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Original article

Determinants of low levels of brain natriuretic peptide in morbid obesity

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SUMMARY

Background & aims: morbid obesity is associated with cardiovascular comorbidity. A noteworthy feature of this relationship could regard low levels of brain natriuretic peptide (BNP). The study investigates the relationship between BNP and obesity-related markers in a morbid obese population, along with echocardiographic and vascular parameters.

Methods: in 154 morbid obese patients we evaluated anthropometric parameters, glycometabolic/lipid profile, bioimpedentiometry, echocardiography, visceral fat area and flow-mediated dilation (FMD) by ultrasonography.

Results: we divided population in two groups on the basis of median BMI levels; patients with higher BMI had significantly lower BNP ($p = .008$), FMD ($p = .014$) and HDL-C ($p = .001$) and showed a more impaired heart function. A similar trend emerged subdividing patients on the basis of median visceral fat area. BNP showed a significant inverse correlation with BMI ($p < .001$), left ventricular mass ($p = .026$) and inter-ventricular septum thickness ($p = .007$) and a significant positive correlation with FMD ($p = .008$), HDL-C ($p = .022$), and ejection fraction ($p = .013$). BMI and triglycerides were independent predictors of BNP levels.

Conclusions: patients with higher BMI show lower BNP levels associated with greater total body fat amount. The correlation of BNP with endothelium-dependent vasodilation and cardiac impairment could represent another link between obesity and cardiovascular damage.

1. Introduction

Obesity, a chronic pathology with multi-factorial etiopathogenesis and multiple clinical manifestations, is showing an increasing prevalence all over the world [1]. A peculiar aspect of this "pandemic" spread is the rise of morbid obesity, characterized by a body mass index (BMI) above 40 kg/m^2 [2]. This growing prevalence is associated with a significant increase of obesity-associated co-morbidities, such as diabetes, dyslipidemia, steatohepatitis, hypertension, ischemic cardiomyopathy, osteoarticular, respiratory and neoplastic pathologies, with loss in life expectancy and quality of life [3].

A noteworthy feature of the relationship between obesity/visceral adiposity and cardiovascular impairment concerns brain natriuretic peptide (BNP) circulating levels [4,5]. Several recent studies have shown the inverse correlation between BMI, waist circumference and BNP concentration, both in hypertensive and heart failure subjects [6,7]; indeed, obese and overweight subjects show BNP circulating levels significantly lower than non obese subjects [8]. The reasons of this paradox are not fully understood, with different Authors suggesting that overall adiposity, visceral fat and concomitant hyperinsulinemia could play a key role [9,10]. To our knowledge, no data about this issue are available in morbid obesity.

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The purpose of our study is to investigate the relationship between BNP and obesity-related markers (BMI, visceral fat, insulin resistance, lipids) in a morbid obese population, along with echocardiographic and vascular parameters.

2. Materials and methods

154 morbid obese patients (52 males, 102 females, mean BMI 44.79 kg/m^2) referring to our clinic to evaluate eligibility for bariatric surgery, were included in the study. Inclusion criteria were BMI $\geq$40 kg/m^2 or $\geq$35 kg/m^2 with co-morbidities and age between 18 and 65 years. We excluded from the study those with liver and renal insufficiency, heart failure (NYHA II-IV), secondary causes of obesity, major psychiatric diseases.

The study protocol was approved by Ethics Committee of our Institution, and all subjects provided their written informed consent. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

In all patients we evaluated weight, height, BMI, waist and hip circumference, blood pressure.

2.1. Serum analyses

The following parameters were determined: glycemia (automated analyzer), insulinemia (Elisa), total cholesterol (TC), triglycerides (TG, enzymatic colorimetric method), LDL cholesterol (LDL-C, Friedewald formula), HDL cholesterol (HDL-C, enzymatic colorimetric method following precipitation with polyethylene glycol), brain natriuretic peptide (BNP, Triage test – two-site immunoenzymatic "sandwich" assay). The homeostasis model assessment-insulin resistance (HOMA-IR) was used to determine insulin-resistance. We also performed bioimpedentiometry, echocardiography, ultrasonography measurement of visceral fat area and flow-mediated dilation at brachial artery.

2.2. Bioimpedentiometry

Bioimpedentiometry (50 kHz, amplitude 50 mA, Body Composition Analyzer TBF-410GS, Tanita, Tokyo, Japan) with electrodes applied to the foot plantar surface was used to determine fat mass in kilograms and as a percentage of body weight.

