Cardiometabolic Disorders in Hypertensive Women with Abdominal Obesity

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Abstract

Background: Studies show increased waist circumference as a relevant indicator of increased cardiovascular risk (CVR).
Objective: To identify structural and functional cardiac abnormalities in nondiabetic hypertensive women with abdominal obesity (AO).
Methods: Cross-sectional study with 120 hypertensive women, aged 40-65, stratified into: group with no abdominal obesity (NAO, n=42) and with abdominal obesity (QAO, n=78), and waist circumference < or ≥88 cm, respectively. Clinical evaluation, biochemical tests, Doppler echocardiography and carotid ultrasound were conducted.
Results: Average age was 53±1 in the groups. Although the systolic blood pressure (BP) was higher in the WAO group, it did not reach statistical significance (145±2 mmHg vs. 140±2 mmHg, p=0.098). The WAO group had higher diastolic BP (90±1 mmHg vs. 85±1 mmHg, p<0.05), greater number of criteria (3.1±0.1 vs. 1.4±0.1, p<0.001) and prevalence of metabolic syndrome (62.8% vs. 11.9%; p<0.001). Despite normal blood glucose levels, WAO patients had higher HOMA-IR levels (2.62±0.22 vs. 1.61±0.17 p<0.01) and HOMA-beta levels (358±57 vs. 200±22, p<0.05). In the echocardiographic evaluation, systolic function was similar in both groups, but the WAO group presented evidence of diastolic dysfunction by tissue Doppler and higher prevalence of left ventricular hypertrophy (29.2% vs. 2.4%), with no difference between the carotid artery intima-media thickness.
Conclusions: In this sample of nondiabetic hypertensive women, abdominal obesity was associated with higher levels of diastolic blood pressure, reduced insulin sensitivity and cardiac issues, especially left ventricular hypertrophy and diastolic dysfunction. However, there was no evidence of subclinical carotid atherosclerosis in hypertensive patients with and without abdominal obesity.

Keywords: Hypertension; Abdominal obesity; Insulin resistance; Metabolic X syndrome; Cardiovascular system

Introduction

Weight gain and increased waist circumference are important prognostic indicators of systemic arterial hypertension (SAH) and abdominal obesity (AO) is a relevant indicator of increased cardiovascular risk (CVR). Recent studies suggest that AO is more strongly associated with blood pressure (BP) than general adiposity and its association with SAH is recognized. In fact, there seems to be a direct influence of body mass index (BMI) and waist circumference on BP levels since adolescence. Additionally, it is well documented that weight loss causes reduced BP. Besides this direct influence on BP, AO is recognized as one of the main characteristics of metabolic syndrome (MS) and probably one of the most important CVR factors of the syndrome.

Compared to the BMI analysis, AO, which correlates with visceral fat, is the one that is most associated with metabolic disorders and abdominal circumference is the best criterion to define it.
Differences between sexes can be noted as far as cardiovascular complications and target organ damage are concerned. It has been found that for the same degree of BP elevation, the development of left ventricular hypertrophy is less frequent in women.\textsuperscript{11}

Due to its epidemic dimensions, AO has been given the status of a global public health problem, and a better understanding of the metabolic effects and resulting cardiovascular damage will certainly contribute to the strengthening of preventive measures in a population of obese hypertensive women. This study aims to identify metabolic and cardiac disorders in a sample of hypertensive nondiabetic women with AO compared with non-obese hypertensive women.

**Methods**

Cross-sectional study of a convenience sample of hypertensive women aged 40-65, selected in the outpatient facility of Clínica de Hipertensão Arterial e Doenças Metabólicas Associadas of Hospital Universitário Pedro Ernesto (HUPE) and Policlínica Piquet Carneiro of Universidade do Estado do Rio de Janeiro.

The study was approved by the HUPE Research Ethics Committee under no. 2320/2008 and all participants have read and signed an Informed Consent Form according to Resolution CNS 466/12.

Patients with evidence of secondary hypertension, diabetes mellitus, systemic diseases and/or use of lipid-lowering agents were excluded.

The patients were stratified into two groups: no abdominal obesity (NAO) and with abdominal obesity (WAO), according to the measured waist circumference < or ≥8 cm, respectively.

