD, %	24,151	21.3	25.1	23.3	<0.0001
LVH, %	24,151	4.7	7.0	5.1	<0.0001
CAD, %	24,151	11.1	12.2	10.4	0.01
MI, %	24,151	4.3	4.8	3.9	0.07
CHF, %	24,151	1.9	2.9	3.7	<0.0001
Stroke, %	24,151	3.7	4.9	4.8	<0.0001
PVD, %	24,151	3.5	4.1	3.7	0.09

microalbuminuria (27%) and in 335 of 1,092 with overt proteinuria (31%). Table 2 shows the proportions of patients with each range of albuminuria, stratified by CKD stage. The percentages of patients (in whom measures of kidney function were available) with CKD stages 3, 4, or 5 and normoalbuminuria were 41, 26, and 29%, respectively.

Table 3 shows renal and cardiovascular data stratified by level of albuminuria. In 24,151 patients, history of CVD was reported, but due to missing laboratory data, the presence of renal dysfunction was only evaluable in 11,315 patients. Decreased renal function (eCrCl <60 ml/min; determined by the CG formula) was noted in 20.5% of the patients with normoalbuminuria, while 30.7% of the patients with eCrCl <60 ml/min had microalbuminuria.

Albuminuria significantly correlated with decreased renal function at the time of assessment (measured by sCr and eCrCl) and estimates of kidney function below well-established cutoff points. Additionally, albuminuria correlated significantly with the presence of any CVD, and several individual components thereof (LVH, CHF, stroke, and CAD). However, a large number of patients with normal UAE or microalbuminuria had significant renal dysfunction (20.5 and 30.7%, respectively).

Table 4 presents the predictors of renal function determined by logistic regression. Age and BMI contributed the greatest proportion of variance explained in the model, with age generating the greatest loss in eCrC (13.9 ml/min per 10 years; thus approximately 1.4 ml/

Table 4. Variables associated with CG eCrCl

Variable	Cumulative proportion of variance explained, %	Estimated impact on eCrCl[a]
Age (per 10 years)	35.4	**–13.9 (–14.3, –13.5)**
BMI (per 5 kg/cm^2)	44.7	**3.8 (1.2, 6.3)**
Race/ethnicity (ref. Caucasian)	45.1	
African		–1.7 (–4.9, –1.4)
Asian		0.0 (–2.1, 2.1)
Hispanic		**–8.8 (–10.9, –6.6)**
Other		1.1 (–1.2, 3.4)
Missing		–1.2 (–2.4, 0.1)
Region (ref. Europe)	45.5	
Africa		–1.2 (–3.6, 1.2)
Asia		–1.3 (–3.6, 0.9)
Central/South America		0.9 (–1.4, 3.1)
North America		**3.4 (2.3, 4.6)**
Oceania		**3.2 (1.4, 5.0)**
Hypertension	45.7	**–2.4 (–3.3, –1.5)**
Sex (ref. female)	45.9	
Male		1.0 (0.0, 2.0)
Missing		**9.4 (5.6, 13.2)**
Urinary ACR (per doubling)	46.0	**–0.5 (–0.8, –0.3)**
Duration of diabetes (per 5 years)	46.2	**–0.7 (–1.1, –0.4)**
Retinopathy	46.2	**–2.5 (–3.8, –1.2)**
HbA_{1c} missing	46.3	**–2.1 (–3.1, –1.0)**
Hyperlipidemia	46.4	**–1.5 (–2.3, –0.7)**
HbA_{1c} (per %)	46.4	**0.4 (0.1, 0.6)**
Weight (per 5 kg)	46.4	**1.3 (0.4, 2.3)**
Height (per 10 cm)	46.4	**–2.1 (–4.0, –0.2)**

[a] Data are expressed as calculated effect (95% CI). Data in bold are factors in which the 95% CI does not span 1.

min per year), followed by Hispanic race (8.8 ml/ml in CrCl), the only significant racial contributor, and hypertension (2.4 ml/min in CrCl). Other factors significantly affecting eCrCl were duration of diabetes, diabetic retinopathy, hyperlipidemia, HbA_{1c} level, and anthropometric data.

Table 5 presents the variables associated with eCrCl <60 ml/min. Age and BMI contributed the greatest proportion of deviance explained. UAE was associated with renal dysfunction [odds ratio (OR) 1.11, 95% confidence interval (CI) 1.08–1.14]. Other significant factors included Hispanic race, presence of diabetic retinopathy, male sex (which conferred an advantage), duration of diabetes, and location in North America.

