Journal of Diabetes and Its Complications 27 (2013) 370–375

Contents lists available at SciVerse ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Cardiovascular risk factors and complications associated with albuminuria and impaired renal function in insulin-treated diabetes☆

Kris Doggen [a,*], Frank Nobels [b], André J. Scheen [c], Paul Van Crombrugge [b], Viviane Van Casteren [a], Chantal Mathieu [d]

[a] Health Services Research Unit, Scientific Institute of Public Health, Brussels, Belgium
[b] Department of Endocrinology, O.L.Vrouwziekenhuis, Aalst, Belgium
[c] Department of Medicine, CHU Sart Tilman, Liège, Belgium
[d] Department of Endocrinology, UZ Gasthuisberg, Leuven, Belgium

ARTICLE INFO

Article history:
Received 5 October 2012
Received in revised form 19 February 2013
Accepted 19 February 2013
Available online 26 March 2013

Keywords:
Albuminuria
Impaired renal function
Cardiovascular complications

ABSTRACT

Aims: To establish the association between albuminuria and cardiovascular risk factors as well as micro- and macrovascular complications in type 1 and insulin-treated type 2 diabetes, both in the presence and in the absence of reduced estimated glomerular filtration rate (eGFR).
Methods: Cross-sectional study including 7640 insulin-treated diabetic patients (33% type 1) treated in specialist diabetes centers. Albuminuria was defined as ≥30 mg/g, 20 mg/L, 20 μg/min or 30 mg/24 h. Reduced eGFR was defined as <60 mL/min/1.73 m^2 (CKD-EPI equations).
Results: Albuminuria, reduced eGFR or a combination was more prevalent in type 2 (21.5%, 15.9% and 16.5%) than in type 1 diabetes (16.1%, 4.7% and 4.0%, all $P < 0.001$ vs. type 2). Albuminuria was associated with poorer control of blood pressure, blood lipids and glycemia as well as higher prevalence of retinopathy and macrovascular disease, regardless of preserved/reduced eGFR or diabetes type. Reduced eGFR was associated with higher prevalence of micro- and macrovascular complications especially in type 2 diabetes. Combined presence of albuminuria and reduced eGFR was associated with the worst cardiovascular outcomes.
Conclusions: Albuminuria and impaired renal function are prevalent in type 1 and insulin-treated type 2 diabetes. Albuminuria, but also normoalbuminuric renal impairment, is associated with micro- and macrovascular complications.

1. Introduction

Chronic kidney disease (CKD) is a risk factor for cardiovascular (CV) morbidity and mortality both among non-diabetic and diabetic individuals (Sarnak et al., 2003). Because diabetes is the main cause of CKD (Gross et al., 2005), much attention has gone to elucidating how the additional presence of diabetic kidney disease (DKD) adversely affects the already increased CV risk among diabetic patients (de Boer et al., 2009; Foley et al., 2005; Ninomiya et al., 2009; Targher et al., 2011).

The natural history of DKD consists of progression from micro-albuminuria to macroalbuminuria and overt proteinuria (Gross et al., 2005). However, albuminuria as such is an independent CV risk factor (de Zeeuw et al., 2004; Gerstein et al., 2001), also in non-diabetic individuals, suggesting that its presence is not only a marker of early stage DKD. On the other hand, renal impairment, defined as estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2, may also occur in the absence of albuminuria in people with diabetes (Kramer, Nguyen, Curhan, & Hsu, 2003), so-called normoalbuminuric renal impairment. Previous studies have shown that in type 2 diabetes, renal impairment is associated with normoalbuminuria in as many as 50% of the cases (Ito et al., 2010; Kramer et al., 2003; Kramer et al., 2007; MacIsaac et al., 2004; Penno et al., 2011; Retnakaran, Cull, Thorne, Adler, & Holman, 2006; Rigalleau et al., 2007; Thomas et al., 2009; Yokoyama et al., 2009). This may be due to high prevalence of concomitant treatment for hypertension and dyslipidemia, preventing the development of albuminuria (Pavkov et al., 2009), but may also be due to other causes of renal disease in individuals with diabetes, in particular ischemic renal function impairment.

Among normoalbuminuric type 2 diabetic patients, renal impairment is associated with a higher prevalence of CV risk factors and micro- and macrovascular complications compared to patients with preserved renal function (Ito et al., 2010; Penno et al., 2011; Solini et al., 2012; Thomas et al., 2009; Yokoyama et al., 2009). Consistent with these cross-sectional observations, a number of prospective studies in type 2 diabetes have reinforced the view that albuminuria and renal

☆ Conflict of interest statement: The authors declare that they have no conflict of interest.

* Corresponding author. Scientific Institute of Public Health, Rue J. Wytsman 14, 1050 Brussels, Belgium. Tel.: +32 0 2 642 57 22; fax: +32 0 2 642 54 10.
E-mail address: kris.doggen@wiv-isp.be (K. Doggen).

1056-8727/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jdiacomp.2013.02.008

impairment are each independent predictors of CV morbidity and mortality (de Boer et al., 2009; Drury et al., 2010; Ninomiya et al., 2009; Targher et al., 2011). However, in type 1 diabetes, the association of albuminuria and renal impairment with CV risk has rarely been studied and only in small cohorts (Caramori, Fioretto, & Mauer, 2003). There are reasons to believe that the impact of the association between albuminuria and renal function impairment may differ between type 1 and type 2 diabetes. Indeed, in type 1 diabetes a more homogeneous renal phenotype is observed, which is more tightly associated with glycemic and blood pressure control than in type 2 diabetes (Fioretto, Caramori, & Mauer, 2008; Kramer et al., 2003).

The aims of the present study were (a) to investigate the association between albuminuria and other cardiovascular risk factors and the occurrence of micro- and macrovascular complications in diabetic patients with or without renal impairment, and (b) to investigate whether this association differed between type 1 and type 2 diabetes. We used data from a large cross-sectional study among insulin-treated diabetic patients attending hospital-based specialist diabetes centers in Belgium.

