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Ongoing treatment with renin-angiotensin-aldosterone-blocking agents does not predict normoalbuminuric renal impairment in a general type 2 diabetes population ☆

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ABSTRACT

Aim: To examine the prevalence and the clinical characteristics associated with normoalbuminuric renal impairment (RI) in a general type 2 diabetes (T2D) population.
Methods: We included 94 446 patients with T2D (56% men, age 68.3 ± 11.6 years, BMI 29.6 ± 5.3 kg/m^2, diabetes duration 8.5 ± 7.1 years; means ± SD) with renal function (serum creatinine) reported to the Swedish National Diabetes Register (NDR) in 2009. RI was defined as estimated glomerular filtration (eGFR) < 60 ml/min/1.73 m^2 and albuminuria as a urinary albumin excretion rate (AER) > 20 μg/min. We linked the NDR to the Swedish Prescribed Drug Register, and the Swedish Cause of Death and the Hospital Discharge Register to evaluate ongoing medication and clinical outcomes.
Results: 17% of the patients had RI, and 62% of these patients were normoalbuminuric. This group of patients had better metabolic control, lower BMI, lower systolic blood pressure and were more often women, non-smokers and more seldom had a history of cardiovascular disease as compared with patients with albuminuric RI. 28% of the patients with normoalbuminuric RI had no ongoing treatment with any RAAS-blocking agent. Retinopathy was most common in patients with RI and albuminuria (31%).
Conclusions: The majority of patients with type 2 diabetes and RI were normoalbuminuric despite the fact that 25% of these patients had no ongoing treatment with RAAS-blocking agents. Thus, RI in many patients with type 2 diabetes is likely to be caused by other factors than diabetic microvascular disease and ongoing RAAS-blockade.

1. Introduction

The incidence and prevalence of type 2 diabetes (T2D) is increasing globally (Wild et al., 2004). Having diabetes increases the risk of developing end stage of renal disease (ESRD) 10–12 times (Brancati et al., 1997). Diabetic nephropathy (DN) is currently the main underlying primary disease for need of renal replacement therapies, i.e. dialysis and kidney transplantation, in many countries (Williams, 2010). Albuminuria is a well-known risk factor for development of DN and predicts progression to ESRD (de Zeeuw et al., 2004). In addition, both albuminuria and reduced renal function are independent predictors of cardiovascular disease (CVD), as well as cardiovascular and all-cause mortality (Sasso et al., 2012). Even though T2D is one of the leading causes of ESRD, not all patients with T2D develop renal dysfunction and ESRD during their lifetime (Adler et al., 2003). Recent studies have shown that albuminuria does not always precede development of renal impairment (RI) in T2D and other markers are therefore needed to monitor renal function (Ito et al., 2010; Kramer et al., 2007). Around 10–20% of all patients with T2D have normoalbuminuric RI (Penno et al., 2011; Rigalleau et al., 2007a; Yokoyama et al., 2009) and, in fact, the majority of patients with T2D and RI are normoalbuminuric (MacIsaac et al., 2004; Thomas et al., 2009). Concomitant retinopathy is often used as a clinical indicator of DN, but the association between retinopathy and nephropathy in T2D is relatively weak and only

Abbreviations: eGFR, estimated glomerular filtration rate; MDRD, Modified Diet in Renal Disease; C-G, Cockcroft-Gault; ESRD, end stage renal disease; T2D, type 2 diabetes; AER, albumin excretion rate; NDR, Swedish National Diabetes Register; CVD, cardiovascular disease; CHF, chronic heart failure; RAAS, renin-angiotensin aldosterone system.

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approximately 40% of patients with RI and microalbuminuria have any degree of concomitant retinopathy (Chen, Zheng, & Huang, 2012).

The cause of normoalbuminuric RI in T2D is considered to be multifactorial, and hypertension, aging, obesity and lipid toxicity with development of glomerulo- and nephrosclerosis contribute (Gambara et al., 1993; Kramer et al., 2003). Distinct sets of cardiovascular risk factors have been associated with the absence of albuminuria in patients with T2D and RI (Afghahi et al., 2011; Retnakaran et al., 2006), suggesting a potentially more favourable cardiovascular risk profile. This is supported by prospective studies where patients with T2D and normoalbuminuric RI have a lower risk of cardiovascular events and mortality (Agarwal et al., 2012). This finding could potentially be explained by ongoing treatment with renin-angiotensin-aldosterone-system (RAAS) inhibition, reducing albuminuria by alteration of renal hemodynamics (de Zeeuw et al., 2004), but different underlying renal pathophysiological mechanisms may contribute (Keller et al., 1996; MacIsaac et al., 2006; Penno et al., 2011).

The objectives of this study were to examine the prevalence of normoalbuminuric RI in an unselected general type 2 diabetes population in the Swedish National Diabetes Register (NDR) and to study the clinical characteristics associated with the normoalbuminuric RI. In addition, we studied the use and impact of treatment with RAAS-blocking agents.

