ORIGINAL ARTICLE

Cardiovascular risk in overweight/obese and lean hypertensive patients

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KEYWORDS
Cardiovascular risk; Obesity; Overweight; Arterial hypertension

Abstract
Introduction: Obesity and hypertension have been identified as independent risk factors for cardiovascular disease. Nevertheless, the role of obesity in the development and progression of target-organ disease in hypertensive patients is controversial. The objective of this study was to assess the impact of body weight on cardiovascular risk factors, target-organ disease and global cardiovascular risk in hypertensive patients in a primary care setting.

Methods: A cross-sectional observational study was carried in Vila Nova de Gaia, Portugal (n=150). A detailed medical and personal history was obtained and a physical examination was performed. Venous blood and 24-hour urine samples were collected, and an electrocardiogram was performed. Cardiovascular risk was assessed using the Framingham score. The statistical analysis was performed using SPSS®. A p-value <0.05 was considered statistically significant.

Results: The sample was 71.8% female, with a mean age of 74.3±10.8 years. The prevalence of obesity was 29.5%. Overweight/obese subjects presented lower mean HDL cholesterol (51.2±13.9 mg/dl vs. 65.4±35.2, p<0.005), higher triglycerides (137.8±70.4 mg/dl vs. 111.5±68.8 mg/dl, p=0.001), higher fasting glucose (111.9±32.8 mg/dl vs. 98.4±13.1 mg/dl, p<0.011) and more frequent mild valve disease (57.9% vs. 29.6%, p=0.021). Global cardiovascular risk was also significantly higher (10.9±7.7 vs. 6.5±5.7, p<0.001).

Conclusion: Overweight and obesity appear to be related to a less favorable lipid and blood glucose profile and higher cardiovascular risk in hypertensive patients. On the basis of our findings we suggest strict metabolic monitoring and improved education on weight reduction and control at primary health care clinics.

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Introduction

Obesity is a major health problem in developed countries. According to a World Health Organization report, over 200 million men and nearly 300 million women were obese in 2008. Sedentary lifestyles, increasingly lipid-rich diets and reduced energy expenditure are among the main risk factors for obesity.

Obesity is closely linked to hypertension. It is well documented that obese patients are more likely to be hypertensive than lean individuals and that excess weight is predictive of subsequent onset of hypertension. In the Framingham Heart Study, 70% of cases of hypertension in men and 61% in women were directly attributed to excess adiposity, and it is estimated that each 5-kg increase in body weight leads to a mean increase of 4 mmHg in systolic blood pressure (BP) in both genders. An analysis comparing data from two National Health and Nutrition Examination Surveys (NHANES), 1998–1994 and 1999–2004, also showed that increased body mass index (BMI) accounted for nearly all of the increased prevalence of hypertension in men and for some of the increased prevalence in women.

Both obesity and hypertension have been identified as independent risk factors for cardiovascular disease in the Framingham Heart Study.

Nevertheless, the role of obesity in the development and progression of target-organ disease in hypertensive patients is controversial. Analysis of the Framingham Heart Study shows that the risk ratio for cardiovascular events was basically similar in lean and obese hypertensives. These studies are in contrast to several large-scale prospective studies that showed obese hypertensives to be at a lower risk of cardiovascular disease than lean hypertensives. A review of 11 prospective studies suggested that the risk of major coronary artery disease-related events in lean hypertensive men was not higher than in overweight/obese (OW/Ob) hypertensive men. It is difficult to explain the discordant results of the various studies, and several studies have been carried since then in order to assess and compare cardiovascular risk in obese and non-obese hypertensive patients.

The objective of this study was to evaluate the impact of increased body weight on cardiovascular risk factors and global cardiovascular risk in hypertensive patients in a primary care setting.

Methods

Study design

A cross-sectional, observational, descriptive and analytical study was performed in the city of Vila Nova de Gaia, Portugal.

The study population consisted of individuals with a known diagnosis of hypertension, enrolled in a primary care unit in the city. Patients without a telephone, and those who were hospitalized or institutionalized, were excluded.

The sample size of 142 participants was calculated with the Survey System online calculator (www.surveysystem.com), for a population of 2805 diagnosed hypertensive patients in the primary care unit.
with a 95% confidence interval and confidence level of 8. To cover for possible losses, this number was increased to 160 individuals. A simple randomized sample of hypertensive patients was selected using random number generating software (http://www.random.org). The response rate was 97.5%, corresponding to 156 hypertensive subjects.