2. Subjects, materials and methods

2.1. Study population

Data were collected in 2009 as part of a nation-wide quality improvement (QI) initiative in hospital-based specialist diabetes centers in Belgium (N = 113). Details of this QI initiative have previously been published (Debacker et al., 2008a), which show that it yields valid data for monitoring of quality of care and of disease burden among diabetic patients treated in secondary care.

The study population of this QI initiative was limited to adult diabetic patients who were treated with at least 2 insulin injections per day (N = 105,975). Centers were asked to complete a standardized electronic questionnaire by reviewing charts for a sample of 10% of these patients (with a minimum of 50 patients and including at least 25 patients with type 1 diabetes). This yielded data of 11,303 patients.

For the present study, patients without reported diabetes duration, with prior need for renal replacement therapy (either dialysis or transplantation) or without reported indicators of kidney function (urinary albumin and serum creatinine) were excluded (N = 3663). Patients without reported indicators of kidney function did not significantly differ from the final sample in terms of age, sex and diabetes duration.

2.2. Biochemical measurements and patient classification

All reported laboratory test results were obtained using center-specific methods and were abstracted from the patient medical file. No attempts were made to standardize the data.

Serum creatinine values were used to estimate GFR using the Chronic Kidney Disease—Epidemiology Collaboration (CKD-EPI) equation for non-black patients (Levey et al., 2009). Reduced eGFR was defined as eGFR <60 mL/min per 1.73 m^2 (Levey et al., 2003). We performed additional analyses using the original, 4-variable Modification of Diet in Renal Disease (MDRD) Study equation for non-black patients (Levey et al., 2003), which yielded essentially the same results as with the CKD-EPI equation (data not shown).

Results of albuminuria testing were reported as the albumin–creatinine ratio (ACR, mg/g, 26% of all reported test results) or albumin concentration (mg/L, 56%) for spot urine samples or as μg/min or mg/24 h for timed (2%) or 24-h (15%) collections. Cut-offs for micro- and macroalbuminuria were defined as follows: 30 and 300 mg/g, 20 and 200 mg/L, 20 and 200 μg/min, 30 and 300 mg/24 h. These, or lower, cut-offs have previously been shown to predict new cardiovascular events in type 2 diabetes (Viana et al., 2012). For the purpose of this study, the term “albuminuria” was defined as micro- or macroalbuminuria, while the absence of albuminuria implied normoalbuminuria.

LDL cholesterol plasma levels were not measured directly but estimated by the Friedewald formula for patients with plasma triglycerides <400 mg/dL (Friedewald, Levy, & Fredrickson, 1972).

All HbA1c determinations were DCCT aligned and Belgian clinical laboratories continuously participate in a project of external quality assurance making HbA1c results comparable between different laboratories (Debacker et al., 2008b).

2.3. Cardiovascular complications

History of micro- and macrovascular disease, including lower limb ulceration or amputation, was abstracted from the patient medical file. Presence of retinopathy was defined as non-proliferative diabetic retinopathy or worse.

2.4. Statistical analysis

Data are presented as mean ± standard deviation, unless specified otherwise. Data were analyzed using linear or logistic regression, allowing for main effects (separate contributions of reduced eGFR and albuminuria) and interaction effects (combined contribution of reduced eGFR and albuminuria). Generalized estimating equations (GEE), specifying an exchangeable correlation structure and robust standard errors, were used to obtain estimates for regression coefficients and standard errors which were corrected for the correlation of outcomes within centers. Similar results were obtained using a different modeling approach, which involved generalized linear mixed models with random intercepts at the center-level. Only the results of the GEE models are reported here. Outcomes (CV risk factors and complications) were adjusted for age, sex and diabetes duration. Further adjustment for body mass index (BMI), smoking status and treatment status lowered statistical power, as these covariates were not known for all patients, but yielded similar coefficients compared to models adjusted only for age, sex and diabetes duration. It was assumed that the effects of age, sex and diabetes duration were similar in all centers. Tables 2 and 3 in the Results section present marginal (population-averaged) predicted means and proportions, along with their 95% confidence intervals (CI).

As this study was based on chart review, we assessed whether missingness of the outcome status was associated with reduced eGFR and/or albuminuria. Missingness of outcome status was generally low: of 22 incompletely known outcome variables, missingness exceeded 5% only for smoking status (5.5%), BMI (5.7%) and retinopathy status (9.7%). Moreover, the difference in missingness never exceeded more than 3 percentage points between albuminuria and eGFR categories. Therefore, it is unlikely that missingness will have confounded the studied associations.

All analyses were done in Stata (version 10.1) using the xtgee function. Statistical significance was defined as $P < 0.05$. No adjustment was made for multiple testing.

3. Results

3.1. Characteristics of the sample

The sample consisted of 7640 diabetic patients, of whom 33.2% had type 1 diabetes. In type 1 diabetes, mean age was 46.7 ± 15.2 years, while it was 67.3 ± 11.5 years in type 2 diabetes. Mean diabetes duration was 18.8 ± 12.9 and 15.2 ± 8.9 years in type 1 and type 2 diabetes respectively. Male patients were overrepresented in type 1

diabetes (57.7%) while both sexes were equally represented in type 2 diabetes. All patients injected insulin at least twice a day. Rates of antihypertensive and lipid-lowering treatment were 39.5% and 36.4% in type 1 diabetes and 84.0% and 72.6% in type 2 diabetes.

