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Original article

Microalbuminuria, but not reduced eGFR, is associated with cardiovascular subclinical organ damage in type 2 diabetes

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Abstract

Aim. – This study explored the association between reduced estimated glomerular filtration rate (eGFR) and microalbuminuria vs. subclinical organ damage in patients with type 2 diabetes.

Methods. – Data from middle-aged patients with type 2 diabetes ($n = 706$) treated in primary care were analyzed for microalbuminura, defined as a urinary albumin/creatinine ratio (uACR) ≥ 3.0 mmol/mol, and reduced eGFR, defined as < 60 mL/min/1.73 m^2, in relation to blood pressure, pulse wave velocity (PWV), left ventricular mass index (LVMI), and carotid intima–media thickness (IMT) and lumen diameter (LD).

Results. – Patients with microalbuminuria had significantly higher 24-h ambulatory systolic blood pressure (ASBP) compared with subjects with uACR < 3 mg/mmol: 137 vs. 128 mmHg ($P < 0.001$). There were no differences in ASBP in patients with eGFR < 60 mL/min/1.73 m^2. However, patients with vs. without microalbuminuria had increased PWV (11.4 vs. 10.1 m/s; $P < 0.001$), LVMI (134.4 vs. 118.6 g/m^2; $P < 0.001$), LD (7.01 ± 0.93 vs. 6.46 ± 0.74 mm; $P < 0.001$) and IMT (0.78 vs. 0.74 mm; $P = 0.047$), respectively. The associations between uACR vs. PWV and LVMI were more robust after adjusting for age, diabetes duration, ASBP, HbA_{1c}, LDL-cholesterol, and antihypertensive and lipid-lowering therapy compared with uACR vs. IMT. There were no statistically significant differences in PWV, LVMI or IMT between patients with reduced (< 60 mL/min/1.73 m^2) vs. normal eGFR.

Conclusion. – Levels of urinary albumin excretion, but not reduced eGFR, were associated with increased arterial stiffness, left ventricular mass and atherosclerosis in patients with type 2 diabetes.

Keywords: Albuminuria; GFR; Cardiovascular disease markers; Atherosclerosis; Type 2 diabetes

1. Introduction

Microalbuminuria is associated with atherosclerosis risk factors as well as cardiovascular disease (CVD) [1–3], which may be explained in part by endothelial damage or dysfunction [4]. However, it is less clear whether modestly impaired renal function per se, as reflected by a decreased glomerular filtration rate (GFR), represents a risk factor for the development of atherosclerosis.

According to the 2002 clinical practice guidelines, renal impairment can also refer to chronic kidney disease (CKD) and, in adults, is defined as either kidney damage (including persistent proteinuria) or GFR < 60 mL/min/1.73 m^2 for ≥ 3 months [5,6]. A reduced GFR has been proposed as a risk factor for CVD in type 2 diabetes (T2D), and some studies have suggested that a decreased GFR is associated with an increased CVD risk in T2D

Abbreviations: ACE, Angiotensin-converting enzyme; ADA, American Diabetes Association; ARB, Angiotensin II receptor blocker; BMI, Body mass index; CARDIPP, Cardiovascular Risk Factors in Patients with Diabetes: a Prospective Study in Primary Care; CG, Cockcroft–Gault; CKD, Chronic kidney disease; CVD, Cardiovascular disease; DBP, Diastolic blood pressure; eGFR, Estimated glomerular filtration rate; IMT, Intima–media thickness (common carotid artery); KDOQI, Kidney Disease Outcomes Quality Initiative; MDRD, Modification of Diet in Renal Disease; LD, Lumen diameter (common carotid artery); LVH, Left ventricular hypertrophy; LVMI, Left ventricular mass index (body surface area); OAD, Oral antidiabetic drug; PWV, Pulse wave velocity; RAAS, Renin–angiotensin–aldosterone system; ASBP, Ambulatory systolic blood pressure; SBP, Systolic blood pressure; SD, Standard deviation; uACR, Urinary albumin/creatinine ratio.

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independently of microalbuminuria [7,8]. The aim of the present study was to explore the relationships between estimated GFR (eGFR) and microalbuminuria and subclinical vascular organ damage in T2D patients.

2. Patients and methods

Data from 706 patients who participated in the Cardiovascular Risk Factors in Patients with Diabetes: a Prospective Study in Primary Care (CARDIPP) was analyzed. The study was launched in 2005 and baseline data collection was completed in November 2008. The general aim of CARDIPP was to investigate cardiovascular risk factors in middle-aged patients with T2D to facilitate early and individually adjusted risk intervention. Patients aged 55–65 years were consecutively recruited during their usual annual follow-ups at 22 primary healthcare centres in the counties of Östergötland and Jönköping, Sweden, irrespective of their previous blood pressure and CVD status. The centres varied in size and were located in different geographical areas, but all followed the national guidelines for diabetes care. Patients with severe concomitant diseases such as cognitive impairment and cancer were not included.