Table 6 shows that in our model of the variables associated with CVD, the greatest significant contributors to cardiovascular risk (composite and individual components) included age, history of hypertension, family history of CVD, hyperlipidemia, height, history of diabetic retinopathy, and duration of hypertension. Other factors (for example, albuminuria), although statistically significant, explained successively smaller proportions of the deviance and contributed little to the overall predicted risk.

A history of hypertension was strongly predictive of the presence of any CVD (OR 2.23, 95% CI 2.06–2.41), CAD (OR 2.25, 95% CI 2.02–2.52), and LVH (OR 3.53, 95% CI 2.95–4.22).

Table 5. Variables associated with CG eCrCl <60 ml/min

Variable	Cumulative proportion of deviance explained, %	OR (95% CI)[a]
Age (per 10 years)	20.6	**3.67 (3.43, 3.92)**
BMI (per 5 kg/cm^2)	24.6	**0.57 (0.54, 0.61)**
Urinary ACR (per doubling)	25.5	**1.11 (1.08, 1.14)**
Race/ethnicity (ref. Caucasian)	26.1	
African		1.06 (0.63, 1.79)
Asian		1.12 (0.84, 1.49)
Hispanic		**3.20 (2.40, 4.25)**
Other		1.11 (0.81, 1.52)
Missing		**1.21 (1.03, 1.42)**
Duration of hypertension missing	26.5	**0.73 (0.65, 0.81)**
Retinopathy	26.8	**1.46 (1.25, 1.70)**
Sex (ref. female)	27.0	
Male		**0.79 (0.71, 0.88)**
Missing		**0.44 (0.26, 0.75)**
Duration of diabetes (per 5 years)	27.1	**1.08 (0.04, 1.13)**
HbA_{1c} missing	27.2	**1.24 (1.08, 1.42)**
Hyperlipidemia	27.2	**1.12 (1.01, 1.25)**
Diabetic foot	27.3	1.26 (0.98, 1.60)
Region (ref. Europe)	27.3	
Africa		0.84 (0.58, 1.19)
Asia		1.14 (0.84, 1.55)
Central/South America		0.78 (0.57, 1.06)
North America		**0.82 (0.70, 0.96)**
Oceania		1.00 (0.80, 1.26)
Smoking history (ref. no)	27.4	1.11 (0.98, 1.26)
Duration of hypertension (per 5 years)	27.4	1.03 (0.99, 1.08)

[a] Data are expressed as calculated effect. Data in bold are factors in which the 95% CI does not span 1.

There was a significant inverse correlation between diastolic BP and any CVD (OR 0.97 per 5 mm Hg, 95% CI 0.95–0.98), CAD, MI, CHF, and PVD.

African race was associated with a reduced risk (OR 0.50, 95% CI 0.35–0.71) of prevalent (reported) CVD compared to Caucasian race. A history of diabetic foot lesions was strongly correlated with the presence of PVD (OR 4.18, 95% CI 3.40–5.14). A reported family history of diabetes was protective for CVD (OR 0.82, 95% CI 0.77–0.88) and most of its individual components (CAD, MI, LVH, stroke, and PVD).

A history of smoking was associated with an increased risk of CAD (OR 1.16, 95% CI 1.05–1.29), MI (OR 1.57, 95% CI 1.37–1.81), stroke (OR 1.41, 95% CI 1.21–1.64), and PVD (OR 1.77, 95% CI 1.51–2.06).

Each doubling of the UAE rate was associated with an increased risk of any CVD (OR 1.03, 95% CI 1.01–1.05), LVH (OR 1.04, 95% CI 1.01–1.07), and CHF (OR 1.15, 95% CI 1.10–1.20).

Discussion

This global, cross-sectional study examined the prevalence of albuminuria in a referred, clinic- or office-based study cohort. For these additional analyses, we chose to use the CG formula to estimate kidney function because of its greater accuracy over the MDRD equation