Data collection

The participants were invited by telephone to attend the primary care unit for a personal interview with the principal investigator. When possible the interview took place on a day when the patient had a scheduled consultation, to avoid travel costs. The nature and purpose of the study were explained, and data confidentiality was assured. Written informed consent was obtained according to the Helsinki Declaration of the World Medical Association.

A detailed medical and personal history was obtained. Cardiac disease was defined as documented history of myocardial infarction, angina, heart failure or revascularization surgery. Cerebrovascular disease was defined as documented history of transient ischemic attack (TIA) or stroke. Clinical peripheral arterial disease was defined as a previous diagnosis or current symptoms. Whenever necessary, clinical information was confirmed by the patient’s medical record, particularly for possibly doubtful variables (history of TIA or peripheral arterial disease).

A physical examination was performed which included anthropometric measures, BP, ankle-brachial index (ABI) and fundoscopy.

Body weight and height were assessed using a calibrated mechanical scale platform (Jofre® model 6, Portugal), with a maximum capacity of 110 kg and 100 g resolution for weight, and a maximum capacity of 250 mm and 1 mm resolution for height. These measures were obtained with individuals wearing light clothing and barefoot, following the techniques recommended by Lohman et al. BMI was calculated as weight in kg divided by height in meters squared, and classified using the cut-offs recommended by the World Health Organization: BMI ≤18.4 kg/m² underweight, 18.5–24.9 kg/m² normal, 25.0–29.9 kg/m² overweight, 30.0–34.9 kg/m² moderate obesity, and 35.0–39.9 kg/m² severe obesity.

Waist circumference was measured above the navel, and averaged from three consecutive measurements for greater accuracy. Abdominal obesity was defined as >102 cm (males) or >88 cm (females).

BP was assessed with a validated Omron® M-5 manual sphygmomanometer, with a maximum of 300 mmHg and resolution of 2 mmHg. Individuals were assessed after a minimum of 10 minutes rest in a sitting position. Three readings were taken on the left arm, two minutes apart; the first value was discarded, and the mean of the two subsequent measurements was considered for the statistical analysis, as described in the guidelines of the European Society of Hypertension. ABI was assessed using an appropriate cuff size (width at least 40% of the limb circumference) and the ankle cuff was placed just above the malleoli with the straight wrapping method, in accordance with the American Heart Association guidelines (http://circ.ahajournals.org/content/early/2012/11/15/CIR.0b013e318276fbcb.full.pdf). Subclinical peripheral arterial disease was defined as an ABI <0.9.

Fundoscopy was performed by the principal investigator. If pupil dilation was not possible, advanced retinopathy was assumed (defined as the presence of hemorrhage, papilledema or exudates) in order to avoid misdiagnosis as milder forms of retinopathy.

Laboratory tests were performed. All subjects remained on their usual diet, with no changes in food intake except for an overnight fast of 12–13 hours. Subsequently, a fasting blood sample was taken to measure glucose, creatinine, and serum lipid concentrations (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), and 24-hour urine was collected for assessment of urinary albumin excretion.

Fasting glucose was used to define the presence of impaired fasting glucose for values between 102 and 126 mg/dl. Diabetes was defined as a previous diagnosis or anti-diabetic treatment, fasting glucose >126 mg/dl, or casual blood glucose >200 mg/dl in the presence of suggestive symptoms.

Dyslipidemia was defined as a previous diagnosis or lipid-lowering treatment, or LDL cholesterol >115 mg/dl or HDL cholesterol <40 mg/dl (males) or <46 mg/dl (females) or triglycerides >150 mg/dl.

Renal function was assessed by serum creatinine (normal 1.3–1.5 mg/dl in males, or 1.2–1.4 mg/dl in females; renal disease above these values), albumin urinary excretion in 24-hour urine (defined as microalbuminuria if 30–300 mg/24 hours) and creatinine clearance (CrCl) by the Cockcroft-Gault formula. The online calculator at http://www.nephron.com/cgi-bin/CGSI.cgi was used to calculate CrCl.

An electrocardiogram was performed in all participants and, when necessary to clarify other symptoms, an echocardiogram. Left ventricular hypertrophy (LVH) was defined electrocardiographically as a Sokolow-Lyon index >38 mm or, echocardiographically, by left ventricular mass index >125 g/m² (males) or >110 g/m² (females).

