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Original Article

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Risk factors for the development of albuminuria and renal impairment in type 2 diabetes—the Swedish National Diabetes Register (NDR)

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Abstract

Background. The aim of this study was to identify clinical risk factors associated with the development of albuminuria and renal impairment in patients with type 2 diabetes (T2D). In addition, we evaluated if different equations to estimate renal function had an impact on interpretation of data. This was done in a nationwide population-based study using data from the Swedish National Diabetes Register.

Methods. Three thousand and six hundred sixty-seven patients with T2D aged 30–74 years with no signs of renal dysfunction at baseline (no albuminuria and eGFR >60 mL/min/1.73 m^2 according to MDRD) were followed up for 5 years (2002–2007). Renal outcomes, development of albuminuria and/or renal impairment [eGFR <60 mL/min/1.73 m^2 by MDRD or eCrCl >60 mL/min by Cockgroft–Gault (C–G)] were assessed at follow-up. Univariate regression analyses and stepwise regression models were used to identify significant clinical risk factors for renal outcomes.

Results. Twenty percent of patients developed albuminuria, and 11% renal impairment; thus, ~6–7% of all patients developed non-albuminuric renal impairment. Development of albuminuria or renal impairment was independently associated with high age (all $P < 0.001$), high systolic BP (all $P < 0.02$) and elevated triglycerides (all $P < 0.02$). Additional independent risk factors for albuminuria were high BMI ($P < 0.01$), high HbA1c ($P < 0.001$), smoking ($P < 0.001$), HDL ($P < 0.05$) and male sex ($P < 0.001$), and for renal impairment elevated plasma creatinine at baseline and female sex (both $P < 0.001$). High BMI was an independent risk factor for renal impairment when defined by MDRD ($P < 0.01$), but low BMI was when defined by C–G ($P < 0.001$). Adverse effects of BMI on HbA1c, blood pressure and lipids accounted for ~50% of the increase risk for albuminuria, and for 41% of the increased risk for renal impairment (MDRD).

Conclusions. Distinct sets of risk factors were associated with the development of albuminuria and renal impairment consistent with the concept that they are not entirely linked in patients with type 2 diabetes. Obesity and serum triglycerides are semi-novel risk factors for development of renal dysfunction and BMI accounted for a substantial proportion of the increased risk. The equations used to estimate renal function (MDRD vs. C–G) had an impact on interpretation of data, especially with regard to body composition and gender

Keywords: albuminuria; obesity; renal impairment; risk factors; type 2 diabetes

Introduction

Diabetes is estimated to increase the risk of developing end-stage renal disease (ESRD) 10–12-fold [1]. Diabetes, and especially type 2 diabetes (T2D), is currently the main reason for start of renal replacement therapy, i.e. dialysis or kidney transplantation, in many countries [2]. Even though T2D is one of the leading causes of ESRD, not all patients with T2D develop renal dysfunction and ESRD during their lifetime [3]. Development of albuminuria is used as a sensitive clinical risk marker and predictor to identify those at risk of future development of renal dysfunction and ESRD [4]. But recent studies have shown that albuminuria does not always precede development of renal impairment in T2D [5], implicating that other markers than albuminuria are needed to monitor renal function in these patients.

The primary aim of this study was to study the development of renal dysfunction defined as albuminuria and/or renal impairment in patients with T2D during 5 years of follow-up, and to identify clinical risk factors associated with the development of renal dysfunction. In addition,

Table 1. Clinical characteristics and risk factors at baseline (2002) and at follow-up in all patients (n = 3667), and in patients who developed albuminuria or renal impairment (MDRD <60 mL/min/1.73 m^2) during follow-up (2007)