Clinical, anthropometric and laboratory evaluation

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained from the mean of three measurements using the digital device OMRON (HEM-705CP model, Healthcare Inc., Illinois, USA), in the waiting room, with the patients in the sitting position and after 5 minutes of rest. Arm cuffs of different sizes were used according to the patient’s arm circumference placed approximately 2 cm above the cubital fold.

To measure weight and height, digital scale with a Filizola anthropometer was used (Rio de Janeiro, Brazil), with capacity for 180 kg and precision of 100 g and, for the circumferences, 0.5 cm-wide inelastic measuring tape was used. The patients were barefoot and wearing light clothes. The neck circumference was measured at the lower half of the neck; the abdominal circumference was measured by connecting the midpoints between the last rib and the iliac crest; and the hip circumference was measured at the height of the greater trochanters.

After a 12-hour fast, blood and urine was collected for biochemical tests. Blood insulin (using the electrochemiluminescence method) allowed calculating the HOMA-IR indexes \{[glucose in mmol/L x insulin in mcU/L]/22.5]\ and HOMA-beta \{[20 x insulin (mcU/L)] / (glucose (mmol/L) — 3.5)\}. High-sensitivity C-reactive protein (CRP) was measured using the nephelometry method using BN II (Siemens AG Inc., Munich, Germany). In an isolated urine sample, creatinine (colorimetric method) and albumin (nephelometry) were measured to determine the albumin/urinary creatinine ratio.

With the results from the laboratory tests, the metabolic profile of patients was evaluated and considered abnormal when contained at least one of the conditions was present: blood glucose ≥100 mg/dL, total cholesterol > 240 mg/dL, HDL-col < 50 mg/dL, triglycerides > 150 mg/dL. Finally, the Framingham cardiovascular risk score was determined.\textsuperscript{12}

**Two-dimensional Doppler echocardiography**

Examination was conducted by a single observer using Vivid-3 PRO (General Electric, USA) and 1.5-3.6 MHz sector transducer. The calculation of left ventricular mass...
Table 1
Clinical and anthropometric data of the groups

<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>NAO n=42</th>
<th>WAO n=78</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.8±1.0</td>
<td>53.1±0.8</td>
<td>0.580</td>
</tr>
<tr>
<td>Hypertension time (years)</td>
<td>6.5±0.7</td>
<td>7.4±0.6</td>
<td>0.224</td>
</tr>
<tr>
<td>Smoking n (%)</td>
<td>10 (23.8)</td>
<td>11 (14.1)</td>
<td>0.212</td>
</tr>
<tr>
<td>Menopause n (%)</td>
<td>31 (73.8)</td>
<td>52 (66.7)</td>
<td>0.535</td>
</tr>
<tr>
<td>Metabolic syndrome n (%)</td>
<td>5 (11.9)</td>
<td>49 (62.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MS criteria</td>
<td>1.4±0.1</td>
<td>3.1±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.8±1.2</td>
<td>80.0±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.3±0.4</td>
<td>31.6±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>81.1±0.8</td>
<td>99.3±0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pelvic circumference (cm)</td>
<td>90.3±0.9</td>
<td>107.4±1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>32.3±0.4</td>
<td>35.2±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>140±2</td>
<td>145±2</td>
<td>0.098</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>85±1</td>
<td>90±1</td>
<td>0.016</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>103±1</td>
<td>108±2</td>
<td>0.014</td>
</tr>
<tr>
<td>Pulse Pressure (mmHg)</td>
<td>57±2</td>
<td>55±1</td>
<td>0.657</td>
</tr>
<tr>
<td>Number of anti-hypertensive drugs</td>
<td>1.8±0.1</td>
<td>1.8±0.1</td>
<td>0.836</td>
</tr>
<tr>
<td>Framingham score</td>
<td>16.3±0.5</td>
<td>15.3±0.5</td>
<td>0.184</td>
</tr>
</tbody>
</table>

Results expressed as mean±standard error of the mean or proportions in n (%).