3.2. Prevalence of albuminuria and reduced eGFR

Table 1 shows that 24.9% and 53.9% of type 1 and type 2 diabetic patients respectively had CKD (albuminuria and/or reduced eGFR). Albuminuria was observed in 20.2% and 38.0% of type 1 and type 2 diabetic patients respectively (Table 1). Macroalbuminuria was present in 4.6% and 9.3% of type 1 and type 2 diabetic patients respectively. Reduced eGFR was observed in 8.7% and 32.5% of type 1 and type 2 diabetic patients respectively (Table 1). Using the Kidney Disease Outcomes Quality Initiative (KDOQI) classification for CKD, 7.3% and 1.4% of type 1 and 27.2% and 5.3% of type 2 diabetic patients were in CKD stage 3 (30–59 mL/min per 1.73 m^2) and stages 4–5 (<30 mL/min per 1.73 m^2) respectively. The prevalence of albuminuria in CKD stages 3 and 4–5 was 44.1% and 55.6% in type 1 and 47.2% and 70.5% in type 2 diabetic patients respectively. Among patients with CKD and known retinopathy status, 310 out of 588 type 1 diabetic patients (52.7%) and 1017 out of 2425 type 2 diabetic patients (41.9%) concomitantly had retinopathy (any stage), and among patients with coexistence of CKD and retinopathy, most also had albuminuria (82.3% and 73.7% respectively). Note that patients on renal replacement therapy (dialysis or kidney transplantation) were excluded from the analysis (317 patients [2.8%] out of a total of 11,303 patients).

Albuminuria was absent in 54.1% and 49.1% of type 1 and type 2 diabetic patients with reduced eGFR respectively (P > 0.05 between diabetes types, Table 1). Odds of normoalbuminuria (vs. albuminuria) among patients with reduced eGFR increased with age, decreased with diabetes duration, were higher in females and were lower in patients with retinopathy (data not shown).

3.3. Characteristics of patients with albuminuria and/or reduced eGFR

Table 1 shows patient characteristics, stratified by the presence of albuminuria and/or reduced eGFR. Independent of diabetes type, albuminuria was associated with longer diabetes duration, male sex, smoking, lower eGFR and more frequent antihypertensive treatment (consisting mostly of angiotensin II converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB)), both in patients with preserved and reduced eGFR. Albuminuria was associated with higher age in patients with preserved eGFR but with lower age in patients with reduced eGFR. Reduced eGFR by itself was independently associated with higher age, longer diabetes duration, female sex, less frequent smoking, higher BMI (in type 1 diabetes), more frequent antihypertensive treatment, more frequent lipid-lowering treatment and less frequent treatment with oral antidiabetic drugs (in type 2 diabetes), regardless of albuminuria.

3.4. Cardiovascular risk factors

Table 2 shows that albuminuria was associated with poorer control of blood pressure, blood lipids and HbA1c, mostly independent of eGFR.

Table 1
Demographic and selected clinical parameters of type 1 (T1) and insulin-treated type 2 (T2) diabetic patients with albuminuria and/or reduced eGFR (N = 7640).

	Type (N)	Albuminuria (alb) and/or reduced eGFR (ReGFR)				Total	P_{alb}	P_{eGFR}	$P_{alb:eGFR}$
		alb − ReGFR-	*alb + ReGFR −*	*alb − ReGFR +*	*alb + ReGFR +*				
No. (%)	T1	1908 (75.1)	410 (16.1)	120 (4.7)	102 (4.0)	2540 (100.0)	–	–	–
	T2	2351 (46.1)	1094 (21.5)	812 (15.9)	843 (16.5)	5100 (100.0)	–	–	–
Age, years	T1	44.6 ± 14.3	47.1 ± 14.4	65.5 ± 12.2	61.5 ± 14.0	46.7 ± 15.2	0.021	<0.001	0.005
	T2	63.7 ± 11.2	65.2 ± 11.4	74.0 ± 8.2	73.6 ± 9.8	67.3 ± 11.5	<0.001	<0.001	0.002
Diabetes duration, years	T1	17.3 ± 12.0	19.6 ± 13.0	27.3 ± 15.3	32.7 ± 13.7	18.8 ± 12.9	0.001	<0.001	0.127
	T2	13.7 ± 8.4	15.0 ± 8.6	17.0 ± 9.1	17.8 ± 9.5	15.2 ± 8.9	<0.001	<0.001	0.426
Female sex (%)	T1	795 (41.7)	151 (36.8)	82 (68.3)	47 (46.1)	1075 (42.3)	0.051	<0.001	0.006
	T2	1171 (49.8)	454 (41.5)	549 (67.6)	399 (47.3)	2573 (50.5)	<0.001	<0.001	<0.001
Current smoker (%)	T1 (2408)	413 (22.8)	118 (30.4)	19 (16.8)	17 (17.2)	567 (23.5)	0.004	0.090	0.336
	T2 (4814)	344 (15.4)	187 (18.1)	38 (5.0)	61 (7.7)	630 (13.1)	0.055	<0.001	0.237
BMI, kg/m^2	T1 (2418)	25.6 ± 4.2	26.1 ± 4.9	27.0 ± 5.1	27.3 ± 5.1	25.8 ± 4.4	0.093	0.003	0.851
	T2 (4786)	31.1 ± 6.0	31.8 ± 6.1	31.5 ± 6.0	31.2 ± 6.1	31.3 ± 6.1	0.001	0.140	0.010
Serum creatinine, μmol/L[a]	T1	70.7 (61.9–80.4)	76.0 (65.4–76.0)	114.9 (95.5–134.4)	133.9 (114.9–171.5)	73.4 (63.6–86.6)	<0.001	<0.001	0.111
	T2	72.5 (61.9–83.1)	76.9 (64.5–88.4)	108.7 (95.0–129.9)	124.6 (107.8–163.5)	83.1 (69.8–103.4)	0.001	<0.001	<0.001
Estimated GFR, mL/min per 1.73 m^2	T1	101.0 ± 20.1	95.0 ± 21.3	45.5 ± 13.7	41.3 ± 13.6	95.0 ± 25.5	<0.001	<0.001	0.953
	T2	85.5 ± 15.2	83.5 ± 17.0	45.9 ± 11.5	40.7 ± 13.1	71.4 ± 24.5	0.001	<0.001	<0.001
Antihypertensive treatment (%)	T1 (2509)	570 (30.3)	245 (60.2)	82 (68.9)	93 (92.1)	990 (39.5)	<0.001	<0.001	0.248
	T2 (5063)	1755 (75.4)	951 (87.3)	752 (93.2)	794 (94.7)	4252 (84.0)	<0.001	<0.001	0.016
Treatment with ACE-I or ARB (%)	T1 (2521)	471 (24.9)	222 (54.3)	63 (52.5)	89 (88.1)	845 (33.5)	<0.001	<0.001	0.064
	T2 (5054)	1417 (60.9)	822 (75.7)	611 (75.7)	657 (78.8)	3507 (69.4)	<0.001	<0.001	<0.001
Lipid-lowering treatment (%)	T1 (2533)	618 (32.4)	174 (42.9)	70 (58.3)	60 (58.8)	922 (36.4)	<0.001	<0.001	0.296
	T2 (5066)	1642 (70.3)	783 (72.0)	620 (76.8)	632 (75.6)	3677 (72.6)	0.098	<0.001	0.206
Basal-bolus insulin therapy (%)	T1 (2536)	1850 (97.1)	384 (94.1)	112 (93.3)	96 (94.1)	2442 (96.3)	0.028	0.007	0.167
	T2 (5085)	1248 (49.7)	533 (49.1)	345 (42.5)	399 (47.4)	2525 (49.7)	0.230	<0.001	0.007
Oral antidiabetic drugs (%)	T1 (2537)	143 (7.5)	43 (10.5)	15 (12.5)	10 (9.9)	211 (8.3)	0.061	0.083	0.356
	T2 (5082)	1407 (60.1)	682 (62.6)	396 (48.8)	316 (37.7)	2801 (55.1)	0.091	<0.001	<0.001