Cardiovascular risk was assessed according to the Framingham score (using the online calculator at http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof), since we aimed to assess the risk for both fatal and non-fatal cardiovascular events, and the Systematic Coronary Risk Evaluation (SCORE), although validated in European populations, only assesses the risk for fatal events. Furthermore, the age range limitations of SCORE (45–64 years) would exclude older patients, who represent a growing proportion of hypertensive patients observed in primary care.

Statistical analysis

The statistical analysis was performed using SPSS® version 12.0. Data are shown as mean ± standard deviation. Differences between groups were analyzed with Pearson’s chi-square test for discrete or categorical variables, while one-way analysis of variance was used for continuous variables. Multivariate analysis of variance was used to assess the independent effect of each variable while adjusting for the influence of potential confounders. A p-value of <0.05 was considered statistically significant.
The study was approved by the ethics committee of the São João Primary Care Center/University of Porto Medical School.

Results

The overall population characteristics are summarized in Table 1.

The mean age of the study sample was 74.3 years. Lean subjects were older (77.0±9.7 vs. 73.2±11.1, p=0.002), and so adjustments for age were performed in the statistical analysis. Females accounted for 71.8% of the participants. Mean systolic and diastolic BP were 136.6±18.2 mmHg and 71.0±9.9, respectively, showing good BP control. These data are consistent with the therapeutic approach in this sample, as only a minority of participants were on anti-hypertensive monotherapy (3.0%) (Table 1). Although overall BP control was acceptable, 21.8% (n=34) were not under any pharmacological treatment.

The prevalence of obesity was 29.5%, and the most common BMI class was obesity grade I (20.5%). The distribution by BMI class is summarized in Table 1. The mean waist circumference of the overall sample was 103.6±9.2 cm.

An overall prevalence of dyslipidemia of 79.5% was found (Table 2). No statistical differences were found between normal weight and OW/Ob hypertensive individuals. Although mean total cholesterol and LDL cholesterol did not differ between the two groups, mean HDL cholesterol was lower in OW/Ob patients compared to normal weight participants (51.2±13.9 mg/dl vs. 65.4±35.2, p<0.001). Mean triglyceride levels were also significantly higher in the OW/Ob group (137.8±70.4 mg/dl vs. 111.5±68.8 mg/dl, p=0.034).

The prevalence of type 2 diabetes was higher in the OW/Ob group (44.6% vs. 13.6%), and this difference was statistically significant (p<0.001). Fasting glucose levels were higher in this group as well (111.9±32.8 mg/dl vs. 98.4±13.1 mg/dl, p<0.011). No statistical differences were found in impaired fasting glucose (Table 2).

Of the 156 participants, 102 underwent 24-hour urinary albumin assessment (65.4%). The prevalence of microalbuminuria was 15.7%, and did not differ between the groups (p=0.558). A tendency was observed for higher mean urinary albumin excretion in the OW/Ob group (35.3±103.8 mg/24 hours vs. 19.6±23.8 mg/24 hours), although this was not statistically significant (p=0.466) (Table 3).

The prevalence of target-organ disease is described in Table 4. In the overall sample, the most prevalent was cardiac disease, followed in order of decreasing prevalence by mild valve disease (50.5%), LVH (accordine to echocardiographic criteria, 16.2%), heart failure (10.3%) and myocardial infarction (5.1%). The least prevalent was peripheral arterial disease, with no cases identified (0.0%).

Unadjusted p values only showed significant differences between the groups in the case of LVH (using electrocardiographic criteria). Nevertheless, after multivariate analysis of variance for age, gender, duration of hypertension and dyslipidemia, only the grade of valve disease remained statistically significant (p=0.021). Mild valve disease was more frequent in OW/Ob than in their lean counterparts (57.9% vs. 29.6%). Nevertheless, the same effect was not observed for moderate valve disease, which may be due to the small