	All patients (n = 3667)		Albuminuria in 2007 (n = 729)		Renal impairment in 2007 (n = 407)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Age (years)	60.3 ± 8.2	65.3 ± 8.2	61.7 ± 8.0	66.7 ± 8.0	64.6 ± 6.5	69.6 ± 6.5
Sex (men/women, %)	61/39	61/39	67/33	67/33	49/51	49/51
Diabetes duration (years)	7.5 ± 6.2	12.5 ± 6.2	7.9 ± 6.3	12.9 ± 6.3	7.8 ± 6.5	12.8 ± 6.5
HbA1c (DCCT, %)	7.1 ± 1.1	7.2 ± 1.1^{b}	7.3 ± 1.2***	7.4 ± 1.2***	7.2 ± 1.2	7.1 ± 1.0
Systolic blood pressure (mmHg)	140 ± 17	137 ± 16^{c}	144 ± 17***	141 ± 17^{c,***}	146 ± 17***	138 ± 17^{c}
Diastolic blood pressure (mmHg)	79 ± 9	76 ± 9^{c}	80 ± 9***	76 ± 10^{c,*}	79 ± 9	74 ± 9^{c,**}
Pulse pressure (mmHg)	61 ± 15	62 ± 14	64 ± 15***	65 ± 16***	67 ± 16***	64 ± 15^{b,***}
BMI (kg/m^2)	29.0 ± 4.8	29.0 ± 4.9	29.7 ± 4.7***	29.7 ± 4.9***	29.8 ± 5.0***	29.9 ± 5.1**
Total cholesterol (mmol/L)	5.06 ± 1.0	4.60 ± 0.9^{c}	5.08 ± 1.0	4.62 ± 1.0^{c}	5.05 ± 0.99	4.58 ± 1.0^{c}
LDL cholesterol (mmol/L)	3.02 ± 0.9	2.54 ± 0.8^{c}	3.04 ± 0.9	2.55 ± 0.9^{c}	3.77 ± 1.0	2.47 ± 0.9^{c}
Triglycerides (mmol/L)	1.61 ± 0.7	1.59 ± 0.9	1.74 ± 0.7***	1.75 ± 1.0***	1.77 ± 0.77***	1.79 ± 0.8***
HDL cholesterol (mmol/L)	1.32 ± 0.4	1.37 ± 0.4^{c}	1.25 ± 0.4***	1.30 ± 0.4***	1.28 ± 0.38	1.32 ± 0.4
Creatinine (μmol/L)	79 ± 14	77 ± 19^{c}	79 ± 14	80 ± 24***	82 ± 14***	108 ± 23^{c,***}
eGFR (MDRD) (mL/min/1.73 m^2)	80 ± 16	83 ± 20^{c}	81 ± 17	82 ± 23	73 ± 13***	52 ± 7^{c,***}
eCrCl (C–G) (mL/min)	103 ± 30	101 ± 33^{c}	105 ± 30	101 ± 36^{b}	93 ± 24***	65 ± 16^{c,***}
Antihypertensive medication (%)	54	76^{c}	67***	89^{c,***}	69***	90^{c,***}
Hypertension (%)	75	83^{c}	85***	94^{c,***}	89***	94^{a,***}
Lipid-lowering drugs (%)	39	64^{c}	42	67	45*	72^{c,**}
Smoker (%)	17	14^{b}	20*	18^{c,**}	14	13
Previous CHD (%)	15	21^{c}	21***	29^{c,***}	21**	29^{b,***}
Previous stroke (%)	5	7^{c}	6	10^{b}	6	11^{b,*}

Means and proportions (%) are given. The proportion of patients having data reported on smoking and blood lipids at follow-up were 94% and 82–93%, respectively.

CHD, coronary heart disease; eGFR (MDRD), estimated glomerular filtration rate according to MDRD; eCrCl (C–G), estimated creatinine clearance according to Cockcroft–Gault.

$^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$—significance levels for differences between baseline and follow-up within groups adjusted for age and sex at GLM regression.

*P < 0.05, **P < 0.01, ***P < 0.001—significance levels for differences at baseline or at follow-up, respectively, between all patients and patients with albuminuria or renal impairments at follow-up.

as the secondary aim, we evaluated if using two different equations to estimate glomerular filtration rate (GFR), i.e. the MDRD and Cockcroft–Gault equations, may have an impact on the interpretation of data. This was done in a nationwide population-based study using the data from the Swedish National Diabetes Register (NDR).

Materials and methods

Subjects

The NDR was initiated in 1996. Reporting to NDR is based on information collected, at least once yearly, during patient visits. The register is population-based, nationwide, and ~95% of hospital-based outpatient clinics and 60% of primary healthcare centres participate. In this study, we selected patients with T2D who in 2002 had no reported signs of renal dysfunction, i.e. no albuminuria (urine albumin excretion <20 mg/min) and an estimated glomerular filtration rate (eGFR; MDRD) >60 mL/min/1.73 m^2 [6]. Five years later, in 2007, development of renal dysfunction was assessed. Patients included in the study had to be alive and have complete datasets on albuminuria and s-creatinine both at baseline and at follow-up. Altogether, 3667 patients were included in the study.

Methods and definitions

Diabetes was diagnosed using the Swedish and the ADA criteria of a fasting plasma glucose of 7.0 mmol/L (126 mg/dL) or higher, or current antidiabetic therapy. T2D was defined using the epidemiological definition, i.e. treatment with diet only, treatment with hypoglycaemic agents only, or age at onset of diabetes 40 years or older, and treatment with insulin alone or combination with oral agents. Hypertension was defined as treatment with antihypertensive drugs or, in untreated patients, systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥90 mmHg. Smoking was defined as smoking one or more cigarettes per day, or using a pipe, or a subject who had stopped smoking within the past 3 months. BMI was defined as weight by height squared (kilogram per square metre). Normal weight was defined as BMI of 18–24.9 kg/m^2, overweight as BMI 25–29.9 kg/m^2, obesity 30–34.9 kg/m^2, and severe obesity as BMI ≥35 kg/m^2.