Table 6. Risk factors for CVD

	Any CVD		CAD OR (95% CI)	MI OR (95% CI)	LVH OR (95% CI)	CHF OR (95% CI)	Stroke OR (95% CI)	PVD OR (95% CI)
	cumulative % deviance explained	OR (95% CI)						
Age (per 10 years)	5.09	**1.59 (1.53–1.65)**	**1.60 (1.52–1.67)**	**1.34 (1.25–1.44)**	**1.22 (1.15–1.30)**	**1.93 (1.74–2.13)**	**1.72 (1.59–1.85)**	**1.29 (1.20–1.40)**
Hypertension	7.97	**2.23 (2.06–2.41)**	**2.25 (2.02–2.52)**	**1.68 (1.43–1.97)**	**3.53 (2.95–4.22)**	**1.45 (1.17–1.80)**	**2.22 (1.87–2.63)**	**1.35 (1.14–1.60)**
Family history of CVD	9.64	**1.81 (1.68–1.95)**	**1.74 (1.59–1.91)**	**1.69 (1.47–1.94)**	**1.96 (1.73–2.21)**	**1.52 (1.26–1.84)**	**1.51 (1.31–1.74)**	**1.37 (1.18–1.60)**
Hyperlipidemia	10.94	**1.81 (1.69–1.94)**	**1.94 (1.77–2.12)**	**1.88 (1.64–2.16)**	**1.75 (1.55–1.98)**	**1.47 (1.23–1.76)**	**1.37 (1.20–1.57)**	**1.75 (1.51–2.03)**
Height (per 10 cm)	11.51	**1.10 (1.05–1.16)**	**1.14 (1.07–1.22)**	**1.12 (1.02–1.23)**	1.00 (0.92–1.09)	1.01 (0.90–1.15)	**1.20 (1.09–1.32)**	1.06 (0.96–1.17)
Retinopathy	12.08	**1.56 (1.41–1.72)**	**1.42 (1.25–1.60)**	1.19 (0.98–1.44)	**1.67 (1.43–1.95)**	**1.48 (1.17–1.87)**	**1.36 (1.13–1.62)**	**2.04 (1.70–2.44)**
Duration of BP (per 5 years)	12.57	**1.16 (1.13–1.19)**	**1.14 (1.10–1.18)**	**1.15 (1.09–1.22)**	**1.15 (1.10–1.21)**	**1.18 (1.10–1.26)**	**1.17 (1.12–1.23)**	**1.07 (1.01–1.14)**
Race/ethnicity (ref. Caucasian)	13.03							
African		**0.50 (0.35–0.71)**	**0.35 (0.21–0.60)**	**0.20 (0.08–0.51)**	1.44 (0.82–2.54)	1.30 (0.60–2.83)	0.48 (0.20–1.16)	0.59 (0.29–1.21)
Asian		0.94 (0.81–1.09)	0.92 (0.75–1.12)	0.81 (0.61–1.07)	1.02 (0.76–1.37)	**0.51 (0.32–0.80)**	1.16 (0.87–1.54)	**0.47 (0.33–0.68)**
Hispanic		1.17 (0.96–1.41)	**0.35 (0.25–0.50)**	0.81 (0.57–1.16)	**2.06 (1.50–2.84)**	0.78 (0.46–1.31)	0.77 (0.48–1.24)	**2.00 (1.45–2.75)**
Other		**0.59 (0.47–0.75)**	**0.47 (0.33–0.66)**	**0.52 (0.33–0.82)**	**0.61 (0.39–0.96)**	**0.40 (0.20–0.79)**	**0.48 (0.27–0.86)**	0.84 (0.54–1.30)
Missing		**0.66 (0.60–0.74)**	**0.49 (0.42–0.57)**	1.11 (0.92–1.34)	**0.80 (0.67–0.95)**	**0.70 (0.54–0.90)**	1.04 (0.85–1.27)	0.82 (0.67–1.01)
Region (ref. Europe)	13.36							
Africa		**0.69 (0.58–0.83)**	0.94 (0.75–1.18)	1.16 (0.84–1.60)	**0.24 (0.16–0.36)**	**0.48 (0.27–0.84)**	0.83 (0.56–1.22)	1.01 (0.71–1.44)
Asia		**0.63 (0.54–0.74)**	0.88 (0.71–1.08)	**0.51 (0.38–0.70)**	**0.49 (0.36–0.66)**	**0.56 (0.35–0.89)**	1.01 (0.76–1.35)	**0.50 (0.35–0.73)**
