Abdominal Obesity, Insulin Resistance and Hypertension: Impact on Left Ventricular Mass and Function in Women

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Summary

Objective: To evaluate the relationship between central obesity, hyperinsulinemia and arterial hypertension with left ventricular mass and geometry in women.

Methods: This study included 70 women (35-68 years), divided into four groups according to the presence of central obesity and hypertension. Visceral fat area was determined. Blood glucose and plasma insulin were determined before and two hours after an oral 75g glucose load, and the patients were submitted to cardilogical evaluation.

Results: Compared to NT-OB, HT-OB presented higher levels of plasma insulin at 2h-OGTT (127.5 ± 73.0 *vs* 86.8 ± 42.7 μU/ml; $p=0.05$) and reduced E wave/A wave ratio (E/A) (0.8 ± 0.1 *vs* 1.2 ± 0.3; $p < 0.05$). Compared to NT-NO, HT-NO showed higher insulin levels before glucose load (7.46 ± 3.1 *vs* 4.32 ± 2.1 μU/ml; $p < 0.05$), higher HOMAr (1.59 ± 0.72 *vs* 0.93 ± 0.48 mmol.mU/l²; $p=0.006$), higher leptin level (19.1 ± 9.6 *vs* 7.4 ± 3.5 ng/ml; $p=0.028$), greater VF area (84.40 ± 55.7 *vs* 37.50 ± 23.0 cm²; $p=0.036$), increased IVSTd (9.6 ± 1.2 *vs* 8.2 ± 1.7 mm; $p <0.05$) and (LVM/height) (95.8 ± 22.3 *vs* 78.4 ± 15.5 g/m; $p < 0.05$). Multiple linear regression analysis showed age, BMI and fasting glucose as determinants on LVM/height ($R^2 = 0.59$; $p < 0.05$).

Conclusion: Our results indicate an association among hypertension, central obesity and left ventricular hypertrophy through increases in sympathetic activity and insulin resistance. (Arq Bras Cardiol 2007;89(2):77-82)

Key words: Obesity; hypertension; insulin resistance; hypertrophy, left ventricular.

Introduction

Obesity, now recognized as an independent risk factor for cardiovascular disease (CVD), is strongly associated with other risk factors, including hypertension[1-3]. Complex mechanisms link increasing body weight with increasing blood pressure. Upper-body obesity, as compared to lower-body obesity, is most closely associated with obesity-related hypertension, and hyperinsulinemia has been suggested to be involved in the genesis of arterial hypertension in obese individuals[2,3]. In the Framingham Study, for every 10 lb weight gain (1 lb ~ 0,453 Kg), systolic blood pressure increased , on average, 4.5 mm Hg[4]. Some suggest that leptin may also increase blood pressure[5,6].

As demonstrated by some investigators[7-9], hypertensive obese patients show anatomic and hemodynamics abnormalities due to excess weight, including increase in intravascular volume, with enlargement of the vascular bed, as well as increases in heart rate and cardiac output.

It has been suggested that excessive oxygen consumption, due to higher metabolism in increased adipose tissue, associated with hypervolemia, contributes to left ventricular hypertrophy[7]. It has been reported that while hypertensive non-obese patients show concentric left ventricular hypertrophy due to an increase in afterload[10], obese patients, even the normotensives, show eccentric left ventricular hypertrophy due to an increase in preload. Hypertensive obese patients may present both these mechanisms.

The aim of this study was to further evaluate the relation between central obesity, hyperinsulinemia and hypertension with left ventricular mass and geometry in women.

