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Original Article

Differential associations between glomerular filtration rate and duration of obesity depending on the presence or absence of left ventricular diastolic dysfunction

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ABSTRACT

Background: A robust and consistent association between increasing body mass index (BMI) and chronic kidney disease (CKD) has been reported in several observational studies. Obesity remains the main preventable risk factor for CKD because it largely mediates diabetes and hypertension, the 2 most common etiologies for end-stage kidney disease (ESKD). Obesity is associated weakly with early stages of kidney disease but strongly with kidney progression to ESKD, even after adjustment for hypertension and diabetes.
Aim: To assess the relationship between estimated glomerular filtration rate (eGFR) and trans-thoracic echocardiography left ventricular function parameters in a cohort of patients with obesity.
Materials & methods: Cross-sectional study involving 324 obese (BMI = 44.0 ± 2.2 Kg/m^2) apparently healthy asymptomatic patients with an eGFR >60 ml/min/1.73 m^2. Each patient underwent transthoracic echocardiography and a blood testing. The eGFR was addressed by the CKD-EPI formula.
Results: All patients had a normal systolic function whereas 24.5% disclosed diastolic dysfunction (DD). Hypertension and type 2 diabetes mellitus prevalence were 34.5% and 4.5% (respectively). All patients disclosed an eGFR >60 ml/min while none of them disclosed hyperfiltration (eGFR >120 ml/min). eGFR correlated inversely with BMI and the duration of obesity and positively with diastolic function parameters ($P < 0.001$ for all, respectively). Patients with diastolic dysfunction displayed lower eGFR ($P < 0.0005$) and longer duration of obesity ($P < 0.0005$).
Conclusions: Obesity and its duration are likely to impose hemodynamic changes affecting simultaneously both heart (diastolic dysfunction) and kidney (decreased glomerular filtration rate). Larger prospective studies are warranted.

1. Introduction

Concurrent with the worldwide obesity and diabetes mellitus epidemics [1,2] there is a third epidemic of chronic kidney disease (CKD). The latter statement is supported by robust and consistent associations between CKD risk and increasing body mass index reported by several observational studies [3–5]. Obesity remains the main preventable risk factor for CKD because it largely mediates diabetes and hypertension, the 2 most common etiologies for end-stage kidney disease [6]. Furthermore, obesity itself may increase CKD risk by increasing the metabolic demands on the kidney, which leads to hyperfiltration, higher glomerular capillary pressures and glomerular hypertrophy [7,8].

The histological changes seen in the kidneys of morbidly obese adults frequently resemble those associated with secondary focal segmental glomerulosclerosis [9]. Pathways through which obesity might cause renal disease are not well understood; nevertheless, recent data point out that ectopic lipid accumulation (i.e. fatty kidney infiltration) is associated with structural and functional changes of mesangial cells, podocytes, and proximal tubular cells promoting the development of focal segmental glomerulosclerosis as a maladaptive response to hyperfiltration and albuminuria [10].

The most important index of renal function is the estimated glomerular filtration rate (eGFR) which can be calculated from creatinine besides other parameters (i.e. age, gender, weight and race, among others). Noteworthy, there is uncertainty regarding which formula best represents renal function in morbidly obese patients. Relying only on creatinine concentration to calculate GFR can lead to underestimation of renal malfunction in obese patients taking into account body size confounders [11]. Hence, assessment of renal function in morbidly obese patients requires an accurate method to improve patient safety with drug dosing as well as to ensure early detection of renal failure, among others.

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Since its appearance in the medical literature, the more accurate Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation has replaced the Modification of Diet in Renal Disease equation (MDRD) [12], especially at higher GFR, with less bias and greater accuracy [13]. Noteworthy, Cohen et al. data, using the CKD-EPI equation have been the first to suggest that morbid obesity may be an independent factor related to CKD in women [4].

Since publication of the Framingham Heart Study [14], obesity has been established as a coronary risk factor. Ever since, several other longitudinal studies have identified obesity as significantly increasing the incidence of coronary artery disease and heart failure for both genders [15,16]. Furthermore, a body mass index (BMI, Kg/m^2) increment of 1 kg/m^2 has been quantified to increase the risk of heart failure by 5% to 7% independent of other classic risk factors [17].

Impairment of cardiac function has been reported to correlate with BMI [18] and duration of obesity [19–21]. Most studies have reported abnormal diastolic function [22,23] without consistently associated systolic dysfunction in asymptomatic obese patients.

Since diastolic dysfunction is of paramount importance for cardiac hemodynamics – particularly during anesthesia – and glomerular filtration rate is fundamental for intravenous fluid management and drug dosage titrations, we conducted the current cross-sectional pilot study to assess the relationship among 1) eGFR (using the CKD-EPI formula), 2) obesity and its duration, and 3) echocardiographic parameters in a large sample of obese persons consecutively recruited in an obesity outpatient clinic in Barcelona, Spain, from January 1st 2012 until December 31st 2014.

