The Predictive Value of CRP Levels on Future Severe Renal Disease in Overweight and Obese Subjects Without Diabetes Mellitus and Hypertension

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ABSTRACT: *Background:* Obesity and related disorders have a high prevalence all over the world. Increased C-reactive protein (CRP) value in obese individuals and its potential adverse effects have been reported. Here we have investigated the relationship between CRP levels and renal functions in nondiabetic, nonhypertensive, overweight, and obese individuals. The aim of this study was to evaluate the predictive value of CRP levels on future severe renal disease. *Methods:* One hundred sixty individuals were included in the study. They were grouped as normal weight, overweight, and obese. Anthropometric measurements, renal function tests, and serum hsCRP values were obtained. Mean values were compared and correlation analysis was performed. Results: Significant differences were detected between the groups according to body mass index, waist circumference (WC), and body fat percentage. There was a significant difference with respect to creatinine clearance (CC). Difference in the mean urinary albumin excretion (UAE) was significant between normal-weight and overweight subjects. There was a linear increase in serum CRP values in parallel to the increase in body weight; mean values were significant between groups. A positive correlation was detected between CC and body mass index and WC, and there were significant correlations between CRP and anthropometric measurements, CC and UAE. *Conclusions:* This study showed that increased CRP levels in nondiabetic, nonhypertensive, overweight, and obese individuals could possibly associated with impaired renal functions that might be originating from endothelial dysfunction. Determination of cutoff levels of CRP, as in cardiovascular diseases, may be useful for early estimation and prevention of renal diseases. **KEY INDEXING TERMS:** Obesity; Overweight; Anthropometric measurements; C-reactive protein; Renal functions. **[Am J Med Sci 2007;334(6):444–451.]**

A body fat percentage (BFP), higher than 25% in males and 35% in females, is defined as obesity.[1,2] In the United States, it has been reported that at least 64% of adults are overweight and more than 30% are classified as obese.[3] Although there is limited knowledge about the Turkish population, it is known that 25.2% of males and nearly half of the female population (44.2%) over the age of 30 years are obese,[4] and these rates increase with age. Due to the presence of many obesity-related disorders, such as coronary artery disease (CAD), diabetes mellitus type 2 (DM-2), hypertension (HT), hyperlipidemia (HL), some malignancies, gallstone disease, gout, obstructive sleep apnea syndrome, and stroke, obesity ranks as one of the most serious health problems that we face today.

C-reactive protein (CRP) is a sensitive indicator of systemic inflammation. Serum CRP concentrations are considered as a risk factor for cardiovascular disease and have prognostic importance in patients who have coronary disease.[5] CRP may also be a significant parameter for renal diseases.[6]

The CRP value may change with the degree of obesity,[7] and this effect may be secondary to the release of a proinflammatory cytokine (such as interleukin-6) from the adipocytes.[8] Additionally, studies about the negative effects of obesity on the kidneys, especially in patients with renal diseases, and the relationship between obesity and CRP and abnormal renal functions and CRP have been reported.[8–12] Several studies have examined the asso-

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ciation between renal function disorders and inflammatory cytokines.[13,14] These studies have indicated that cytokines such as TGF-β1 may be associated with the progression of renal disease in patients with obesity and hypertensive renal disease. One study indicated that TGF-β1 might be considered a useful marker to evaluate the severity and progression of hypertensive renal disease.[13] A second study[14] indicated that TGF-β1 overproduction might be considered as the mechanism of pathophysiology in progressive renal function impairment in obese hypertensive individuals.

On the other hand, the relationship between CRP and renal functions in nondiabetic, nonhypertensive, overweight, and obese individuals, compared with normal-weight individuals, has been relatively under-reported.

We hypothesized that CRP may be a predictor of renal impairment in these groups of individuals. The aim of this study was to investigate the effects of the CRP levels of both groups on renal functions and to evaluate the predictive value of CRP levels on future severe renal disease. This important issue has been addressed in the current study.

Patients and Methods

Male and female patients, between the ages of 20 and 45 years, admitted to the Internal Medicine Polyclinic at the Medical Faculty of Abant Izzet Baysal University, Duzce, Turkey, between January and March 2004, were involved in the study. Anthropometric measurements, renal function tests, and serum CRP values were obtained for each participant. Mean values of these parameters were compared, and the degree of relationship between them was demonstrated.

One hundred and sixty individuals (105 female and 55 male) participated for the study and continued follow-up visits from a group of 186 individuals who accepted to involve to this study at the beginning. Twenty-six of 186 individuals who had previously agreed to participate were unable to complete the necessary measurements due to various reasons such as failure to turn up for appointments, collection of urine, etc. Therefore, they were excluded from the study. No special measures were taken to establish and in place to minimize the attrition rate.