Laboratory analyses were performed at local laboratories. HbA1c was analysed with the HPLC Mono-S method. However, in this study, all HbA1c values were converted to the DCCT standard values using the formula: HbA1c (DCCT) = [0.923 × HbA1c (Mono-S) + 1.345]; R2 = 0.998. LDL cholesterol values were calculated using Friedewald's formula: LDL cholesterol = total cholesterol − HDL cholesterol − (0.45 × triglycerides) if triglycerides <4.0 mmol/L. Plasma creatinine was analysed at laboratories local to each clinical centre.

Microalbuminuria was defined as urine albumin excretion 20–200 μg/min, and macroalbuminuria as urine albumin excretion >200 μg/min, in two out of three consecutive tests. eGFR (mL/min/1.73 m^2) according to MDRD was calculated for males as 175 × [plasma creatinine (μmol/L)/88.4] × age and for females as 175 × [plasma creatinine (μmol/L)/88.4] × age × 0.742. Estimated creatinine clearance (eCrCl; mL/min) according to Cockcroft–Gault [7] was calculated using the equation for males as [140 − age × weight (kg) × 1.23/plasma creatinine (μmol/L)] and for females as [140 − age × weight (kg) × 1.23 × 0.85/plasma creatinine (μmol/L)]. Renal outcomes assessed at follow-up were development of renal dysfunction, i.e. micro- or macroalbuminuria, and/or development of renal impairment assessed as eGFR <60 mL/min/1.73 m^2 or eCrCl <60 mL/min from 2002 to 2007.

Statistical methods

Univariate logistic regression analyses were performed with the development of albuminuria or renal impairment defined as an eGFR <60 mL/

Table 2. Development of albuminuria and renal impairment (n = 3667)

	All patients (n = 3667)	Albuminuria (n = 729)	Renal impairment (eGFR <60 mL/min/1.73 m^2; MDRD) (n = 407)	Renal impairment (eCrCl <60 mL/min; C–G) (n = 241)
Microalbuminuria[a], %	597 (16.3)	597 (81.9)	84 (20.6)	55 (22.8)
Macroalbuminuria[b], %	132 (3.6)	132 (18.1)	33 (8.1)	21 (8.7)
Albuminuria[c], %	729 (19.9)		117 (28.7)	76 (31.5)
eGFR (MDRD)[d] <60 mL/min, %	407 (11.1)	117 (16.1)		165 (68.5)
eCrCl (C–G)[e] <60 mL/min, %	241 (6.7)	76 (10.4)	165 (40.5)	

Numbers (n) and proportions (%) are given.
[a]U-albumin excretion 20–200 µg/min.
[b]U-albumin excretion >200 µg/min.
[c]Micro- or macroalbuminuria.
[d]Estimated glomerular filtration rate according to MDRD.
[e]Estimated creatinine clearance according to Cockcroft–Gault.

Table 3. Univariate logistic regression analyses with odds ratios (95% CI) for baseline variables as predictors for the development of albuminuria or renal impairment (n = 3667)