Data are presented as frequencies (%) or means ± standard deviation. The final three columns show P values for the association with albuminuria (P_{alb}), reduced eGFR (P_{eGFR}), and the combined presence of albuminuria and reduced eGFR ($P_{alb:eGFR}$).

[a] Presented as median (IQR). P values were calculated using linear regression on log-transformed values.

Table 2
Cardiovascular risk factor control as a function of the presence of albuminuria and/or reduced eGFR.

	Type (N)	Albuminuria (alb) and/or reduced eGFR (ReGFR)				Total	P_{alb}	P_{eGFR}	$P_{alb:eGFR}$
		alb − ReGFR −	*alb + ReGFR −*	*alb − ReGFR +*	*alb + ReGFR +*				
Systolic BP, mmHg	T1 (2526)	127.1 (126.1–128.0)	131.1 (129.2–132.9)	127.6 (124.9–130.3)	136.7 (132.6–140.9)	128.2 (127.2–129.1)	<0.001	0.703	0.015
	T2 (5078)	135.9 (134.6–137.1)	139.4 (137.9–141.0)	135.6 (134.2–137.0)	139.0 (137.4–140.6)	137.1 (136.0–138.2)	<0.001	0.636	0.949
Diastolic BP, mmHg	T1 (2526)	74.2 (73.5–75.0)	76.0 (75.0–76.9)	73.7 (71.8–75.6)	75.5 (73.4–77.6)	74.5 (73.8–75.2)	0.001	0.540	0.948
	T2 (5072)	75.8 (75.1–76.6)	76.9 (76.1–77.8)	75.2 (74.3–76.1)	76.3 (75.3–77.4)	76.0 (75.4–76.7)	0.001	0.145	0.951
TC, mg/dL	T1 (2511)	181.5 (179.8–183.2)	185.1 (181.6–188.5)	182.4 (176.5–188.4)	188.8 (179.6–198.0)	182.4 (180.9–184.0)	0.074	0.771	0.612
	T2 (5043)	171.8 (169.9–173.8)	176.3 (173.2–179.4)	170.2 (167.2–173.3)	175.5 (172.1–178.8)	173.2 (171.4–174.9)	0.010	0.310	0.756
LDL-C, mg/dL	T1 (2438)	97.5 (96.0–98.9)	99.9 (96.6–103.3)	97.6 (92.5–102.6)	106.9 (98.8–115.1)	98.3 (96.9–99.7)	0.162	0.971	0.150
	T2 (4838)	92.8 (91.1–94.5)	95.8 (93.2–98.5)	90.6 (88.0–93.2)	94.2 (91.3–97.1)	93.3 (91.8–94.8)	0.042	0.098	0.775
HDL-C, mg/dL	T1 (2486)	63.8 (62.7–64.8)	61.1 (59.3–62.9)	57.9 (54.0–61.8)	54.6 (49.8–59.5)	62.7 (61.7–63.6)	0.009	0.004	0.856
	T2 (4.990)	50.8 (50.1–51.4)	49.2 (48.3–50.2)	47.3 (46.1–48.5)	46.6 (45.4–47.8)	49.2 (48.6–49.8)	0.007	<0.001	0.364
fasting TG, mg/dL	T1 (1331)	93.1 (88.9–97.4)	107.9 (99.8–116.0)	106.1 (92.4–119.8)	130.6 (115.4–145.9)	97.7 (94.0–101.5)	0.001	0.103	0.432
	T2 (3000)	131.6 (127.3–135.9)	147.9 (140.0–155.9)	147.3 (140.2–154.3)	158.5 (150.6–166.3)	142.0 (137.9–146.1)	<0.001	<0.001	0.381
HbA1c, % [mmol/mol]	T1 (2531)	7.90 (7.83–7.97) [62.8 (62.1–63.6)]	8.29 (8.15–8.44) [67.1 (65.6–68.7)]	8.04 (7.79–8.29) [64.3 (61.6–67.1)]	8.12 (7.89–8.35) [65.2 (62.7–67.7)]	7.98 (7.92–8.05) [63.7 (63.0–64.4)]	<0.001	0.269	0.073
	T2 (5081)	7.55 (7.48–7.61) [59.0 (58.3–59.7)]	7.90 (7.79–8.00) [62.8 (61.7–63.9)]	7.59 (7.49–7.68) [59.4 (58.4–60.4)]	7.67 (7.57–7.76) [60.3 (59.2–61.3)]	7.65 (7.59–7.71) [60.1 (59.4–60.7)]	<0.001	0.455	0.001

Data are presented as means (95% confidence interval). All values were adjusted for age, sex and diabetes duration in linear regression models. The final three columns show P values for the association with albuminuria (P_{alb}), reduced eGFR (P_{eGFR}), and the combined presence of albuminuria and reduced eGFR ($P_{alb:eGFR}$).
Abbreviations: BP, blood pressure; TC, total cholesterol; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; TG, triglycerides.

