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Obesity and changes in urine albumin/creatinine ratio in patients with type 2 diabetes: The DEMAND Study

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Abstract *Background and aims:* Obesity is a potential risk factor for renal disease in non-diabetic subjects. It remains unclear whether this also applies to diabetic patients. We investigated whether obesity predicted changes in albumin excretion rate in individuals with type 2 diabetes.

Methods and results: Fifty Italian diabetes outpatient clinics enrolled a random sample of 1289 patients. A morning spot urine sample was collected to determine urinary albumin/creatinine ratio (ACR) at baseline and after 1 year from the study initiation. Progression of albumin excretion was defined as a doubling in ACR, while regression was defined as a 50% reduction. Multivariate logistic regression analyses were used to evaluate correlates of these outcomes. Data are expressed as odds ratios (OR) with 95% confidence intervals (CI).

The risk of progression increased by 7% (OR = 1.07; 95%CI 1.00–1.15) for every 5-cm increase in waist circumference measured at baseline, and by 17% (OR = 1.17; 95%CI 1.03–1.33) for every one-unit increase in BMI during follow-up. The likelihood of regression was not independently associated with any of the variables investigated. The effect of obesity

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on progression of ACR was independent of metabolic control, blood pressure, treatment, and baseline level of albumin excretion.
Conclusions: We found a tight link between obesity and changes in albumin excretion in diabetic subjects, suggesting potential benefits of interventions on body weight on end-organ renal damage.

Introduction

Increasing values of urinary albumin excretion (UAE) are a risk factor for renal and cardiovascular disease [1,2], as well as for mortality [3]. Diabetes, hypertension, smoking and other factors are known to be associated with the development and progression of microalbuminuria (MAU) [4—6]. Abdominal obesity, measured by waist circumference, has recently received attention as a potential risk factor for renal disease in people who do not have diabetes [7—10]. It has been shown that abdominal obesity may be an early risk factor for increased albuminuria, independent of blood glucose, blood pressure, and renal function [7]. In a population-based longitudinal study, changes in weight were associated with parallel changes in albuminuria [11]. A relationship between abdominal obesity and development of MAU has also been shown in patients with type 1 diabetes [12]. Adipogenic inflammation and endothelial dysfunction related to visceral adiposity have been advocated as possible links between obesity and renal injury [13—15]. Diabetes is associated with a dramatic increase in the risk of end-stage kidney disease, particularly in presence of hypertension. It is still unclear whether obesity could act as an additional risk factor also in patients with type 2 diabetes. While data from the UKPDS show that increased waist circumference at baseline predicted the development of albuminuria independent of other known risk factors [9], it is still not known if changes in obesity indices over time are associated with changes in albumin excretion rate.

We investigate the role of obesity in predicting changes in albumin excretion rate in a cohort of individuals with type 2 diabetes.

Methods

The DEMAND (Developing Education on Microalbuminuria for Awareness of reNal and cardiovascular risk in Diabetes) study is a multicenter study involving 55 Italian Diabetes Outpatient Clinics. Every centre enrolled up to 36 patients during 2 weeks; sampling details have already been published elsewhere [4]. The study consisted of a cross-sectional phase and a longitudinal one.

Study population

Eligibility criteria for the DEMAND study were: T2DM according to WHO criteria [16], age between 18 and 80 years, both genders. Patients were excluded if they had type 1 or gestational diabetes, urinary infections, fever, menstrual cycle, overt diabetic nephropathy. All patients signed an informed consent at study entry.

Data collection

All patients underwent medical examination, and clinical data were collected on diabetes duration, cardiovascular risk factors, comorbidities and pharmacologic treatments, height, weight, waist circumference, and blood pressure (two measurements rounded to the nearest 2 mmHg in the sitting position after at least 5 min rest, using an appropriate-sized cuff; diastolic blood pressure was recorded at the disappearance of Korotkoff sound, phase V). A morning spot urine sample was collected, stored at −20 °C, and then sent on dry ice to a central laboratory (Department of Laboratory Medicine, University Milano-Bicocca, Hospital of Desio, Desio-Milano, Italy) at baseline and after 1 year from study initiation. Urinary albumin and creatinine concentrations were determined by the immune turbidimetric method (albumin tina-quant, Roche Diagnostics) and a kinetic Jaffé method performed with the Autoanalyzer Modular (Hitachi-Roche Diagnostics), respectively. The urinary albumin-to-creatinine ratio (ACR) was then calculated.

Since recent studies suggest that also values below the traditional threshold of 30—300 mg/g of ACR could well be a risk factor for adverse cardiovascular and renal outcomes, we chose to define progression of UAE as a doubling in ACR from baseline to follow-up and regression as a 50% reduction [17—20]. MAU was defined by values of ACR between 30 and 299 mg/g creatinine, while ACR $>$ 300 mg/g defined macroalbuminuria.

Glomerular filtration rate (GFR) was calculated using the MDRD formula [21].

Urinary infections were defined by presence of nitrites or leucocytes $\geq$250 leucocytes/ml in the urine sample. Patients with urinary infections were not included in the statistical analysis.

As normal ranges for glycated haemoglobin varied among different centres, the percentage change with respect to the upper normal value (actual value/upper normal limit) was estimated and multiplied by 6.0.

The study protocol was approved by local Ethics Committees at each participating centre.

Statistical analysis

Correlates of progression of UAE were initially examined by univariate analyses. Baseline characteristics are expressed as mean and standard deviation or median and 10th to 90th percentile range for continuous variables and frequencies and percentages for categorical data. Patients' characteristics according to normo/micro/macroalbuminuria and progression/regression of ACR were compared using Mann—Whitney *U*-test for continuous variables and Pearson χ^2 test