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Overall population characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>74.3±108</td>
</tr>
<tr>
<td>Gender (% , n)</td>
<td>Male 28.2 (44) Female 71.8 (112)</td>
</tr>
<tr>
<td>Body weight, kg (mean ± SD)</td>
<td>71.1±14.1</td>
</tr>
<tr>
<td>Body mass index, kg/m² (mean ± SD)</td>
<td>28.0±5.5</td>
</tr>
<tr>
<td>World Health Organization class, kg/m²</td>
<td>Normal 29.5 (46) Overweight 41.0 (64) Obesity grade I 20.5 (32) Obesity grade II 5.1 (8) Obesity grade III 3.9 (6)</td>
</tr>
<tr>
<td>Waist circumference, cm (mean ± SD)</td>
<td>103.6±9.2</td>
</tr>
<tr>
<td>Blood pressure, mmHg (mean ± SD)</td>
<td>Systolic 136.6±18.2 Diastolic 71.0±9.9</td>
</tr>
<tr>
<td>Antihypertensive treatment (% , n)</td>
<td>Monotherapy 3.0 (6) Double therapy 67.5 (104) Triple therapy 7.8 (12)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Prevalence of dyslipidemia, type 2 diabetes and impaired fasting glucose in the overall sample and by body weight group.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Dyslipidemia (% , n)</td>
<td>79.5 (124)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl (mean ± SD)</td>
<td>193.5±37.9</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl (mean ± SD)</td>
<td>112.6±35.4</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl (mean ± SD)</td>
<td>54.0±22.5</td>
</tr>
<tr>
<td>Triglycerides, mg/dl (mean ± SD)</td>
<td>130.5±70.7</td>
</tr>
<tr>
<td>Type 2 diabetes (% , n)</td>
<td>35.9 (56)</td>
</tr>
<tr>
<td>Impaired fasting glucose (% , n)</td>
<td>11.8 (18)</td>
</tr>
<tr>
<td>Fasting glucose, mg/dl (mean ± SD)</td>
<td>108.2±29.3</td>
</tr>
</tbody>
</table>

BMI: body mass index; HDL cholesterol: high density lipoprotein cholesterol; LDL cholesterol: low density lipoprotein cholesterol. Statistical significance for p<0.05; p values adjusted by multivariate analysis of variance for age and gender.
number of cases (n=6 in lean, and n=2 in OW/Ob). The type of valve disease (aortic regurgitation, aortic stenosis and mitral regurgitation) did not differ significantly between groups. Regarding global cardiovascular risk, the mean Framingham score of the overall sample was 9.6±7.4, significantly higher in the OW/Ob group (n=97), with a mean score of 10.9±7.7 vs. 6.5±5.7 in the lean group (n=43). The number of missing cases was similar in both groups (11.0% vs. 8.5%), and the difference in the mean Framingham score was statistically significant (p<0.001).

**Discussion**

The prevalence of obesity in our sample of hypertensive patients (29.5%) was higher than that reported in the last survey in the general Portuguese population (13.8%). This difference may be explained by the well-known effect of increased body weight on BP values. In our study, OW/Ob subjects did not present a higher prevalence of dyslipidemia. Although mean total cholesterol and LDL cholesterol did not differ between the two groups, mean HDL cholesterol was lower and triglycerides were higher in the OW/Ob group, and these differences were statistically significant. Similar findings were described in a study by Shah et al., which suggests that total cholesterol alone might not be the most appropriate parameter in routine health screening for dyslipidemia in hypertensive patients.

The prevalence of diabetes in this sample of hypertensive patients was higher than in the general Portuguese population (35.9 vs. 11.7%). When analyzed by body weight groups, this difference was mainly due to the higher prevalence of type 2 diabetes in the OW/Ob hypertensive group (44.6%), while the prevalence in normal weight hypertensive subjects was close to that of the general population (13.6%). Thus excess body weight in hypertensive subjects appears to be related to a higher prevalence of diabetes, as suggested in previous studies in the general population.

We found a tendency for increased urinary albumin excretion in OW/Ob hypertensives compared to normal weight hypertensives, although this was not statistically significant (35.3% vs. 19.6%, p=0.464). This is consistent with a study by Viazzi et al. that found a significantly greater prevalence and severity of target-organ disease in obese than in non-obese hypertensive patients, including a higher urinary albumin excretion rate (−0.05±0.52 vs. −0.28±0.43 log albumin to creatinine ratio, p=0.0001).

The most prevalent target-organ disease in our sample was cardiac. The effect of obesity on the development of LVH in hypertensive patients was described by Smieder et al., who showed that LVH was more severe in obese than in lean hypertensives, particularly in white subjects and in men. The same group also reported reduced indicators of ventricular filling in obese hypertensive patients compared to their lean counterparts. DeDivitis et al. and Kannel et al. suggested that depressed myocardial contractility and diastolic dysfunction, when sustained, will eventually lead to premature congestive heart failure, particularly in patients with obesity hypertension.