	Albuminuria (Micro- or macroalbuminuria)			Glomerular filtration rate (MDRD) <60 mL/min/1.73 m^2			Creatinine clearance (Cockcroft–Gault) <60 mL/min		
	Odds ratio (95% CI)	Wald X^2	P-value	Odds ratio (95% CI)	Wald X^2	P-value	Odds ratio (95% CI)	Wald X^2	P-value
Continuous variables									
Age (years)	1.26 (1.16–1.37)	28.0	<0.001	2.04 (1.80–2.32)	119	<0.001	4.65 (3.75–5.77)	196	<0.001
Diabetes duration (years)	1.08 (1.00–1.17)	3.8	0.05	1.07 (0.96–1.18)	1.5	n.s.	1.21 (1.08–1.36)	10.1	0.002
HbA1c (DCCT, %)	1.23 (1.14–1.33)	26.2	<0.001	1.02 (0.92–1.13)	0.1	n.s.	1.01 (0.89–1.15)	0.1	n.s.
Systolic blood pressure (mmHg)	1.33 (1.23–1.44)	49.2	<0.001	1.41 (1.28–1.56)	46.4	<0.001	1.43 (1.27–1.62)	32.4	<0.001
Diastolic blood pressure (mmHg)	1.19 (1.09–1.29)	17.0	<0.001	1.02 (0.92–1.13)	0.1	n.s.	0.79 (0.70–0.91)	11.8	<0.001
Pulse pressure (mmHg)	1.33 (1.20–1.47)	30.2	<0.001	1.61 (1.42–1.83)	56.1	<0.001	1.93 (1.66–2.25)	70.9	<0.001
BMI (kg/m^2)	1.18 (1.09–1.28)	17.6	<0.001	1.21 (1.10–1.33)	14.3	<0.001	0.45 (0.38–0.53)	88.0	<0.001
Total cholesterol (mmol/L)	1.02 (0.94–1.10)	0.2	n.s.	0.98 (0.89–1.09)	0.1	n.s.	1.07 (0.94–1.21)	1.0	n.s.
LDL cholesterol (mmol/L)	1.03 (0.95–1.12)	0.5	n.s.	0.94 (0.85–1.04)	1.4	n.s.	0.97 (0.85–1.10)	0.3	n.s.
Triglycerides (mmol/L)	1.22 (1.13–1.32)	24.2	<0.001	1.25 (1.13–1.38)	20.2	<0.001	1.05 (0.92–1.19)	0.5	n.s.
HDL cholesterol (mmol/L)	0.81 (0.74–0.89)	20.5	<0.001	0.90 (0.81–1.01)	3.4	n.s.	1.18 (1.05–1.33)	8.0	0.005
Creatinine (µmol/L)	1.07 (0.99–1.16)	2.9	n.s.	1.29 (1.16–1.43)	22.2	<0.001	1.09 (0.95–1.24)	1.5	n.s.
eGFR (MDRD) (mL/min/1.73 m^2)	1.02 (0.94–1.10)	0.2	n.s.	0.44 (0.37–0.51)	107	<0.001	0.40 (0.33–0.59)	72.8	<0.001
eCrCl (C–G) (mL/min)	1.07 (0.99–1.16)	2.8	n.s.	0.58 (0.51–0–67)	62.4	<0.001	0.10 (0.07–0.13)	246	<0.001
Dichotomous variables									
Female sex	0.72 (0.61–0.85)	14.4	<0.001	1.75 (1.43–2.13)	28.0	<0.001	2.44 (1.85–3.13)	42.8	<0.001
Antihypertensive medication (%)	1.95 (1.65–2.31)	59.3	<0.001	2.03 (1.63–2.53)	39.6	<0.001	1.84 (1.39–2.43)	18.6	<0.001
Hypertension (%)	2.21 (1.78–2.76)	49.6	<0.001	3.01 (2.21–4.25)	45.5	<0.001	2.53 (1.70–3.76)	21.2	<0.001
Smoker (%)	1.36 (1.10–1.67)	8.4	0.004	0.79 (0.59–1.05)	2.6	n.s.	0.83 (0.57–1.20)	1.0	n.s.

Univariate analysis for each predictor, with significance estimated with Wald X^2 and P-values. Continuous variables were increased per 1 SD.
CI, confidence interval; BP, blood pressure; Total-C, total cholesterol.

min/1.73 m^2 according to the MDRD equation or eCrCl <60 mL/min using the Cockcroft–Gault (C–G) equation at follow-up as dependent variables. Continuous variables as predictors at baseline were age, diabetes duration, HbA1c, systolic blood pressure, pulse pressure, body mass index, total cholesterol, LDL cholesterol, triglycerides, HDL cholesterol and plasma creatinine. They were all increased, per 1 SD, in order to allow a comparison of the strength of odds ratios (OR). Dichotomous predictor variables at baseline were sex, antihypertensive medication, hypertension and smoking. The odds ratio with 95% confidence interval (CI) was estimated for each predictor, and significance was estimated with the Wald X^2 value, with the P-value given. Secondly, multivariate stepwise logistic regressions were performed, giving adjusted odds ratios for the development of albuminuria or renal impairment with clinical characteristics and risk factors at baseline as predictors. Continuous predictor variables were increased per 1 SD. The following predictors were found significant at multivariate stepwise regression: age, diabetes duration, HbA1c, systolic BP, pulse pressure, BMI, triglycerides, HDL cholesterol, plasma creatinine, sex and smoking. Systolic BP was tested in preference to hypertension. The likelihood-ratio X^2 value for global model fit was strongly significant, the C-statistic as a measure of discriminative capacity of model was 0.67–0.87 (range 0.5–1.0; the higher the value, the better the fit), and the Hosmer–Lemeshow X^2 value as a measure of calibration capacity of the model was non-significant, indicating excellent goodness-of-fit. Two models for adjusting the odds ratio for BMI as predictor of the development of albuminuria or renal impairment were used and are presented in Table 5. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NJ, USA).