As dictated by the World Health Organization (WHO) criteria, these individuals were subdivided into three groups: obese (body mass index [BMI] $\geq$ 30 kg/m^2), overweight (25 $\leq$ BMI $<$ 30 kg/ m^2), and normal weight (BMI $<$25 kg/ m^2).[15] Full physical examination, medical history, arterial blood pressure (BP), radial pulse, height, weight, waist circumference (WC), and hip circumference (HC) of all individuals were obtained. Body fat percentage (BFP) was calculated via bioelectrical impedance assay (Body Composition Analyzer, type TBF-300m, Tanita, Tokyo, Japan). Bioelectrical impedance assay (BIA) has been used in a previous study and has demonstrated a high degree of correlation with dual-energy x-ray absorptiometry-derived fat measurements ($R = 0.9$; $P < 0.0001$).[16]

After an overnight fasting period (12 hours), whole blood count, erythrocyte-sedimentation rate (ESR), CRP, blood glucose (BG), plasma insulin, lipid profile including total cholesterol (TC), high-density lipoprotein-cholesterol (HDL), low-density lipoprotein-cholesterol (LDL), and triglyceride (Tg), blood urea nitrogen (BUN), creatinine, and albumin values were measured by using venous blood samples. Insulin resistance was calculated via Homeostatic model assessment (HOMA-IR).[17] In addition, after a 75 g oral glucose loading, a 2nd-hour BG measurement was also carried out. For measurement of ESR, the Westergren method was used.[18] CRP was measured over 2 separate days, first via a nephelometrical method by using a high-sensitivity CRP reagent kit and then via automatic measurement by titration, and the mean value was taken as the final value. Serum creatinine, BUN, total protein, and albumin were assayed by using appropriate kits (Olympus optical, Tokyo, Japan).

A 24-hour urine collection in sterile cool containers (polystyrene tubes, Corning Inc, Corning, NY) was obtained for each subject, and they were sent immediately to the laboratory for testing. Urinary albumin and creatinine were assayed via photometric color (Olympus albumin, Tokyo, Japan) and kinetic color (Jaffe method) tests, respectively. This test was performed twice for each patient to make diagnosis. Urinary albumin excretion (UAE) was represented as milligrams per day, calculated by using the formula: mg/dL urine volume/100. Creatinine clearance (CC) was calculated as milliliters per minute by the formula: urinary creatinine urinary volume/serum creatinine 1440.[19] UAE below 30 mg/d is considered normal. Normal values of CC for adult population are 90 to 140 mL/min/1.73 m^2.[19]

Patients with a history of renal disease or with signs of it, already hypertensive patients and newly diagnosed ones, detected via a 10-day home blood pressure measurement ($\geq$140/90), prediabetics and diabetics (prediabetes are defined as having impaired fasting glucose (FPG, 100 to 125), and/or impaired glucose tolerance (2HPG 140 to 199) and diabetes is defined as FPG $>$126 and/or 2HPG $>$200 according to the criteria of American Diabetes Association, 2003), and patients with any malignant, infectious, immunologic, allergic, or near-onset hypoxic or traumatic (in the last 24 to 48 hours) condition affecting the CRP value were excluded from the study.

Statistics

Statistical analysis was done by SPSS version 13.0. Data are expressed as range and mean $\pm$ standard deviation. Comparisons between the groups were performed via one-way ANOVA post hoc LSD test, and relationships between the measurements were calculated via nonparametric Spearman's correlation test. Relationships between the variables are shown in Figures 1 through 3. Multiple regression analysis was performed to assess the correlations between independent variables (obesity measurements) with serum CRP as dependent variables. A value of $P < 0.05$ was accepted as statistically significant.

Results

One hundred sixty individuals were divided into 3 subgroups: normal weight (32 females, 15 males; 29.4%), overweight (35 females, 22 males; 35.6%), and obese (38 females, 18 males; 35.0%). There was no statistically significant difference between groups according to female/male ratio, detected via χ^2 method ($P = 0.705$). Additionally, there was no statistically significant difference according to age, height, and mean values of systolic and diastolic blood pressures; however, significant differences were detected on the basis of weight, BMI, WC, HC, waist/hip ratio (WHR), and BFP (Table 1 and Table 2).

Statistically significant differences were also observed according to 2nd-hour BG (p = 0.001), HOMA insulin resistance (HOMA-IR) ($P = 0.041$), TC ($P < 0.001$), Tg ($P < 0.001$), LDL-C ($P < 0.001$), BUN ($P = 0.043$), CC ($P < 0.001$), UAE ($P = 0.048$), serum albumin ($P = 0.026$), CRP ($P < 0.001$), and ESR ($P < 0.001$ among the 3 groups (Table 2). The P value for the fasting plasma insulin level was 0.051. Relation-