MS – metabolic syndrome; BMI – body mass index; BP – blood pressure

Statistical analysis
Data were expressed as mean±standard error of the mean using the software application GraphPad Prism version 5.0 (GraphPad Software Inc., USA). To compare continuous variables, the Student’s t test was used after confirming the normal distribution of values. Categorical variables were compared using the chi-square test. In this study, p<0.05 was considered statistically significant.

Results
141 women were selected with previous diagnosis of primary hypertension under outpatient follow-up. Patients were excluded due to incomplete clinical or metabolic evaluation (n=8), diabetes mellitus (n=9), absence of hypertension (n=3) and macroproteinuria (n=1), resulting in a final sample of 120 women with hypertension. After distribution in the NAO groups (n=42) and WAO (n=78), a prevalence of 65% of abdominal obesity was defined in this sample.

Clinical and anthropometric characteristics
Mean age, duration of hypertension, smoking and proportion of menopause were similar in the groups and there was no difference in the number of antihypertensive drugs in use. DBP and mean BP were significantly higher in the WAO group. SBP, higher in the WAO group, did not reach statistical significance. As expected, all anthropometric indexes were significantly higher in this group (Table 1).

Metabolic parameters
Even with no significant difference between blood glucose levels, plasma insulin concentrations (Table 2) and the HOMA-IR levels (1.61±0.17 vs. 2.62±0.22, p=0.002) and HOMA-beta levels (200±22 vs. 358±57, p=0.044) were significantly higher in WAO group (Figure 1). Such group also presented higher levels of serum uric acid (still in the normal range), higher plasma triglycerides, lower HDL-cholesterol levels and higher triglyceride/HDL ratio (Table 2). The WAO group presented a more abnormal profile than the NAO group (68% vs. 56%), although with no statistical significance.
Table 2  
Metabolic parameters and microalbuminuria in the groups

<table>
<thead>
<tr>
<th></th>
<th>NAO n=41</th>
<th>WAO n=72</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dL)</td>
<td>79±2</td>
<td>83±2</td>
<td>0.139</td>
</tr>
<tr>
<td>Insulin (mcU/L)</td>
<td>7.85±0.77</td>
<td>12.59±0.99</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>221±6</td>
<td>204±5</td>
<td>0.030</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>107±9</td>
<td>139±8</td>
<td>0.010</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>55±2</td>
<td>49±1</td>
<td>0.003</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>146±5</td>
<td>128±4</td>
<td>0.009</td>
</tr>
<tr>
<td>TGL/HDL</td>
<td>2.11±0.21</td>
<td>3.07±0.23</td>
<td>0.007</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>4.2±0.2</td>
<td>5.2±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.76±0.02</td>
<td>0.79±0.02</td>
<td>0.310</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>0.26±0.05</td>
<td>0.49±0.05</td>
<td>0.002</td>
</tr>
<tr>
<td>UACR (mg/g)</td>
<td>17±5</td>
<td>19±4</td>
<td>0.750</td>
</tr>
</tbody>
</table>

Results expressed as mean±standard error of the mean  
NAO – no abdominal obesity; WAO – with abdominal obesity;  
TGL – triglycerides; UACR – urine albumin-creatinine ratio

Echocardiography parameters

Interventricular septal thickness, LV posterior wall and LVMI presented significantly higher values in the WAO group. Ejection fraction and shortening percentage were similar in the groups. In the mitral flow analysis, the WAO group showed significantly higher deceleration time and, with tissue Doppler, there was a significant decrease in the E’/A’ ratio (Table 3).

In the evaluation of ventricular geometry, a predominantly normal pattern was found (75%) in the NAO group, while the WAO group had a higher prevalence of left ventricular hypertrophy (LVH: 29.2% vs. 2.4%) distributed similarly through the following patterns: concentric (13.9%) and eccentric (15.3%) (Figure 2).
Figure 2
Ventricular geometry patterns found in the groups without abdominal obesity (NAO) and with abdominal obesity (WAO).
Values expressed as %. Remod – remodeling; LVH – left ventricular hypertrophy

Discussion

In this study, metabolic and cardiac disorders associated with AO were found, which suggested greater CVR in these patients. The higher prevalence and the greater number of criteria for MS associated with higher DBP suggested higher probability of development of cardiovascular events in the WAO group compared to the NAO group. Furthermore, reduced insulin sensitivity with reduced HDL-cholesterol corroborated greater CVR in this population. In the cardiac evaluation, AO was associated with LVH and diastolic dysfunction.