2. Materials And methods

2.1. Patient population

Three hundred and twenty-four ($N = 324$; M 114/F 210) asymptomatic patients without underlying cardiac disease were included in the study. They were consecutively recruited from an Outpatient Obesity Clinic at Centro Médico Teknon in Barcelona, Spain from January 1st 2012 until December 31st 2014. Exclusion criteria were: current coronary artery disease, current/prior angina, or myocardial infarction, current/prior history of arrhythmia, cardiovascular co-morbidity (prior cerebrovascular accidents and/or peripheral vascular disease), current therapy with vasoactive drugs, ACE inhibitors, ARA IIs, diuretics, statins or fibrates, current/prior alcohol consumption averaging >60 g/day, active smoking, eGFR < 60 ml/min, presence of neoplasia and/or systemic disease, prior bariatric surgery and suboptimal echocardiographic window.

From age 18 on, the time period (years) in which patients had sustained a body weight corresponding to a BMI ≥ 30 Kg/m^2 was defined as the duration of obesity (in years). Briefly, the body weight (Kg) corresponding to a BMI of 30 Kg/m^2 was calculated as the squared height times 30, according to a previously reported formula developed by our group [21]. The duration of obesity information was obtained by the same trained observer (JY), using a systematic mode of in-person interview during the initial visit.

Anthropometrical measurements were performed by the same trained observer (JY) after the participants had removed their shoes and heavy clothing. Weight (digital scales: Seca, Germany) and height (portable stadiometers: Holtain, Crymych, UK) were obtained and BMI, defined as weight (Kg) divided by the height squared (in meters) was calculated. All the patients underwent a detailed clinical, biochemical and echocardiography study. Hypertension was defined by the European Study of Hypertension's criteria [24]. Written informed consent was obtained from each patient according to the standards established by the hospital's ethics committee.

2.2. Echocardiography

A standard two-dimensional M-mode color Doppler echocardiography was performed on all the patients using a 2.5 MHz transducer (ALOKA ProSound SSD-4000) by the same experienced echocardiographist (FP) according to an established protocol. Telediastolic and telesystolic left ventricular diameters were measured whereas volume and cardiac output were calculated according to Teicholz's formula [25]. Left ventricular mass (LVM) was calculated by means of Devereux's formula [26]. Left ventricular hypertrophy was defined according to Framingham's criteria (LVM/BSA > 110 g/m^2 in females and LVM/BSA > 134 g/m^2 in males) [26]. Left ventricle (LV), left atrium (LA) and inter-ventricle septum (IVS) measurements were determined according to the American Society of Echocardiography [27]. Intra-observer variability was estimated to be 0.0–1.0 mm and 5% for wall thickness assessment and LV diameters, respectively.

Overall ventricular diastolic function was assessed by early (E) and late (A) peak echo-Doppler mitral inflow velocities. An early mitral flow velocity to late mitral flow velocity ratio (E/A) < 1.0 was considered diagnostic of LVDD, whereas E/A ratios ≥ 1.0 were considered normal (non-LVDD) [28]. In addition, we measured peak E (Em), A (Am), and systolic tissue Doppler velocities by sampling of the mitral annulus. An early mitral annulus velocity to late mitral annulus velocity ratio (Em/Am) < 1.0 was considered diagnostic of LVDD, whereas Em/Am ratios ≥ 1.0 were considered normal (non-LVDD). In advanced stages of diastolic dysfunction (so called pseudonormalized and restrictive), the E/A ratio can be >1. The early mitral inflow velocity – sampled by pulsed Doppler – to the early mitral annulus velocity – sampled by TDI ratio (E/Em) – was obtained as an index of LV filling pressures [29,30].

2.3. Biochemical measurements

Blood samples were drawn from each subject after an overnight fast (10–12 h). Serum was spun at 4000 g for 10 min, immediately divided into aliquots, and frozen at −80 °C until analysis. Serum glucose concentrations were measured in duplicate by the glucose oxidase method with the use of a Beckman Glucose Analyzer II (Beckman Instruments, Brea, CA, USA). The coefficient of variation was 1.9%.

Insulin was measured using an immunocheminoluminometric assay (IMMULITE Diagnostic Products Corporation, Los Angeles, CA, USA). The intra- and inter-assay coefficient of variation was 3% and 7%, respectively. The cross-reactivity with pro-insulin was less than 0.01%. Cholesterol and triglycerides were measured by enzymatic methods, HDL-cholesterol after precipitation of apoB containing lipoproteins and LDL-cholesterol was calculated by Friedwald's formula. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI Eq. (12).

2.4. Statistical analysis

Before statistical analysis, normal distribution and homogeneity of the variances were tested. Qualitative variables are expressed as sample size (number of cases) and percentage (%), and quantitative variables are expressed as mean and standard error of the mean (SEM). The relationship between two qualitative variables was assessed using Chi-squared test with a continuity correction whenever necessary. The differences between eGFR (Fig. 1A) and duration of obesity (Fig. 1B) according to the presence of absence of left ventricular diastolic dysfunction were assessed using unpaired student's t-test. The relationship between two continuous variables was assessed using Pearson's correlation coefficient whereas Mann–Whitney's test was used between binary and continuous variables. A multivariate ANOVA regression analysis was performed with eGFR being the dependent variable and gender, age and BMI being the independent variables (Table 4). The level of statistical significance was set at $P < 0.05$. Data were analyzed and figures constructed using the SPSS 15.0 statistical package (SPSS Inc., Chicago, IL, USA).