Methods

We studied 70 women, from August 2001 to August 2003, ages ranging from 35-68 years, divided into 4 groups: NT-NO (normotensive non-obese/N=17), NT-OB (normotensive obese/N=18), HT-NO (hypertensive non-obese/N=18) and HT-OB (hypertensive obese/N=17). All were recruited from the obesity and hypertension clinics of the Federal University of São Paulo and HSPE. Written informed consent was obtained from all participants, and the study was approved by the Institutional Ethics Committee. Central obesity was defined as weight (Kg) by height (meters) squared ≥ 30 Kg/m² and waist circumference > 88 cm. Hypertension was defined as systolic or diastolic blood pressure ≥ 140 x 90 mm Hg or by self -reported use of antihypertensive medications. Exclusion criteria were self-reported diabetes and cardiac, hepatic and renal dysfunctions. The same observer measured weight, height and waist and hip circumferences. Arterial

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blood pressure was taken after a five-minute rest in the sitting position, with a sphygmomanometer using an appropriate cuff size for arm circumference. The mean of two measurements was considered.

No patient used any antihypertensive medication for at least seven days prior to the study. After a 12-hour fast, serum glucose (glucose oxidase/Hitashi analyzer) and serum insulin (Auto Delfia, Perkin Elmer) were determined at 0 and 120 minutes after a 75g oral glucose load. Fasting leptin (Linco Research, USA) was measured.

Patients were submitted to electrocardiogram (Dixtal), and 24 h-ambulatory blood pressure monitoring (Spacelabs, Redmond, WA) registered blood pressure every 15 minutes during daytime (awake hours) and every 20 minutes during nighttime (sleep hours), based on the patients' report on their activities during day and night. Blood pressure fall during sleep (Δ BP) was calculated by dividing the difference between mean awake systolic blood pressure and mean sleep systolic blood pressure by mean awake systolic blood pressure (ΔBP = mean awake SBP – mean sleep SBP x100/mean awake SBP).

Echocardiogram was performed, by the same examiner, at rest, with the patient at steady state in the left lateral position, using a 2.5 MHz transducer. Two-dimensional guided M-mode measurements of left ventricular diastolic diameter (LVDD), diastolic interventricular septal thickness (IVSTd) and diastolic left ventricular posterior wall (LVPWd) were measured according to the recommendations of the American Society of Echocardiography[11]. Left ventricular mass (LVM) was estimated by Devereux's formula[12] and corrected by height (LVM/ height). The cutoff value of LVM/ height ≥ 102 g/m was adopted for the diagnosis of left ventricular hypertrophy[13-16]. The E wave/A wave ratio (E/A) was used as an indicator of diastolic function. We used left ventricular mass corrected by body surface (LVMI) and relative posterior wall thickness (RPWT), which is the ratio between diastolic left ventricular posterior wall (LVPWd) and left ventricular diastolic diameter (LVDD) multiplied by 2.0 (LVPWd/LVDD x 2.0) to assess ventricular geometry[17]. Eccentric hypertrophy is defined by LVMI ≥ 100g/m² and RPWT < 0.45, while concentric hypertrophy is defined by RPWT ≥ 0.45.

Visceral fat area (density -50 to -250 HU) was obtained by computed tomography (Picker International), at the L4-L5 level, expressed in cm².

Statistical analyses were performed using SPSS 12.0, and significance level was set as $\alpha = 0.05$ ($p < 0.05$). We used ANOVA and Kruskal-Wallis for comparisons among the four groups. Fisher and Chi-Square were used to analyse nominal variables. Student's and Mann-Whitney tests were used to compare two groups. Correlations were analysed through Pearson correlation coefficients. Multiple linear regression analysis was used to determine the influence of age, fasting and 2h- blood glucose, 2h- plasma insulin, BMI, VF and sleep and awake SBP on LVM/ height.

Results

Clinical, laboratorial and tomographic findings are shown in Table 1. Blood pressure measurements are shown in Table 2.

Only 57 % of all hypertensive patients were using antihypertensive medication up to seven days before evaluation. Hypertensive non-obese and hypertensive obese patients were using angiotensin-converting enzyme inhibitors (16.6% and 29%), hydrochlorothiazide (16.6% and 23.5%) and calcium channel blockers (5.5% and 23.5%), respectively.