Studies point out the increase in AO among Brazilian women affecting the CVR.\(^{13}\) In this study, the risk measured using the Framingham score, according to the guideline,\(^{12}\) was slightly higher in NAO women. This finding was not statistically significant, probably due to the small sample size and more frequent smoking in the NAO group. It is a relevant clinical data, as it suggests that the Framingham score may be underestimating the actual CVR in these hypertensive women, as the WAO group presented higher prevalence of MS.

There was an increase in DBP in hypertensive obese women, which is consistent with the findings of Kanai et al.\(^{14}\) who also observed an increase in SBP related to AO. In this study, the SBP was higher in WAO women (without statistical significance) and the 5 mmHg difference between the groups indicates another clinically significant finding, as its maintenance would be sufficient to determine a higher risk of development of cardiovascular complications. In the ASCOT study (Anglo-Scandinavian Cardiac Outcomes Trial)\(^{15}\), it was recognized that the difference in the end of 2.7 mmHg in SBP in the group receiving amlodipine+perindopril compared with the group receiving atenolol+benazepril could reduce the occurrence of coronary events by 4-8%, and stroke by 11-14%.\(^{15}\)

AO is an important marker of dysfunctional adipose tissue for the clinical diagnosis.\(^{16}\) Additionally, neck circumference, higher in the WAO group, seems to be a criterion of central adiposity for anthropometric assessment of women, a fact recently demonstrated by other authors.\(^{17}\)

There was a higher prevalence and significantly higher number of criteria for MS in the WAO group. Although a percentage of patients with AO is metabolically normal, consistently with US epidemiological data published,\(^{18}\) the metabolic profile was more frequently altered in this group, confirming the importance of preventive measures in obese women.

Blood insulin and insulin resistance indexes were significantly higher in the WAO group. This makes it important to use these markers in medical practice, especially among obese hypertensive women with normal glucose levels, as they are considered predictors of diabetes mellitus.\(^{19}\) Nonetheless, these indexes have been questioned as predictors of progressive development of abnormal glucose tolerance up to the final progression to diabetes mellitus,\(^{20}\) and other
indexes have been proposed to better assess insulin sensitivity, although they require further validation for clinical use.\textsuperscript{21}

Obesity and SAH are classic components of MS. There is a demonstrated association between obesity and SAH with left ventricular hypertrophy, increasing CVR. Hyperinsulinemia has been considered a link between obesity, SAH and diabetes due to the increase in adrenergic tone and renal reabsorption of sodium.\textsuperscript{22}

C-reactive protein (CRP) is an inflammatory marker and an independent predictor of risk for cardiovascular diseases.\textsuperscript{23} Abdominal fat is considered a predictor of high CRP concentrations due to the significant expression of this protein in deposits of abdominal fat, visceral fat and subcutaneous fat in white, black and Hispanic populations.\textsuperscript{24} Women with a BMI above 28.3 kg/m\textsuperscript{2} presented serum CRP levels 12 times higher than women with lower BMI, representing a four-fold increased risk for coronary artery disease.\textsuperscript{25} In this study, the WAO group presented higher levels of high-sensitivity CRP and, in addition to that, these findings confirm the role of inflammatory phenomenon concomitant with hypertension and obesity.\textsuperscript{26} It should be noted that the JUPITER study (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin)\textsuperscript{27} reinforced the role of CRP as an inflammatory biomarker and an independent predictor of future vascular events, improving overall CVR classification, even with normal cholesterol levels.\textsuperscript{27}

The WAO group presented higher CRP and microalbuminuria values. The association between AO and microalbuminuria has been confirmed, determining increased CVR in hypertensive individuals.\textsuperscript{28} However, microalbuminuria was not more prominent in the WAO group, either due to the sample size or, more likely, due to the absence of severe endothelial dysfunction in these patients considering the age and the short time of hypertensive disease.

