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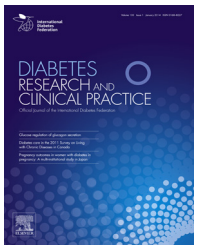

Impact of morbid obesity on the kidney function of patients with type 2 diabetes

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ABSTRACT

Aims: Type 2 diabetes and obesity impair kidney function. We examined their respective contributions to urinary albumin excretion (UAE) and glomerular filtration rate (GFR) in patients with type 2 diabetes and morbid obesity.

Methods: Cross-sectional, monocentric study of kidney function in patients with type 2 diabetes classified into four body mass index (BMI) stages: non-obese (<25 kg/m^2, $n = 157$); overweight (25 to <30, $n = 311$); obesity (30 to <40, $n = 310$); and morbid obesity (≥40, $n = 77$), with 84 similarly staged controls without diabetes. UAE classes were defined as normal (<30 μg/mg creatinine), microalbuminuria (30–299), or macroalbuminuria (≥300) from 3 consecutive urine samples. GFR was measured by ^{51}Cr EDTA plasma disappearance (adjusted and unadjusted to 1.73 m^2 body surface area, as obesity increases body surface).

Results: Participants with type 2 diabetes had same age, diabetes duration, and HbA1c across BMI stages. UAE was higher in participants with type 2 diabetes ($p < 0.0001$), and increased with obesity stages ($p < 0.0001$). After adjustment for age, sex, systolic blood pressure and type 2 diabetes status, morbid obesity was associated with a risk of microalbuminuria (OR 1.99, 95%CI 1.35–2.98, $p = 0.0007$) and macroalbuminuria (OR 2.33, 95%CI 1.25–4.22, $p = 0.006$). The body surface adjusted GFR was lower in patients with type 2 diabetes than in controls ($p < 0.0001$), and declined with obesity stages, contrary to controls. An interaction of diabetes and obesity was seen with unadjusted GFR values ($p = 0.002$).

Conclusions: Morbid obesity interacts with type 2 diabetes to aggravate UAE and GFR. Treatment strategies should focus on both conditions to protect kidney function in these patients.

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1. Introduction

The obesity burden is a major health problem, because it is a risk factor for conditions like diabetes or hypertension, pulmonary, or renal diseases. Type 2 diabetes is currently the most important source for end stage renal disease (ESRD), in addition to hypertension. However, obesity per se is another source for kidney disease [1].

Type 2 diabetes is currently frequent in young patients, who usually develop weight excess before overt diabetes. Until recently, patients with type 2 diabetes died prematurely from cardiovascular diseases. However, better prevention for cardiovascular complications allows more frequent survival till ESRD occurs [2]. So, improved cardiovascular prognosis and younger age at type 2 diabetes onset promote increased incidence of ESRD in the patients with type 2 diabetes, a health problem with major economic issues [3,4].

The nature of kidney disease is heterogeneous in patients with type 2 diabetes. Classical histological examinations reported in equal proportions findings seen in type 1 diabetes, in essential hypertension, and a mix of these two latter ones [5]. Such findings are consistent with the pictures reported in animal models of type 2 diabetes and obesity like in the Zucker rat [6]. Also, fat surrounding the kidneys, especially in the renal sinus as reported in obesity, can provoke albuminuria by itself in humans [7].

On the basis of the frequent association between type 2 diabetes and obesity, we ascertained the respective contributions of type 2 diabetes and of obesity to kidney function characterized by the urinary albumin excretion (UAE) and the glomerular filtration rate (GFR) during a prospective study. The GFR was measured directly using the ^{51}Cr EDTA plasma disappearance technique. We found an interaction between type 2 diabetes and obesity effects on both risks: elevated UAE and reduced GFR. We also calculated the fractional renal clearance of albumin (Fract Alb Cl), which indicates alterations of the glomerular function.

2. Materials and methods

2.1. Study design

This was a cross-sectional, prospective study conducted in the Diabetes-Endocrinology-Nutrition department of the Bichat-Claude Bernard University Hospital in Paris, France. From January 2012 to December 2013, 855 patients attending a one-day hospitalization for thorough evaluation of their conditions were asked on a consecutive basis to participate to the study. The following selection criteria were used: type 2 diabetes and various degrees of overweight as described below, no disease other than those known to be associated with type 2 diabetes and/or overweight such as hypertension or dyslipidemia. Eighty-four control participants without diabetes were recruited on a voluntary basis among employees of our institution. All participants gave their informed written consent. The study protocol was approved by the local Ethics Committee.

2.2. Measurement methods

Height, weight, and blood pressure were recorded by nurses. Current medications, demographic parameters, symptoms and signs were recorded by dedicated physicians (NB, NM, FT, and BH). Blood samples were taken on the fasting state for routine biologic analyses (glycemia, lipids, plasma creatinine, glycated hemoglobin (HbA1c), and hemogram). Blood pressure was measured with an automatic device (Dynamap®, France) using a cuff sized to the patient morphology, in a sitting position. Blood pressure was assessed three times consecutively at 3-min intervals, and the median value was recorded. The albumin concentration in the plasma and urine was measured by nephelometry [8]. The GFR was determined by the plasma disappearance of ^{51}Cr EDTA, as described earlier [9]. The GFR data were analyzed with and without adjustment to 1.73 m^2 body surface area.

2.3. Definition of parameters

The participants were considered as with type 2 diabetes using the ADA criteria [10]. Body mass index (BMI) was calculated as weight in kg divided by squared height in m. The participants were classified as having normal weight (BMI <25 kg/m^2), overweight (25 to <30 kg/m^2), obesity (30 to <40 kg/m^2), or morbid obesity (≥ 40 kg/m^2). Their levels of UAE were classified from 3 consecutive urine samples collected during outpatient visits before their hospital stays as persistently normal, microalbuminuria, or macroalbuminuria, if their urinary albumin/creatinine ratios (μg/mg) ranged ≥ 2 times within the following values: <30, 30–300, or >300. The GFR was measured using ^{51}Cr EDTA plasma disappearance technique [9]. Correction of values for body surface area used the Du Bois and Du Bois classical equation [11]. The measured values were compared with two estimated GFR (eGFR) from plasma creatinine, the Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations [12,13]. The GFR values are predominantly dependent on age, and an increase in GFR (glomerular hyperfiltration) may be a risk factor for ESRD, especially in diabetes. Thus, we classified each participant as having glomerular hyperfiltration, normal GFR, or reduced GFR from their body surface-adjusted GFR value by comparison to the 95% limits of the regression line between GFR and age in controls (range 20–80 years) we published previously, using the same measurement technique [9]. The Fract Alb Cl was calculated from the urinary clearance of albumin divided by the adjusted GFR measurement.

2.4. Statistical analyses

Results are presented as mean (SD) values for quantitative parameters with normal distributions, or as median (quartile ranges) values for the others, or as numbers (percentages), for the qualitative parameters. Analyses of covariance (ANCOVA) were performed on quantitative variables, after adjustment on confounders. Data were log-transformed before analysis, or non-parametric tests were used when the normality of the distribution was rejected by the Shapiro–Wilk W-test. Qualitative traits were analyzed by χ^2, or Mantel–Haenszel tests.