Altogether, CARDIPP enrolled 761 patients, but because of missing data for microalbuminuria in 32 patients and no information on creatinine levels in 25 cases, 55 patients were excluded, leaving a total study sample of 706 subjects with a mean age of 61 ± 3 years and mean duration of T2D of 7 ± 6 years. The present study was approved by the regional ethics review board based in Linköping, and all participants gave their written informed consent.

A questionnaire also investigated the participants' lifestyle habits, including alcohol consumption and smoking status, while a standard medical history provided data on diabetes duration and ongoing medication.

As for diabetes treatments, 203 patients (28.8%) were treated by lifestyle recommendations only, 288 patients (40.8%) were treated by oral antidiabetic drugs (OADs) and 215 (30.5%) patients by insulin, either alone or in combination with OADs. Of the OADs, metformin was the most frequently used agent ($n = 372$, 52.7%), followed by sulphonylureas ($n = 107$, 15.2%). Among antihypertensive drugs, the use of renin–angiotensin–aldosterone system (RAAS) blockers such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) predominated ($n = 311$, 44.1%), followed by beta-blockers ($n = 250$, 35.4%), calcium antagonists ($n = 112$, 15.9%), thiazides ($n = 74$, 10.5%) and loop diuretics ($n = 53$, 7.5%). Treatment with lipid-lowering agents (statins) was found in 396 subjects (56.1%) and low-dose acetylsalicylic acid in 204 patients (28.9%).

Urine and blood samples for laboratory analyses were taken in the morning following at least 10 h of fasting. Routine blood tests were done and analyzed at the healthcare centres. The Swedish standard high-performance liquid chromatography (HPCL) Mono-S method was used to measure HbA_{1c}, although the data were then converted to Diabetes Control and Complications Trial (DCCT) standards (%) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units (mmol/mol). Other clinical data such as body weight, height and waist circumference were also recorded. Blood pressure was calculated as the average of three sitting measurements taken 1-min apart by specially trained nurses at each primary healthcare centre, and 24-h ambulatory blood pressure monitoring was performed with a Spacelabs Medical 90217 ABPM device (Spacelabs Healthcare, Issaquah, WA, USA).

Blood and urine samples were frozen for later analyses of plasma cystatin C, and urinary albumin excretion (UAE) rate was measured using the urinary albumin/creatinine ratio (uACR). Microalbuminuria was defined as uACR ≥ 3.0 mg/mmol for both men and women in accordance with the American Diabetes Association (ADA) definition [9]. However, as the larger muscle volume in men can affect uACR, this calculation was further supplemented by the UK National Institute for Health and Care Excellence (NICE) recommendations of uACR > 2.5 mg/mmol for men and > 3.5 mg/mmol for women [6]. Renal glomerular function was defined by eGFR, calculated by the Modification of Diet in Renal Disease (MDRD) study equation [10], as defined in Table 48 in the Kidney Disease Outcomes Quality Initiative (KDOQI) chronic kidney disease (CKD) guidelines [5]. Although patients' race was not noted, Caucasians are generally still strongly predominant in the Swedish population. As far as the present authors are aware, there were no black African participants in the study that generated the MDRD equation.

Reduced GFR was defined as < 60 mL/min/1.73 m^2, as in stage 3 of the CKD classification system, representing a loss of at least half the normal glomerular kidney function [5]. Also calculated were the eGFR based on cystatin C levels and absolute eGFR, using the Cockcroft–Gault equation.

Clinical physiological examinations were performed at the Department of Physiology of Linköping University Hospital and at County Hospital Ryhov in Jönköping. Common carotid intima–media thickness (IMT) was determined during diastole from still images of 10-mm sections taken in close proximity to the carotid bulb, using B-mode ultrasound to obtain mean carotid lumen diameter (LD) and far-wall IMT. Mean IMT and LD values calculated from two registrations on each side were used for all analyses. Arterial stiffness was evaluated in supine position by pulse wave velocity (PWV), measured as the transit time between carotid and femoral arterial pulse waves, and calculated by measurement of the surface distance at jugulum–carotid and jugulum–femoral locations, and by electrocardiogram (ECG)-gated recordings of the carotid and femoral arterial pulse waves using the foot-to-foot method, with the foot of the wave defined by the end of diastole. Echocardiography was performed with the patient in a left semilateral position, while left ventricular mass (LVM) was determined using the method described by Devereux and Reichek [11]; body surface area was calculated and expressed as g/m^2, as is most commonly recommended [12]. The LVM index (LVMI) based on height at an allometric power of 2.7 adapted for overweight patients to avoid underdiagnosis of left ventricular (LVH) [13] was also calculated.