Central/ South America		0.83 (0.66–1.03)	0.97 (0.71–1.33)	**1.64 (1.13–2.37)**	0.79 (0.56–1.13)	1.39 (0.86–2.25)	1.15 (0.72–1.85)	**0.51 (0.32–0.80)**
North America		**0.67 (0.60–0.75)**	**0.82 (0.71–0.94)**	**1.38 (1.14–1.66)**	**0.38 (0.31–0.47)**	**0.64 (0.49–0.85)**	**0.78 (0.61–0.99)**	0.96 (0.78–1.19)
Oceania		**0.58 (0.50–0.67)**	**0.59 (0.48–0.72)**	1.22 (0.95–1.57)	**0.43 (0.32–0.57)**	0.81 (0.58–1.14)	1.05 (0.80–1.37)	**0.51 (0.36–0.71)**
Smoking history	13.63	**1.33 (1.23–1.44)**	**1.16 (1.05–1.29)**	**1.57 (1.37–1.81)**	1.08 (0.94–1.24)	1.16 (0.95–1.42)	**1.41 (1.21–1.64)**	**1.77 (1.51–2.06)**
Diabetic foot disease	13.76	**1.49 (1.28–1.73)**	1.06 (0.87–1.28)	**1.39 (1.08–1.79)**	1.18 (0.93–1.50)	**1.45 (1.06–2.00)**	1.17 (0.89–1.53)	**4.18 (3.40–5.14)**
Duration of diabetes (per 5 years)	13.86	**1.08 (1.05–1.11)**	**1.10 (1.06–1.14)**	**1.10 (1.05–1.16)**	1.02 (0.97–1.07)	1.00 (0.93–1.08)	1.04 (0.99–1.10)	**1.06 (1.00–1.12)**
Family history of diabetes	13.98	**0.82 (0.77–0.88)**	**0.79 (0.72–0.87)**	**0.85 (0.74–0.98)**	**0.88 (0.78–1.00)**	0.86 (0.72–1.04)	**0.87 (0.75–1.00)**	**0.80 (0.69–0.93)**
Sex (ref. female)	14.04							
Male		**1.19 (1.09–1.30)**	**1.12 (1.00–1.26)**	**2.12 (1.78–2.52)**	1.08 (0.92–1.25)	1.14 (0.91–1.43)	1.06 (0.89–1.26)	**1.30 (1.08–1.56)**
Missing		1.12 (0.81–1.55)	0.81 (0.51–1.31)	1.64 (0.90–2.97)	0.95 (0.54–1.65)	1.23 (0.59–2.60)	0.95 (0.49–1.84)	1.08 (0.55–2.12)
Diastolic BP (per 5 mm Hg)	14.08	**0.97 (0.95–0.98)**	**0.95 (0.92–0.97)**	**0.89 (0.86–0.92)**	**1.05 (1.02–1.08)**	**0.93 (0.88–0.97)**	0.97 (0.94–1.01)	**0.93 (0.90–0.97)**
Urinary ACR (per doubling)	14.11	**1.03 (1.01–1.05)**	0.99 (0.96–1.01)	1.03 (0.99–1.06)	**1.04 (1.01–1.07)**	**1.15 (1.10–1.20)**	1.02 (0.99–1.06)	1.01 0.97–1.05)
HbA_{1c} missing	14.13	**1.11 (1.02–1.19)**	1.08 (0.98–1.19)	1.06 (0.91–1.23)	0.90 (0.79–1.03)	1.15 (0.94–1.40)	**1.17 (1.01–1.35)**	0.89 (0.75–1.05)
Weight (per 5 kg)	14.15	**1.01 (1.00–1.03)**	**1.02 (1.00–1.03)**	1.00 (0.97–1.02)	**1.05 (1.02–1.07)**	1.02 (0.98–1.05)	**0.96 (0.93–0.99)**	**0.98 (0.95–1.00)**
HbA_{1c} (per %)	14.16	**1.03 (1.00–1.06)**	**1.04 (1.00–1.07)**	**1.05 (1.00–1.11)**	1.02 (0.97–1.06)	0.99 (0.92–1.06)	1.00 (0.95–1.06)	1.03 (0.97–1.09)
Duration of diabetes missing	14.18	**0.87 (0.76–1.00)**	0.94 (0.79–1.12)	**0.61 (0.45–0.83)**	**0.73 (0.56–0.96)**	1.07 (0.77–1.48)	0.97 (0.74–1.25)	1.01 (0.75–1.36)