No association between reduced eGFR and other CV risk factors was found, except for (low) HDL cholesterol and (high) fasting triglycerides. Of note, among type 1 diabetic patients with reduced eGFR the association between albuminuria and systolic blood pressure was more pronounced than among those with preserved eGFR (significant interaction between albuminuria and reduced eGFR, $P = 0.015$). This was not the case in type 2 diabetes. The association of albuminuria with HbA1c was less pronounced among patients with reduced eGFR compared to patients with preserved eGFR (trend in type 1 diabetes and significant interaction in type 2 diabetes, $P < 0.001$).

3.5. Micro- and macrovascular complications

Table 3 shows that in patients with both preserved and reduced eGFR the presence of albuminuria was associated with a significantly higher prevalence of most of the listed diabetic complications. In type 2 diabetes, prevalence of retinopathy or macrovascular disease was higher in patients with reduced eGFR than in those with preserved eGFR regardless of albuminuria status, while this was not the case in type 1 diabetes. This association of reduced eGFR with complication prevalence in type 2 diabetes came in addition to the association with albuminuria. Interestingly, again in type 2 diabetic patients, but not in type 1 diabetic patients, the prevalence of most macrovascular complications was equal or even higher when comparing patients with reduced eGFR to those with isolated albuminuria with preserved eGFR (Table 3).

4. Discussion

The present study investigated the association of albuminuria and renal impairment with CV risk factors and diabetic complications in a population of type 1 diabetic and insulin-treated type 2 diabetic patients. The main findings were that (a) albuminuria, reduced eGFR or a combination of both was more prevalent in the type 2 diabetic patients, (b) in patients with reduced eGFR about half were

Table 3
Prevalence of microvascular and macrovascular complications as a function of the presence of albuminuria and/or reduced eGFR.

	Type (N)	Albuminuria (alb) and/or reduced eGFR (ReGFR)				Total	P_{alb}	P_{eGFR}	$P_{alb:eGFR}$
		alb − ReGFR −	*alb + ReGFR −*	*alb − ReGFR +*	*alb + ReGFR +*				
Retinopathy (any stage), %	T1 (2355)	26.7 (23.9–29.8)	47.1 (41.3–53.0)	28.5 (18.3–41.5)	48.8 (33.9–63.9)	31.1 (28.3–34.0)	<0.001	0.763	0.958
	T2 (4547)	25.1 (22.6–27.8)	40.0 (36.2–43.9)	33.4 (29.6–37.4)	45.6 (40.9–50.3)	32.9 (30.7–35.1)	<0.001	<0.001	0.166
Macrovascular complications									
History of ulcer or gangrene, %	T1 (2494)	1.4 (0.9–2.2)	3.9 (2.5–6.0)	1.8 (0.7–4.7)	5.6 (2.8–10.9)	2.0 (1.4–2.8)	<0.001	0.591	0.858
	T2 (4872)	3.7 (2.9–4.8)	7.5 (5.9–9.5)	8.1 (6.2–10.5)	10.6 (8.6–13.0)	6.3 (5.4–7.2)	<0.001	<0.001	0.077
Lower limb amputations, %	T1 (2496)	0.5 (0.3–1.0)	1.2 (0.6–2.3)	0.7 (0.2–3.1)	1.7 (0.5–5.4)	0.7 (0.4–1.1)	0.054	0.677	0.996
	T2 (4950)	1.2 (0.8–1.9)	3.1 (2.2–4.4)	3.3 (2.2–5.0)	5.5 (4.1–7.4)	2.6 (2.2–3.1)	0.002	0.001	0.250
History of peripheral angioplasty or bypass, %	T1 (2493)	1.0 (0.6–1.6)	1.4 (0.8–2.7)	2.1 (0.8–5.3)	0.8 (0.3–2.5)	1.1 (0.8–1.6)	0.324	0.147	0.077
	T2 (4930)	3.4 (2.7–4.3)	7.3 (5.8–9.0)	7.2 (5.5–9.3)	9.0 (7.1–11.4)	5.7 (4.9–6.7)	<0.001	<0.001	0.013
History of PCI or CABG, %	T1 (2524)	1.7 (1.3–2.3)	3.2 (1.9–5.4)	3.3 (1.8–6.2)	5.7 (3.1–10.4)	2.1 (1.6–2.8)	0.029	0.030	0.838
	T2 (5005)	13.5 (11.8–15.3)	15.5 (13.4–17.9)	20.7 (17.6–24.1)	21.9 (19.1–24.9)	16.4 (14.9–18.0)	0.052	<0.001	0.513
History of MI, %	T1 (2527)	1.5 (1.0–2.2)	2.9 (1.7–4.8)	2.3 (1.1–4.8)	4.2 (2.1–8.2)	1.9 (1.3–2.6)	0.039	0.274	0.991
	T2 (4992)	9.5 (8.4–10.7)	12.2 (10.6–14.1)	12.5 (10.5–14.8)	15.0 (12.5–18.0)	11.4 (10.4–12.6)	0.002	0.004	0.664
History of CVA or TIA, %	T1 (2525)	1.0 (0.6–1.8)	2.0 (1.1–3.8)	0.7 (0.2–2.8)	2.6 (1.0–6.6)	1.2 (0.8–2.0)	0.050	0.546	0.398
	T2 (5000)	6.9 (5.8–8.1)	7.9 (6.5–9.5)	7.8 (6.1–10.1)	11.3 (9.2–13.8)	7.9 (7.1–8.8)	0.237	0.376	0.275
History of macrovascular disease[a], %	T1 (2484)	5.6 (4.6–7.0)	10.9 (8.3–14.2)	7.2 (4.7–11.1)	16.3 (10.3–24.8)	6.9 (5.7–8.2)	<0.001	0.248	0.564
	T2 (4910)	26.6 (24.4–28.9)	36.0 (32.9–39.3)	37.9 (33.8–42.1)	45.5 (41.7–49.4)	33.4 (31.5–35.4)	<0.001	<0.001	0.374