Results

Clinical and biochemical characteristics at baseline and at follow-up

Clinical characteristics and risk factors at baseline and at follow-up in all study participants taken together and in

Table 4. Adjusted odds ratios (95% CI) for baseline variables as predictors for the development of albuminuria or renal impairment at follow-up at stepwise logistic regression (n = 3667)

	Albuminuria (Micro- or macroalbuminuria)			Glomerular filtration rate (MDRD) <60 mL/min/1.73 m^2			Creatinine clearance (Cockcroft–Gault) <60 mL/min		
Variables	OR (95% CI)	Wald X^2 (order)	P-value	OR (95% CI)	Wald X^2 (order)	P-value	OR (95% CI)	Wald X^2 (order)	P-value
Systolic blood pressure (mmHg)	1.25 (1.15–1.37)	27.0 (1)	<0.001	1.18 (1.06–1.31)	8.8 (6)	0.003			
HbA1c (DCCT, %)	1.23 (1.13–1.33)	23.9 (2)	<0.001						
Age (years)	1.27 (1.16–1.40)	26.1 (3)	<0.001	2.00 (1.75–2.28)	101 (1)	<0.001	4.26 (3.38–5.38)	151 (1)	<0.001
Female sex	0.65 (0.55–0.79)	20.5 (5)	<0.001	4.03 (2.97–5.48)	79.5 (4)	<0.001	6.23 (4.08–9.52)	71.5 (3)	<0.001
Smoker (%)	1.50 (1.21–1.86)	13.7 (6)	<0.001						
BMI (kg/m^2)	1.13 (1.04–1.24)	7.4 (7)	0.0064	1.19 (1.06–1.33)	9.1 (5)	0.0026	0.34 (0.27–0.42)	105 (2)	<0.001
Triglycerides (mmol/L)	1.12 (1.02–1.22)	5.8 (8)	0.016	1.20 (1.07–1.34)	10.3 (2)	0.0013	1.39 (1.19–1.61)	17.9 (5)	<0.001
HDL cholesterol (mmol/L)	0.90 (0.82–0.99)	4.0 (4)	0.045						
Creatinine (μmol/L)				2.11 (1.80–2.46)	86.9 (3)	<0.001	2.05 (1.65–2.55)	41.8 (4)	<0.001
Pulse pressure (mmHg)							1.31 (1.09–1.58)	8.4 (6)	0.004

The odds ratio (OR) for each variable was adjusted for all other variables, with significance estimated with Wald X^2 and P-values. Stepwise order entered is given within brackets. Continuous variables were increased per 1 SD.
CI, confidence interval.

Table 5. Adjusted odds ratios (95% CI) for obesity, overweight and BMI at baseline as predictor for the development of albuminuria or renal impairment at follow-up, at logistic regression analyses in 3667 type 2 diabetic patients followed up for 5 years

	Number of patients	Covariates for adjustment	Albuminuria (micro- or macroalbuminuria)		Glomerular filtration rate (MDRD) ≤60 mL/min	
			OR (95% CI)	P-value	OR (95% CI)	P-value
Normal weight (BMI 18–24.9 kg/m^2)	718	Model 1[a]	1.0		1.0	
Overweight (BMI 25–29.9 kg/m^2)	1585		1.28 (1.01–1.63)	0.04	1.53 (1.10–2.14)	0.01
Obesity (BMI 30–34.9 kg/m^2)	963		1.62 (1.25–2.10)	<0.001	1.90 (1.33–2.70)	<0.001
Prominent obesity (BMI ≥35 kg/m^2)	392		1.96 (1.41–2.72)	<0.001	2.26 (1.47–3.48)	<0.001
BMI per 1 SD increase	3667	Model 1[a]	1.26 (1.16–1.37)	<0.001	1.27 (1.14–1.42)	<0.001
BMI per 1 SD increase		Model 2[b]	1.13 (1.04–1.24)	0.007	1.16 (1.04–1.31)	0.011

1-SD increase in BMI corresponded to 5-kg/m^2 increase.
CI, confidence interval.
[a]Model 1: BMI adjusted for age, sex, diabetes duration, serum creatinine at baseline, and smoking.
[b]Model 2: BMI adjusted as in Model 1 and also for HbA1c, systolic blood pressure, triglycerides, and HDL and LDL cholesterol.