Data in bold are factors in which the 95% CI does not span 1.

at normal or near-normal levels of sCr [9], since the great majority of our subjects (78%) had eGFR $\geq$60 ml/min/1.73 m^2. Of note, these formulae were applied to populations in which they were not derived, but other more generalizable estimates of kidney function are lacking. Other newer estimates of kidney function [10] have not been validated in a global cohort.

The most striking finding in this cohort is the large number of diabetic subjects with decreased kidney function with completely normal UAE (20.5%, table 3) or microalbuminuria (30.7%). To our knowledge, this is the largest study performed to estimate this prevalence. Other studies have assessed this relationship in smaller (some prospective) cohorts [11–18], or excluded patients with diabetes [11]. Our results are in agreement with other prospective analyses [17, 18]. Previously, it has been suggested that normoalbuminuric diabetic subjects with renal dysfunction are less likely to progress to renal endpoints (in this case, death or dialysis) than their micro- or macroalbuminuric counterparts [12].

According to our results, although albuminuria significantly correlates with renal function (table 3) in all measures at the time of assessment, it does not appear to strongly predict it; the differences in renal function at each level of albuminuria may not be clinically significant. Since albuminuria is highly variable, it is possible that this intrinsic variability (or

that induced by a single measurement) has diluted the proportion of variance explained by albuminuria in the regression analysis.

Tables 4 and 5 present two methods of assessing predictors of renal function. In both cases, age and BMI contributed the largest cumulative proportion of variance and deviance, respectively. One must interpret this with caution, given the fact that age is a variable in the CG formula for eCrCl, and BMI is a function of weight, which is also a variable in this formula. Also, in this population of patients with albuminuria and renal dysfunction, many patients will succumb to cardiovascular events before a progressive decline in renal function presents [19].

The failure of systolic BP to associate with the composite of cardiovascular variables may be explained by the strong effect of a history of hypertension in the model. Presumably, this variable takes patients receiving antihypertensive treatment into account and thus systolic BP is subsumed under it. Interestingly, an inverse relationship between diastolic BP and the risk of composite CVD has been reported in our [20] and other reports [21]. It appears that this protective effect for any CVD is largely determined by the protective effect for CAD, MI, and CHF, balanced by the risk of LVH. Additionally, renal function does not strongly associate with the composite cardiovascular variables, which may be explained by the fact that albuminuria does (table 6).

There is an interesting reduction in the risk of CVD in Africans compared to Caucasians, and for the African region compared to Europe. This may reflect more generally an increase in the risk of CVD reported in Caucasian Europeans, or may simply underscore the limitations of the reported history of any type of CVD. It may also reflect that Africans with a far shorter average life span die of other causes before CVD has the chance to surface.

Several possibilities exist that might explain our findings of renal dysfunction in the presence of minimal albuminuria or normal albuminuria. First, since data on drugs which block the renin-angiotensin system were not collected in the original DEMAND data, we cannot correlate proteinuria with the use of these agents; it may be that proteinuria has been reasonably well suppressed due to the use of these agents. However, although the rate of loss of renal function may be slowed by these agents, it may not be halted, despite the suppression of proteinuria. Hence, over time patients without significant albuminuria have decreased GFR and may progress to end-stage renal disease, although other non-diabetic renal diseases not prominently associated with albuminuria may be present [22]. Certainly, patients with diabetes and hypertension (and often underlying CVD) are at risk for hypertensive nephrosclerosis, tubulointersitial nephritis due to multidrug use (for example, non-steroidal anti-inflammatory drugs) and episodes of acute kidney injury, which may result in incomplete recovery of renal function and may predict future CKD. This study cannot assess the presence or absence of any of these entities. Interestingly, a report of the pathologic lesions seen in type 2 diabetes argues in favor of two distinctive patterns of glomerular injury, namely Kimmelstiel-Wilson nodules and mesangial sclerosis [23]. Mesangial sclerosis has been reported to be associated with lower amounts of proteinuria compared to the Kimmelstiel-Wilson lesions, but long-term follow-up data are lacking in a large number of these patients [23].

This study has the strength of being a large, international, multiracial cohort. However, it has several limitations, which are similar to those of the original DEMAND report. Albuminuria was estimated based on a single dipstick assessment of a spot urine specimen, and the variability in albumin excretion may dilute the proportion of variance attributed in the regression model. Likewise, kidney function was taken as a single measurement. However, by design, patients known to their physicians as having kidney disease were excluded. Additionally, all the information regarding coexisting disease was reported by the study physician, without independent review.

Appendix

Contributors

Europe: Belgium, Germany, Greece, The Netherlands, Hungary, Norway, Portugal, Romania, Slovakia, Spain, Turkey, United Kingdom.

North America: Canada, Mexico.

Central/South America: Chile, Columbia, Ecuador, El Salvador, Dominican Republic, Venezuela.

Asia: China, Korea, Hong Kong, Indonesia, Saudi Arabia, Malaysia, Singapore, Taiwan, Thailand.

Africa: Kenya, Republic of South Africa.

Oceania: Australia, Philippines.

Disclosure Statement

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The sponsors of the study (Bristol-Myers Squibb and Sanofi-Aventis) contributed to the study design, data collection, and reviewed and commented on drafts of the original DEMAND report, but had no role in data analysis (performed by J.P.D. and L.G.H.), interpretation or writing the report, or reviewing drafts of this current study. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

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