Data are presented as proportions (95% confidence interval). All values were adjusted for age, sex and diabetes duration in logistic regression models. The final three columns show P values for the association with albuminuria (P_{alb}), reduced eGFR (P_{eGFR}), and the combined presence of albuminuria and reduced eGFR ($P_{alb:eGFR}$).
Abbreviations: PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; MI, myocardial infarction; CVA, cerebrovascular accident; TIA, transient ischemic attack.
[a] Composite of all macrovascular events listed above.

normoalbuminuric, regardless of diabetes type, (c) presence of albuminuria correlated with the presence of other CV risk factors and diabetic complications similarly in both diabetes types, and independently of renal impairment, and (d) impaired renal function by itself was associated with a higher prevalence of micro- and macrovascular diabetic complications as well as a higher risk of foot ulcers and amputations, in particular in type 2 diabetic patients.

The prevalence of albuminuria and renal impairment was higher in the type 2 than in type 1 diabetic patients. This may have been in part due to the advanced stage of disease and the older age among these insulin-treated type 2 diabetic patients, although other studies have reported a similarly high prevalence in a mixed population treated with oral antidiabetic drugs only or insulin (Ito et al., 2010; MacIsaac et al., 2004; Meisinger et al., 2008). Interestingly, despite the smaller proportion of patients with renal impairment in type 1 compared to type 2 diabetes, the proportion of normoalbuminuric patients within this group was similar (54.1% and 49.1% respectively, NS). As in previous studies, patients with normoalbuminuric renal impairment were older, had shorter diabetes duration, more often were female and less often had retinopathy compared to patients with albuminuric renal impairment (MacIsaac et al., 2004; Penno et al., 2011; Rigalleau et al., 2007; Thomas et al., 2009). The overall high proportion of normoalbuminuria in patients with renal impairment may have been due to high rates of antihypertensive (especially ACE-I or ARB) and lipid-lowering treatment, either preventing the appearance or causing regression of albuminuria (Pavkov et al., 2009). The present cross-sectional study cannot, however, confirm or refute this hypothesis.

In this study, we confirm the role of albuminuria as a putative CV risk factor, as it was clearly associated with other classical CV risk factors, such as hypertension and dyslipidemia, but also directly with macrovascular disease. This association was present in both diabetes types. The additional presence of renal impairment was not associated with poorer control of risk factors, except for systolic blood pressure in type 1 diabetes and HDL cholesterol and TG levels in type 1 or type 2 diabetes. With regard to blood pressure control, previous studies in type 2 diabetes have shown that among *normoalbuminuric* patients renal impairment was associated with increased systolic blood pressure (Kramer et al., 2007; Penno et al., 2011; Thomas et al., 2009; Yokoyama et al., 2009), although this was not always the case (Ito et al., 2010), including in our study. Among *albuminuric* patients the presence of renal impairment was not associated with increased systolic blood pressure (Penno et al., 2011; Yokoyama et al., 2009). The discrepancy among normoalbuminuric patients between our and previous studies may be related to the high rate of antihypertensive treatment in the present study compared to previous studies (Penno et al., 2011; Thomas et al., 2009). Interestingly, we show that in type 1 diabetes the presence of renal impairment among albuminuric patients is, in contrast to type 2 diabetes, associated with a further increase of systolic blood pressure. The latter finding is consistent with the classical disease progression of kidney disease in type 1 diabetes.

With regard to plasma lipids, only plasma HDL cholesterol and TG showed an additional association with renal impairment. The reason why total cholesterol and LDL cholesterol did not show this association and were not elevated in normoalbuminuric patients with renal impairment, may be due to the high rates of lipid-lowering treatment in this group, consisting mostly (95%) of statins.

With regard to glycemic control, we observed a remarkably lower HbA1c in patients with both albuminuria and renal impairment compared to patients with only albuminuria. Lower HbA1c has been observed among patients on renal replacement therapy due to blood loss, shortened red blood cell survival, red blood cell transfusions, or erythropoietin treatment (Uzu et al., 2009), but these patients were excluded from the present study. The confounding effect of renal anemia on HbA1c values has not yet been systematically studied (Sharif & Baboolal, 2010). While we did not collect data on anemia, a previous study (Thomas et al., 2009) reported a prevalence of 49% among type 2 diabetic patients with both renal impairment and albuminuria. Lower HbA1c in patients with CKD may also have resulted from impaired insulin clearance (Snyder & Berns, 2004).

The RIACE investigators have hypothesized that, based on the relatively low concordance of retinopathy and CKD in type 2 diabetes and on the lower HbA1c among patients with normoalbuminuric renal impairment, this latter phenotype mostly results from macroangiopathy, rather than from microangiopathy (Penno et al., 2011; Penno et al., 2012). The present study shows that among type 2 diabetic patients with CKD, 42% had (non-)proliferative retinopathy, compared to 45% reported by Yokoyama et al. (2009) and only 31% reported in RIACE (Penno et al., 2012). Importantly, the concordance rate in our type 1 diabetic cohort was, as expected, higher (53%), which is in support of the hypothesis that macroangiopathy largely determines the renal phenotype in type 2 diabetes. Nevertheless, and at variance with previous studies (Penno et al., 2011; Thomas et al., 2009; Yokoyama et al., 2009), we did not observe a significantly lower HbA1c among normoalbuminuric patients with renal impairment compared to those with albuminuria.