the two subgroups of patients who developed albuminuria or renal impairment during follow-up are given in Table 1. At baseline, a skewed gender distribution with a male preponderance is seen, possibly mirroring an underestimation of GFR in women by the MDRD equation which was used as inclusion criteria. Interestingly, 75% of patients were reported to have hypertension at baseline, but only 54% were on antihypertensive medication. At follow-up, a reduction in blood pressure and blood lipids (total and LDL cholesterol) is found in all three groups. This reduction is paralleled by an increase in antihypertensive and lipid-lowering medication. A significant increase in HDL cholesterol is seen in all patients taken together but not in patients who have developed albuminuria or renal impairment. Despite a general decrease in both systolic and diastolic blood pressure, pulse pressure increased non-significantly in all patients taken together and patients developing albuminuria. Pulse pressure decreased in patients developing renal impairment. In addition, a significant increase in HbA1c is seen in all patients taken together but not in patients developing albuminuria or renal impairment. An increase in eGFR (MDRD), but not in eCrCl (C–G), is found in all patients taken together. This reduction in eCrCl is paradoxical since it is paralleled by a reduction in serum creatinine. In patients developing albuminuria, a reduction in eCrCl (C–G) is found despite no change in serum creatinine over time. No mean decline in eGFR was found in patients who developed albuminuria. Patients who developed renal impairment had a significantly lower eGFR at baseline as compared with both all patients taken together and those who developed albuminuria (73 ± 13 vs. 80 ± 16 and 81 ± 17 mL/min/1.73 m^2, respectively, both P < 0.001).

Development of albuminuria and renal impairment

Development of albuminuria and renal impairment in patients are given in Table 2. In total, ~20% of patients developed albuminuria during 5 years (4%/year). The majority of patients developed microalbuminuria. Among the patients who developed albuminuria, 16% (MDRD) or 10% (C-G), respectively, developed renal impairment.

Altogether, 11% of patients (2.2%/year) developed renal impairment defined as an eGFR of <60 mL/min/1.73 m^2 according to MDRD and 7% if defined as an eCrCl <60 mL/min according to the C–G equation. Among patients who developed renal impairment according to MDRD, only 1/3 patients also developed albuminuria. Thus, in this study cohort 6–7% of patients developed non-albuminuric renal disease.

Risk factors for development of albuminuria and renal impairment

Univariate analyses. Univariate analyses of risk factors for development of albuminuria and renal impairment are given in Table 3. Old age, male gender, long diabetes duration, high BP (hypertension, high systolic or diastolic BP, and ongoing antihypertensive medication), poor glycaemic control (high HbA1c), smoking, overweight (high BMI), high triglycerides, low HDL cholesterol, and smoking are all associated with development of albuminuria. Old age, female gender, hypertension (hypertension, high systolic BP and ongoing antihypertensive medication), high triglycerides and reduced renal function at baseline (high creatinine, low eGFR and low eCrCl) as well as high BMI are associated with development of renal impairment (eGFR; MDRD). In contrast, low BMI is associated with development of renal impairment when the C–G equation is used to define renal impairment (eCrCl <60 mL/min).

Multivariate analyses. Multivariate analyses of risk factors for development of albuminuria and renal impairment are given in Table 4. Old age, high systolic BP and high triglycerides were independent predictors for both development of albuminuria and renal impairment. Male gender, poor glycaemic control (high HbA1c), low HDL cholesterol and smoking showed an independent and significant association with the development of albuminuria but not with the development of renal impairment. Female gender and a high baseline creatinine were associated with an increased risk of developing renal impairment only. In addition, a high BMI was associated with the development of both albuminuria and renal impairment, but when renal function was estimated using the C–G equation, low BMI was a predictor of renal dysfunction.

As given in Table 5, odds ratios for development of albuminuria or renal impairment (MDRD) were higher in patients with severe obesity vs normal weight (OR 2.0 and 2.3), vs obesity (OR 1.6 and 1.9), and also vs overweight (OR 1.3 and 1.5). Furthermore, adverse effects of BMI on HbA1c, BP and blood lipids accounted for 50% (= 26 − 13/26 × 100) of the increased risk for albuminuria, and thus adverse effects of BMI on unknown mechanisms accounted for the remaining 50% of the increased risk of developing albuminuria. 41% of the increased risk for developing renal impairment (MDRD) was accounted for by adverse effects of BMI on HbA1c, BP and blood lipids but the majority of the increased risk (59%) was accounted for by adverse effects of BMI on unknown mechanisms or risk factors.

Discussion

In this large, nationwide, population-based study, we show that the modifiable risk factors elevated systolic blood pressure and elevated serum triglycerides are independent predictors for development of renal dysfunction in type 2 diabetes, but also that overweight and obesity are strongly related to development of renal disease. Furthermore, our study emphasizes the need for more studies on methods to determine renal function in population-based studies, since the currently used formulae (MDRD and C–G) generate different results, especially with regard to body composition and sex.