Analysis of echocardiographic parameters revealed a slight increase in the left atrial cavity in the WAO group, suggesting atrial hypertension, probably linked to increased blood volume.\textsuperscript{29} A study conducted by Mensah et al.\textsuperscript{30} found that the measure of LVM on echocardiography was bigger in the prediction of the SAH evolution process compared to the variables SBP, DBP and SAH staging.\textsuperscript{20} Although increased BP is important for the emergence of left ventricular hypertrophy,\textsuperscript{20} other factors are also involved in the development and maintenance of hypertrophy, such as obesity,\textsuperscript{32} age,\textsuperscript{33} ethnicity, sodium-high diet, insulin resistance, genetic pattern and neurohumoral factors, including adrenergic factors and renin-angiotensin-aldosterone system.\textsuperscript{34} Consistently, in this study, LVM was higher in WAO group. The impact of waist circumference in the cardiac phenotype according to sex showed that the adverse effects of AO in the structural and functional disorders of the LV were more pronounced among obese hypertensive women, suggesting that waist circumference may provide additional information on the risk of cardiac complications.

In epidemiological studies of hypertensive heart disease, one of the main objectives of echocardiography is the evaluation of LVM and ventricular geometry by calculating the relative wall thickness.\textsuperscript{35} Studies have shown the predictive value of LV hypertrophy for morbid events or mortality, regardless of the presence of other risk factors.\textsuperscript{36,37} Detection of hypertrophy and impairment degree has been associated with increased CVR. In the Framingham Heart Study, an increase of 50 g/m of LVM corrected by the patient’s height, increased 1.73 times the relative risk of mortality even in patients without CVD. It was also found that not only the presence but also the pattern of ventricular hypertrophy, i.e., the ventricular geometry, would value prognostic value.\textsuperscript{35}

In the left ventricular architecture, four types of ventricular geometry were identified. The WAO group revealed clear prevalence of eccentric and concentric hypertrophy and, in the NAO group, the normal geometric pattern prevailed. These data are similar to those described by Messerli et al.\textsuperscript{38}, demonstrated eccentric left ventricular hypertrophy in obese hypertensive individuals, suggesting a major role of obesity in the determination of cardiac morphology in these patients.\textsuperscript{38}

The diastolic function in obesity is worthy of note. The WAO group presented an E/A ratio smaller than the NAO group. Some studies have reported diastolic
ventricular dysfunction in obese individuals, identifying that obesity (by BMI) was associated with left atrial enlargement and diastolic dysfunction\(^9\). Other authors found abnormalities in tissue Doppler related to obesity, corroborating our findings.\(^9\)

According to the results found, hypertension combined with abdominal obesity can damage left diastolic function. This possibly reflects the presence of more severe abnormalities of the heart muscle resulting from high BP association with metabolic and hormonal disorders induced by insulin resistance. However, confirmation of this pathogenic mechanism was not the objective of this study.

It is believed that the association between abdominal obesity and atherosclerosis is due to excessive visceral adipose tissue associated with traditional risk factors. Visceral adipose tissue indirectly measured by waist circumference is recognized as an independent risk factor for atherosclerosis. These results are consistent with the findings of Lear et al.\(^4\), who only found a correlation between visceral adipose tissue and intima-media thickness of carotid arteries in men. The lack of correlation between waist circumference and intima-media thickening of carotid arteries in the women studied is probably also be a result of the young profile of the sample and the low severity of hypertension in these patients.

Conclusions

In this sample of hypertensive nondiabetic women aged 40-65, AO determined higher CVR as it is associated with a greater number of criteria and increased prevalence of MS, higher BP levels (especially diastolic BP) and reduced sensitivity to insulin. Despite these CVR markers in this age group, AO was not associated with signs of subclinical atherosclerosis with similar intima-media thickness of the carotid arteries between groups. This high-risk profile resulted in a higher prevalence of changes in cardiac structure and function associated with AO, especially left ventricular hypertrophy and diastolic dysfunction, with no effects on systolic function. Considering that the Framingham risk score was similar between the groups, this does not seem to be an effective method of evaluation, suggesting the need for a more global CVR estimation in this population of women with hypertension and abdominal obesity.

Potential Conflicts of Interest

This study has no relevant conflicts of interest.

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Academic Association

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