An intriguing observation is the excess prevalence of diabetic complications in type 2 diabetic (and less so in type 1 diabetic) patients with renal function impairment but without albuminuria. Possible explanations may be that in type 2 diabetes the cause of the renal function impairment is still linked to diabetes or will worsen diabetic complications. Such causes may include macroangiopathy (as suggested above) but also other factors related to obesity and insulin resistance, explaining the relatively high prevalence of this normoalbuminuric renal impairment state in type 2 diabetes (15.9%). In type 1 diabetes, on the other hand, the reasons for normoalbuminuric renal impairment might be of a very different nature (e.g. glomerulonephritis), suggested by the relatively rare occurrence of this state in type 1 diabetes (4.7%) thus making the normoalbuminuric renal impairment independent from diabetic complications.

This study has several limitations. First, it is a cross-sectional study, using data from single, non-standardized laboratory measurements. Kidney function was estimated using the CKD-EPI equation, which is not perfect (Silveiro et al., 2011) but performs better than the MDRD equation in type 2 diabetes and is more closely correlated with the overall CV risk of individual patients (Pugliese et al., 2011). Moreover, using the MDRD equation did not alter the general conclusions of this study (data not shown). Finally, we are limited by the reporting of medication use by the physicians of the participating diabetes centers. Misreporting of important medications may occur, with use of medications interfering with renin–angiotensin–aldosterone system (RAAS) possibly leading to misclassification of patients or to misinterpretation of risk.

The large sample size, including results from the largest type 1 diabetic cohort published to date, is a strength of this study. This has allowed for the first time a side-by-side comparison of type 1 and type 2 diabetic patients, unveiling interesting differences and parallels. Patient data originate from routine clinical encounters rather than from a controlled clinical trial, thus improving the generalizability of our results. In contrast to previous multicenter studies in this field (Penno et al., 2011; Yokoyama et al., 2009), our statistical analyses accounted for the clustered nature of outcomes, leading to appropriate inflation of standard errors, and thus limiting the possibility of spurious conclusions.

In conclusion, our results show that albuminuria was independently associated with CV risk factors and diabetic complications in type 1 and type 2 diabetes. Even in the absence of albuminuria, renal impairment was associated with a higher prevalence of diabetic complications, especially in type 2 diabetes. Most of all, our results underscore the high burden of CV complications and risk factors in type 1 and type 2 diabetic patients with markers of kidney disease.

References

Caramori, M. L., Fioretto, P., & Mauer, M. (2003). Low glomerular filtration rate in normoalbuminuric type 1 diabetic patients. *Diabetes*, *52*, 1036–1040.

de Boer, I. H., Katz, R., Cao, J. J., Fried, L. F., Kestenbaum, B., Mukamal, K., et al. (2009). Cystatin C, albuminuria, and mortality among older adults with diabetes. *Diabetes Care*, *32*, 1833–1838.

de Zeeuw, D., Remuzzi, G., Parving, H., Keane, W. F., Zhang, Z., Shahinfar, S., et al. (2004). Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation*, *110*, 921–927.

Debacker, N., Nobels, F., Vandenberghe, H., Van Crombrugge, P., Scheen, A., & Van Casteren, V. (2008a). Organization of a quality-assurance project in all Belgian multidisciplinary diabetes centres treating insulin-treated diabetes patients: 5 years' experience. *Diabetic Medicine*, *25*, 179–185.

Debacker, N., Van Crombrugge, P., Nobels, F., Sourdeau, L., Libeer, J., & Van Casteren, V. (2008b). Het effect van een externe kwaliteitsevaluatie voor HbA1c-bepaling in de Belgische laboratoria. *Vlaams Tijdschrift voor Diabetologie*, *1*, 15–18 (In Dutch).

Drury, P. L., Ting, R., Zannino, D., Ehnholm, C., Flack, J., Whiting, M., et al. (2010). Estimated glomerular filtration rate and albuminuria are independent predictors of cardiovascular events and death in type 2 diabetes mellitus: The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetologia*, *54*, 32–43.

Fioretto, P., Caramori, M. L., & Mauer, M. (2008). The kidney in diabetes: Dynamic pathways of injury and repair. The Camillo Golgi Lecture 2007. *Diabetologia*, *51*, 1347–1355.

Foley, R. N., Murray, A. M., Li, S., Herzog, C. A., McBean, A. M., Eggers, P. W., & Collins, A. J. (2005). Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *Journal of the American Society of Nephrology*, *16*, 489–495.

Friedewald, W. T., Levy, R. I., & Fredrickson, D. S. (1972). Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clinical Chemistry*, *18*, 499–502.

Gerstein, H. C., Mann, J. F., Yi, Q., Zinman, B., Dinneen, S. F., Hoogwerf, B., et al. (2001). Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *Journal of the American Medical Association*, *286*, 421–426.

Gross, J. L., de Azevedo, M. J., Silveiro, S. P., Canani, L. H., Caramori, M. L., & Zelmanovitz, T. (2005). Diabetic nephropathy: Diagnosis, prevention, and treatment. *Diabetes Care*, *28*, 164–176.

Ito, H., Takeuchi, Y., Ishida, H., Antoku, S., Abe, M., Mifune, M., et al. (2010). High frequencies of diabetic micro- and macroangiopathies in patients with type 2 diabetes mellitus with decreased estimated glomerular filtration rate and normoalbuminuria. *Nephrology, Dialysis, Transplantation*, *25*, 1161–1167.

Kramer, C. K., Leitão, C. B., Pinto, L. C., Silveiro, S. P., Gross, J. L., & Canani, L. H. (2007). Clinical and laboratory profile of patients with type 2 diabetes with low glomerular filtration rate and normoalbuminuria. *Diabetes Care*, *30*, 1998–2000.