2.3. Visceral fat area

Visceral fat area (VFA), expressed in cm^2, was measured by ultrasonography (MyLab 50, Esaote, Genoa, Italy) according to Hirooka formula [11]. The thickness of subcutaneous fat layer was measured by using a 7.5-MHz linear array probe and performing a longitudinal scan 1 cm below xiphoid apophysis. Subcutaneous fat thickness was defined as the distance between the skin and external face of the rectus abdominal muscle and expressed in mm. Ultrasonography was always performed by the same operator, an experienced sonographer, the intra-operator inter-day coefficient of variation was 1.8%.

2.4. Flow mediated dilation

Brachial artery ultrasonography (Technos MP; Esaote, Genoa, Italy) was used to measure flow mediated dilation (FMD), the percentage change of arterial diameter from baseline vessel size after reactive hyperaemia at brachial artery. The exam was performed on non-dominant arm while patient was resting in supine position, between 8 a.m. and 10 a.m., after 10–20 min rest in a quiet, dark room with a temperature of ~22 °C. Measurements were performed on a straight, non-branching segment of brachial artery above the ante-cubital fossa, and reactive hyperaemia was induced by blood pressure cuff inflation and deflation. Basal and post-hyperaemia diameter were recorded during end diastole and the average of 3 measurements was used for the analysis.

2.5. Echocardiography

Echocardiograms were acquired with a commercially available device (MyLab 50, Esaote, Genoa, Italy). Left ventricular (LV) diameters (i.e. end-systolic diameter, end-diastolic diameter) were acquired from conventional apical 2-chamber and 4-chamber images, and LV ejection fraction was calculated using biplane Simpson technique. Left ventricular mass was calculated using Devereux formula, indexed for height. The left ventricular diastolic filling pattern was recorded from the apical transducer position in patients the partial left lateral decubitus position during expiratory apnea, with the sample volume situated between the mitral leaflet tips. Tracings were read by two observers, unaware of patients clinical data.

2.6. Statistical analysis

Normal distribution of variables was checked with Kolmogorov–Smirnov test. Normally distributed data are expressed as mean plus standard deviation; non normally distributed data are expressed as median value plus inter-quartile range. Direct comparisons were performed using a Student's T-Test for normally distributed variables and Mann–Whitney U-test for non normally distributed ones. Since many variables explored with direct confrontation are known to be correlated, we performed linear model analysis to test the possible interactions with ANCOVA. Spearman's rank correlation coefficients tested the relationship between the variables. Stepwise regression analysis assessed the independent contribution of several variables to BNP levels, FMD and left ventricular mass. Analyses were performed using SPSS software (version 17.0; SPSS, Inc., Chicago, IL), with statistical significance set at $p < .05$.

3. Results

Characteristics of patients are reported in Table 1, differences between the two genders are displayed in Table 2. We divided population in two groups on the basis of median BMI levels, below/equal or above 43.5 kg/m^2.

Patients with higher BMI (n. 78) had significantly higher systolic and diastolic blood pressure (respectively 140 (IR 130–154) mmHg vs 130 (IR 122.5–140) mmHg, $p < .001$ and 90 (IR 80.5–93.5) mmHg vs 84 (IR 80–90) mmHg, $p = .006$), waist circumference (144.1 ± 14 cm vs 119.9 ± 11 cm, $p < .001$), fat mass percentage (47.9 ± 6% vs 44.1 ± 6%, $p < .001$), visceral fat area (295.5 ± 58 cm^2 vs 212.9 ± 51 cm^2, $p < .001$), HOMA-IR levels (5.6 (IR 3.7–8.4) vs 3.2 (IR 2.1–4.4), $p < .001$) and triglycerides (144 (IR 104.5–197.5) vs 111 (IR 82.8–169), $p = .011$), and significantly lower BNP (8 (IR 6–17.3) pg/ml vs 16 (IR 11–24) pg/ml, $p < .001$), FMD (9.0 ± 6% vs 12.0 ± 6%, $p = .014$) and HDL-C levels (43 (IR 37–49.3) mg/dl vs 49 (IR 42.3–61.8) mg/dl, $p = .001$). No significant differences were found concerning age (44.6 ± 11 vs 42.1 ± 10, $p = .149$) and LDL-C (111.5 ± 28 vs 110.6 ± 26, $p = .841$) between the two groups.

Among echocardiographic parameters, patients with higher BMI showed significantly higher inter-ventricular septum thickness (12.2 ± 2 mm vs 11.0 ± 2 mm, $p < .001$), end-diastolic and end-systolic diameters (respectively 50.5 ± 5 mm vs 48.2 ± 5 mm, $p = .008$ and 29.3 ± 4 mm vs 27.9 ± 4 mm, $p = .048$) and left

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