## Table 3 Prevalence of microalbuminuria, creatinine clearance and urinary albumin excretion in the overall sample and by body weight group.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>BMI &lt;25.0</th>
<th>BMI ≥25.0</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microalbuminuria (%)</td>
<td>15.7 (16)</td>
<td>19.4 (6)</td>
<td>14.1 (10)</td>
<td>0.558</td>
</tr>
<tr>
<td>Urinary albumin excretion, mg/24 hours (mean ± SD)</td>
<td>31.4±90.7</td>
<td>19.6±23.8</td>
<td>35.3±103.8</td>
<td>0.466</td>
</tr>
<tr>
<td>Creatinine clearance by the Cockcroft-Gault method, ml/min (mean ± SD)</td>
<td>73.2±30.1</td>
<td>57.7±25.8</td>
<td>77.2±29.9</td>
<td>0.005</td>
</tr>
</tbody>
</table>

BMI: body mass index. p values adjusted by multivariate analysis of variance for age and gender.

## Table 4 Prevalence of target-organ disease in the overall sample and by body weight group.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>BMI &lt;25.0</th>
<th>BMI ≥25.0</th>
<th>p (unadjusted)</th>
<th>p (adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke (%)</td>
<td>2.6 (4)</td>
<td>4.5 (2)</td>
<td>1.8 (2)</td>
<td>0.352</td>
<td>0.406</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>5.1 (8)</td>
<td>9.0 (4)</td>
<td>3.6 (4)</td>
<td>0.191</td>
<td>0.233</td>
</tr>
<tr>
<td>Coronary disease (%)</td>
<td>3.9 (6)</td>
<td>4.5 (2)</td>
<td>3.5 (4)</td>
<td>0.779</td>
<td>0.897</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>10.3 (16)</td>
<td>18.1 (8)</td>
<td>7.1 (8)</td>
<td>0.051</td>
<td>0.082</td>
</tr>
<tr>
<td>Peripheral arterial disease (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Retinopathy (%)</td>
<td>2.6 (4)</td>
<td>4.5 (2)</td>
<td>1.8 (2)</td>
<td>0.3796</td>
<td>0.757</td>
</tr>
<tr>
<td>Renal disease (%)</td>
<td>5.1 (8)</td>
<td>4.5 (2)</td>
<td>5.6 (6)</td>
<td>0.4203</td>
<td>0.053</td>
</tr>
<tr>
<td>LVH (%)</td>
<td>6.5 (10)</td>
<td>0 (0)</td>
<td>9.8 (10)</td>
<td>0.0101</td>
<td>0.266</td>
</tr>
<tr>
<td>Mild valve disease (%)</td>
<td>50.5 (52)</td>
<td>29.6 (8)</td>
<td>57.9 (44)</td>
<td>0.2176</td>
<td>0.021</td>
</tr>
</tbody>
</table>

BMI: body mass index; LVH: left ventricular hypertrophy. p values adjusted by multivariate analysis of variance for age, gender, duration of hypertension and previous diagnosis of dyslipidemia.
According to Schmieder et al., unloading from the heart the double burden of obesity and hypertension by losing weight and controlling BP should be a major goal in the management of hypertensive patients. There are limited data regarding the direct effects of obesity on the heart valves, since poor echocardiographic windows in obese subjects hamper the quantitative assessment of valve disease. Nevertheless, somewhat counterintuitively, a study assessing the frequency of valvular abnormalities showed a lower prevalence of valvular regurgitation in obese than in normal-weight subjects.

To summarize, in our sample of hypertensive patients, overweight and obesity appear to be associated with a less favorable lipid profile (higher triglycerides and lower HDL cholesterol) and with a higher prevalence of type 2 diabetes. We also found a trend suggesting that overweight and obese patients may be more likely to develop renal subclinical disease, as they appear to have higher urinary albumin excretion. Finally, cardiac target-organ disease, particularly valve disease, also appears to be more prevalent in overweight and obese hypertensive compared with their lean counterparts. More powerful studies are needed to clarify how this effect varies with increasing grade of severity of valve disease.

The use of the Framingham score in this sample showed that although both obese and non-obese diabetic patients are at risk of cardiovascular disease (10-year risk: 10.9% vs. 6.4%, p<0.001), the risk is significantly higher in OW/Ob patients. On the basis of our findings we suggest strict metabolic monitoring and improved education on weight reduction and control at primary health care clinics.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data and that all the patients included in the study received sufficient information and gave their written informed consent to participate in the study.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Funding and acknowledgements

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Conflicts of interest

The authors have no conflicts of interest to declare.

References