Kramer, H. J., Nguyen, Q. D., Curhan, G., & Hsu, C. (2003). Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. *Journal of the American Medical Association*, *289*, 3273–3277.

Levey, A. S., Coresh, J., Balk, E., Kausz, A. T., Levin, A., Steffes, M. W., et al. (2003). National Kidney Foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Annals of Internal Medicine*, *139*, 137–147.

Levey, A. S., Stevens, L. A., Schmid, C. H., Zhang, Y. L., Castro, A. F., Feldman, H. I., et al. (2009). A new equation to estimate glomerular filtration rate. *Annals of Internal Medicine*, *150*, 604–612.

MacIsaac, R. J., Tsalamandris, C., Panagiotopoulos, S., Smith, T. J., McNeil, K. J., & Jerums, G. (2004). Nonalbuminuric renal insufficiency in type 2 diabetes. *Diabetes Care*, *27*, 195–200.

Meisinger, C., Heier, M., Landgraf, R., Happich, M., Wichmann, H. -E., & Piehlmeier, W. (2008). Albuminuria, cardiovascular risk factors and disease management in subjects with type 2 diabetes: A cross sectional study. *BMC Health Services Research*, *8*, 226.

Ninomiya, T., Perkovic, V., de Galan, B. E., Zoungas, S., Pillai, A., Jardine, M., et al. (2009). Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *Journal of the American Society of Nephrology*, *20*, 1813–1821.

Pavkov, M. E., Mason, C. C., Bennett, P. H., Curtis, J. M., Knowler, W. C., & Nelson, R. G. (2009). Change in the distribution of albuminuria according to estimated glomerular filtration rate in Pima Indians with type 2 diabetes. *Diabetes Care*, *32*, 1845–1850.

Penno, G., Solini, A., Bonora, E., Fondelli, C., Orsi, E., Zerbini, G., et al. (2011). Clinical significance of nonalbuminuric renal impairment in type 2 diabetes. *Journal of Hypertension*, *29*, 1802–1809.

Penno, G., Solini, A., Zoppini, G., Orsi, E., Zerbini, G., Trevisan, R., et al. (2012). Rate and determinants of association between advanced retinopathy and chronic kidney disease in patients with type 2 diabetes: The Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicenter study. *Diabetes Care*, *35*, 2317–2323.

Pugliese, G., Solini, A., Bonora, E., Orsi, E., Zerbini, G., Giorgino, F., et al. (2011). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation provides a better definition of cardiovascular burden associated with CKD than the Modification of Diet in Renal Disease (MDRD) Study formula in subjects with type 2 diabetes. *Atherosclerosis*, *218*, 194–199.

Retnakaran, R., Cull, C. A., Thorne, K. I., Adler, A. I., & Holman, R. R. (2006). Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. *Diabetes*, *55*, 1832–1839.

Rigalleau, V., Lasseur, C., Raffaitin, C., Beauvieux, M. -C., Barthe, N., Chauveau, P., et al. (2007). Normoalbuminuric renal-insufficient diabetic patients: A lower-risk group. *Diabetes Care*, *30*, 2034–2039.

Sarnak, M. J., Levey, A. S., Schoolwerth, A. C., Coresh, J., Culleton, B., Hamm, L. L., et al. (2003). Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation*, *108*(17), 2154–2169.

Sharif, A., & Baboolal, K. (2010). Diagnostic application of the A1c assay in renal disease. *Journal of the American Society of Nephrology*, *21*, 383–385.

Silveiro, S. P., Araújo, G. N., Ferreira, M. N., Souza, F. D. S., Yamaguchi, H. M., & Camargo, E. G. (2011). Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation pronouncedly underestimates glomerular filtration rate in type 2 diabetes. *Diabetes Care*, *34*, 2353–2355.

Snyder, R. W., & Berns, J. S. (2004). Use of insulin and oral hypoglycemic medications in patients with diabetes mellitus and advanced kidney disease. *Seminars in Dialysis*, *17*, 365–370.

Solini, A., Penno, G., Bonora, E., Fondelli, C., Orsi, E., Arosio, M., et al. (2012). Diverging association of reduced glomerular filtration rate and albuminuria with coronary and noncoronary events in patients with type 2 diabetes. *Diabetes Care*, *35*, 143–149.

Targher, G., Zoppini, G., Chonchol, M., Negri, C., Stoico, V., Perrone, F., et al. (2011). Glomerular filtration rate, albuminuria and risk of cardiovascular and all-cause mortality in type 2 diabetic individuals. *Nutrition, Metabolism, and Cardiovascular Diseases*, *21*, 294–301.

Thomas, M. C., MacIsaac, R. J., Jerums, G., Weekes, A., Moran, J., Shaw, J. E., et al. (2009). Nonalbuminuric renal impairment in type 2 diabetic patients and in the general population (national evaluation of the frequency of renal impairment cO-existing with NIDDM [NEFRON] 11). *Diabetes Care*, *32*, 1497–1502.

Uzu, T., Hatta, T., Deji, N., Izumiya, T., Ueda, H., Miyazawa, I., et al. (2009). Target for glycemic control in type 2 diabetic patients on hemodialysis: Effects of anemia and erythropoietin injection on hemoglobin A(1c). *Therapeutic Apheresis and Dialysis*, *13*, 89–94.

Viana, L. V., Gross, J. L., Camargo, J. L., Zelmanovitz, T., Rocha, E. P., & Azevedo, M. J. (2012). Prediction of cardiovascular events, diabetic nephropathy, and mortality by albumin concentration in a spot urine sample in patients with type 2 diabetes. *Journal of Diabetes and its Complications*, *26*, 407–412.

Yokoyama, H., Sone, H., Oishi, M., Kawai, K., Fukumoto, Y., & Kobayashi, M. (2009). Prevalence of albuminuria and renal insufficiency and associated clinical factors in type 2 diabetes: The Japan Diabetes Clinical Data Management study (JDDM15). *Nephrology, Dialysis, Transplantation*, *24*, 1212–1219.