The importance of elevated blood pressure is well documented from previous studies [4,8], and blood pressure control and antihypertensive medication have been shown to reduce the incidence of albuminuria [9,10] and the development of end-stage renal disease [11]. Other studies have shown that dyslipidaemia may play an important role in the initiation and progression of diabetic renal disease [12], and recent experimental studies have demonstrated a direct effect of saturated fatty acids on podocyte function and thus a potential link between dyslipidaemia, systemic or organ-specific insulin resistance and the development of albuminuria [13]. The role of hypertriglyceridaemia in progression of renal disease is also supported by data from the FIELD Study where treatment with fenofibrate decreased the progression to microalbuminuria [14]. Hypertriglyceridaemia is also a feature in obesity and insulin resistance, two additional risk factors for development of renal dysfunction [15,16]. In our study, the majority of patients only had a slight reduction in GFR, and it is thus unlikely that the elevation of triglycerides could be explained by renal dysfunction per se [17].

Male sex, poor glycaemic control, low HDL cholesterol, high BMI and smoking were independently associated with development of albuminuria, and this has also been described in other prospective studies [8,18–20], but in this study, they were not independently associated with development of renal impairment. Instead, female sex was associated with development of renal impairment as previously described in the UKPDS [4], and a skewed gender distribution, with a larger proportion of men, was seen already at baseline. Previous population-based studies have detected similar gender differences [21–23], suggesting a possible misclassification of renal function in women. It could therefore be speculated that renal function in women is underestimated when using creatinine-based estimations of glomerular filtration rate despite gender adjustments, and this may partly be supported by the fact that women have a slower progression to ESRD [24].

In this study, obesity has a substantial effect on the development of renal dysfunction, both albuminuria and renal impairment, with an increasing odds with increase in BMI, ranging from a 1.3- and 1.5-fold increase in patients with overweight to a 2- and 2.3-fold increase in patients with severe obesity. Adjustments were made for age, sex, duration, smoking and serum creatinine (Model 1) as recommended by the WHO, and in order not to underestimate the risk associated with BMI, factors closely related

to BMI such as hypertension, hyperlipidaemia and hyperglycaemia are not considered confounding, and adjustments for these factors were therefore not made [25]. In comparison, 1471 non-diabetic subjects developing ESRD BMI >35 kg/m^2 associated with a 5-fold increase, BMI 30–34.9 kg/m^2 associated with a 3-fold increase, and BMI 25–29.9 kg/m^2 with a 1.5-fold increase in relative risk, with adjustment for covariates comparable with Model 1 in this study [26,27]. Different forms of obesity-related chronic kidney diseases (CKD) have previously been described and have been associated with endothelial dysfunction, microalbuminuria, reduced GFR and increase in cardiovascular risk. Concurrent obesity and renal disease accelerate progression rate of renal impairment [28,29]. Morphologically, obesity-related glomerulopathy is characterized by glomerular enlargement and focal segmental glomerulosclerosis [30]. Physiologically, hyperfiltration may lead to glomerular capillary injury and sclerosis, in a fashion similar as in animal experiments [31]. An increased GFR has been found in obesity [32], and this hyperfiltration decreases after weight loss in morbid obesity [33,34].

In our study, adverse effects of obesity on glycaemic control, blood pressure and blood lipids accounted for approximately one-half of the increased risk for albuminuria and ~40% of the increased risk for renal impairment. Thus, adverse effects of obesity by unknown pathways account for a substantial proportion of the increased risk for both albuminuria and renal impairment. Suggested pathways or mediator of unknown effects of obesity include insulin resistance, low-grade inflammation and endothelial dysfunction, pathways that previously have been suggested as potential mechanisms for development of renal dysfunction [15,16,35].

In this observational nationwide and population-based study, we confirm many of the previous findings in the randomized controlled trial UKPDS [4] in type 2 diabetic patients given routine treatments. But in contrast to the UKPDS, where patients with newly diagnosed type 2 diabetes were included, these patients had mean diabetes duration of 7.5 years at baseline. Despite this difference, similar proportions of patients, 4.0% per year, developed albuminuria over a 5-year period [4], and this is also comparable with other previous studies [3,8,20,36]. In addition, 2.2% per year developed renal impairment, an annual rate similar to the UKPDS [4]. The UKPDS reported conflicting and paradoxical data on the relationship between anthropometric measurements and development of albuminuria and renal impairment. Female sex, increased height and decreased central obesity were all associated with development of renal impairment and, in contrast, male sex and increased central obesity with development of albuminuria. No data on BMI were reported. In this study, a strong association was found between obesity and development of renal dysfunction as previously mentioned. Unfortunately, data on waist circumference were not available. In addition, we show that the equation used to estimate renal function is of importance and has a major impact on interpretation of the anthropometric data. In line with the findings in the UKPDS, we found that low BMI was a predictor of renal dysfunction when renal function was estimated using the Cockcroft–Gault equation, but when using the MDRD, high BMI and obesity are independent predictors of renal impairment. This is further supported by other studies linking obesity with development of renal impairment and end-stage renal disease in both diabetic and non-diabetic renal disease [26,27,37–39], strongly underlining that renal function using the MDRD equation should be preferred when analysing the association with BMI.