2. Patients and methods

2.1. Patients

The NDR was initiated in 1996. Reporting to NDR is based on information collected at least once yearly during patient visits (Gudbjornsdottir et al., 2003). The registry is population-based, nation-wide and 95% of hospital-based outpatient clinics and 75% of primary health care centres participate. The patients included in this study had to have T2D, be alive during year 2009, and have a serum creatinine value reported to NDR. Patients with reported serum creatinine values <20 or >800 μmol/L, as well as recipients of a kidney transplant were excluded (n = 55). Other clinical variables reported to NDR during 2009 (age, gender, diabetes duration, BMI, smoking, physical activity, HbA1c, lipid profile, blood pressure, albuminuria) were used when available.

The Swedish Prescribed Drug Register contains detailed information on all prescribed medications purchased from all pharmacies in Sweden. We linked NDR and the Swedish Prescribed Drug Register to evaluate ongoing anti-diabetic, lipid-lowering, antihypertensive and aspirin medications. We only included patients who had filled at least 2 prescriptions within 9 months before the date of the last serum creatinine value reported during 2009 (1st of April, 2008 until 31st of December, 2009). We excluded patients with medication dispensed by automatic dosing (ApoDos) at any time-point from this analysis.

Data on diabetes retinopathy and previous cardiovascular events were retrieved by data linkage with the Hospital Discharge Registers (National Board of Health and Welfare, Sweden), a validated alternative to hospital discharge records. A flow chart of patients included in the study is shown in Figure 1. Finally 94446 patients fulfilled the inclusion criteria and were included in the study. All included patients have agreed by informed consent to be reported to the NDR and participate in the study. The Regional Ethics Review Board at the University of Gothenburg approved the study.

2.2. 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 concurrent treatment with insulin alone or combination with oral agents. Body mass index, BMI (kg/m^2) was calculated as weight/height^2. Hypertension was defined as treatment with antihypertensive agents, or, in untreated patients, systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. A smoker was defined as a patient smoking one or more cigarettes per day, or using a pipe, or who had stopped smoking within the past three months.

Microalbuminuria was defined as urine albumin excretion 20–200 μg/min in two out of three consecutive tests, and macroalbuminuria as urine albumin excretion >200 μg/min. Estimated glomerular filtration (eGFR) (ml/min/1.73 m^2) was calculated according to MDRD (Levey et al., 1999) (for males as 175 × [plasma creatinine (μmol/L)/88.4] × age and for females 175 × [plasma creatinine (μmol / L)/88.4] × age × 0.742). Serum creatinine was analysed at laboratories local to each clinical center. HbA_{1c} analyses are quality assured in Sweden. Both diabetes clinics and primary care centres use methods regularly calibrated with the HPLC Mono-S method. In this study, all HbA_{1c} values were converted to the IFCC standard values using the formula: $HbA_{1cIFCC} = (10.11 \times HbA1c\ (MonoS)) - 8.94$. LDL cholesterol values were calculated using Friedewald's formula: LDL cholesterol = total cholesterol − HDL cholesterol − (0.45 × triglycerides), if triglycerides <4.0 mmol/L.

Diabetes retinopathy was defined as any diabetes retinopathy (ICD-9 codes 250.5 and 362.0 and ICD-10 codes H36.0, E10.3, E 11.3 and E14.3). Previous CVD was the composite of non-fatal CHD or stroke, whichever came first. CHD was defined as MI (ICD-10 code I21; www.who.int7classifications/icd/en/), unstable angina (ICD-10 code I20.0), percutaneous coronary intervention and/or coronary artery bypass grafting and stroke, was defined as cerebral infarction, intracerebral haemorrhage or unspecified stroke (ICD-10 codes I61, I63, I64 and I67.9). A history of CHF was defined as ICD-10 code I50; both previous CVD and CHF were used as covariates in all regression analyses.

2.3. Statistical methods

The baseline characteristics are presented as mean values ± one standard deviation (SD) or frequencies (%). Significance across the two groups were analysed by using general linear modelling both for continuous and dichotomous variables (Tables 1 and 2). Comparisons between means and frequencies were not adjusted. In patients with RI (eGFR <60 ml/min/1.73 m^2 according to MDRD), logistic regression were used to estimate adjusted odds ratios (OR) with 95% confidence interval (CI) of the outcomes 1) normoalbuminuric RI and 2) normoalbuminuric RI without ongoing treatment with RAAS-blockade (Tables 3, 4 and 5). All covariates, in the case of adjusting for potential confounding factors, were managed as continuous variables. $P<0.05$ was considered statistically significant. All statistical analyses were performed by use of SAS statistical software version 9.2 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Renal impairment (RI)

Clinical and biochemical characteristics of patients with and without RI are given in Table 1. Seventeen per cent of the patients (n = 19 330) had RI with a mean eGFR of 47 ± 10 ml/min/1.73 m^2. Patients with RI were older, had longer diabetes duration, worse metabolic control (higher HbA1c and triglycerides), higher BMI, higher systolic but lower diastolic blood pressure, and thus, a higher