Only one-third of the patients who developed renal impairment also developed albuminuria during the same time period; thus, 6–7% of the patients in this study population developed renal impairment without albuminuria. Non-albuminuric renal impairment has previously been described in both type 2 diabetic patients [40,41] and non-diabetic subjects [5]. It has been hypothesized that the development of renal impairment is associated with either glomerular or extra-glomerular changes, whereas development of albuminuria is only related to glomerular changes [41]. Interestingly, a recent study has suggested a higher frequency of diabetic micro- and macroangiopathies in patients with type 2 diabetes and non-albuminuric renal impairment [42]. This finding supports that screening for albuminuria alone may not be optimal to detect all patients with high risk of renal impairment and cardiovascular disease, and that a reliable estimation of renal function in this patient population is warranted.

Even though this was a large nationwide and population-based study, baseline data indicate that a relatively healthy cohort of type 2 diabetic patients with a slightly skewed gender distribution was included, and in addition, all patients included in the study had to be alive at follow-up 5 years later; thus, patients who at baseline did not have any renal dysfunction but died in the following 5 years were not investigated. Taken together, this may suggest a possible selection bias, and that the findings may not be entirely generalizable to a general type 2 diabetic population. On the other hand, the major advantage of this study is the large number of patients and renal outcomes, and since this is a nationwide population-based study where patients have been given routine treatments according to national guidelines. The use of local laboratories local to the clinical centres is a weakness, since laboratory methods to analyse creatinine may vary between laboratories over time and reported data from participating centres may vary slightly in accuracy and precision. During this study, a change from classical Jaffe to an enzymatic method or modified Jaffe method was performed in some of the laboratories, a change that would render a slightly higher estimated GFR in subjects with normal renal function but have no effect on GFR in patients with moderately reduced renal function (A. Mårtensson, unpublished work, EQUALIS 14 March 2006). Such a change in method would thus potentially result in a slower deterioration in estimated renal function. But the overall change in renal function over time was similar to the UKPDS where a central laboratory was used, indicating that this weakness seems to be of little importance. Unfortunately, only information on overall blood pressure-lowering medication, and not RAAS blockade specifically, was available in this study. Information on RAAS blockade would have been of interest since this has an impact on both

albuminuria and renal function. Another limitation of this study was that data on albuminuria and renal impairment were insufficient for the interim years 2003–06; therefore, logistic regression, instead of Cox regression, was used to analyse those who had developed albuminuria or renal impairment after 5 years of follow-up, and thus, those who died during the interim years could not be included in the analysis, as mentioned previously. To assess a potential misclassification of albuminuria as an outcome variable after 5 years, additional data on albuminuria during follow-up were available in a subset of patients (n = 1010) classified as having no albuminuria at follow-up. In these patients, an additional ~10% (n = 97) had albuminuria reported at any time point and were thus 'misclassified'. On the other hand, such a small proportion of patients would not impact the overall findings in the study. This is further supported by the fact that the rate of development of albuminuria in this study was similar to previous studies. Finally, the majority of patients in our study were Caucasian, and thus, the results in this study may not be generalizable to other ethnicities.

In conclusion, distinct sets of modifiable risk factors were associated with the development of albuminuria and renal impairment consistent with the concept that they are not entirely linked in type 2 diabetes. Obesity and elevated serum triglycerides are semi-novel risk factors for development of renal dysfunction, and interestingly, glycaemic control only predicted the development of albuminuria but not development of renal impairment. To our surprise, the effects of BMI also accounted for a substantial proportion of the increased risk for both development of albuminuria and renal impairment. In a subset of type 2 diabetic patients, albuminuria does precede development of renal impairment, and non-albuminuric renal impairment was found in 6–7% of this study population. In these patients, screening for microalbuminuria may not be optimal to detect risk of developing renal impairment, and thus, other markers, such as reliable estimates of glomerular filtration rate, are therefore needed to monitor renal function. In population-based studies, the different equations currently used to estimate renal function may have an impact on interpretation of data, and renal function and MDRD should be preferred when analysing the association with BMI.

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