The NT-OB and HT-OB groups showed similar LVM/ height values, which were higher than those of the NT-NO group (107.2 ± 30.7 and 109.1 ± 26.0 g/m), but did not differ from the HT-NO group (95.8 ± 22.3 g/m) (Table 3). LVM/ height values detected LVH in 36.51% (1.6% in the NT-NO, 12.7% in the NT-OB, 11.1% in the HT-NO and 11.1% in the HT-OB) of the group as a whole. In the entire group, 16.0% showed eccentric hypertrophy and 8.0% showed concentric hypertrophy, and the proportions of patients with one or other form of hypertrophy in the four groups were very similar.

Table 1 - Clinical, tomographic and laboratory parameters according to the groups

	NT-NO	NT-OB	HT-NO	HT-OB
Age (years)	46.6 ± 9.1	47.3 ± 5.0	52.6 ± 11.0	50.5 ± 5.1
BMI (Kg/m²)	23.0 ± 2.2	36.0 ± 5.1 *‡	23.8 ± 2.3	36.9 ± 5.8 *‡
Waist (cm)	71.3 ± 7.8	100.3 ± 13.2 *‡	74.5 ± 9.9	101.8 ± 12.2 *‡
WHR	0.8 ± 0.01	0.9 ± 0.06 *	0.8 ± 0.06	0.9 ± 0.07 *
VF (cm²)	37.5 ± 23.0	115.3 ± 57.4 *	84.4 ± 55.7 *	127.7 ± 32.0 *
Gluc 0'(mg/dl)	82.6 ± 9.1	95.9 ± 9.9 *	86.7 ± 6.0 #	93.6 ± 13.0 *‡
Gluc120' (mg/dl)	87.1 ± 29.0	132.8 ± 28.5 *	111.9 ± 27.4 *#	138.7 ± 49.2 *‡
Insul 0'(μU/ml)	4.32 ± 2.1	17.6 ± 7.5 *‡	7.46 ± 3.1 *	16.8 ± 8.7 *‡
Insul120'(μU/ml)	34.7 ± 27.3	86.8 ± 42.7 *‡	49.9 ± 25.3	127.5 ±73.0 *#‡
HOMA r	0.93 ± 0.48	3.96 ± 1.65 *‡	1.59 ± 0.72 *	4.06 ± 2.39 *‡
Leptin (ng/ml)	7.4 ± 3.5	21.4 ± 10.1 *	19.1 ± 9.6 *	24.2 ± 13.5 *

** p<0.05 vs NT-NO; # p<0.05 vs NT-OB; ‡ p<0.05 vs HT-NO. HOMA r index - mmol.mU/l²); WHR - waist-to-hip ratio; VF - visceral fat area.*

Table 2 - Blood pressure measurements (office and 24h-ABPM) in the groups

	NT-NO	NT-OB	HT-NO	HT-OB
O-SBP (mm Hg)	116,5 ± 7,1	125,6 ± 8,8 *	137,8 ± 14,3 *#	147,9 ± 13,5*#‡
O-DBP (mm Hg)	75,8 ± 3,9	80,6 ± 6,5 *	86,6 ± 9,4 #	96,5 ± 6,5 *#‡
O-HR (bpm)	78,0 ± 4,7	80,3 ± 3,6	75,9 ± 8,7 §	80,5 ± 3,9
24h-SBP	115,9 ± 12,1	118,0 ± 5,5	133,3 ± 12,2 *#	143,7 ± 17,3
24h-DBP	71,8 ± 9,1	71,4 ± 5,5	85,4 ± 8,8 *#	86,5 ± 14,5 *#
24h-HR (bpm)	73,9 ± 8,3	78,4 ± 10,1	77,2 ± 9,7	85,3 ± 10,9 ‡
ASBP (mm Hg)	118,3 ± 12,8	120,9 ± 5,5	136,3 ± 13,0 *#	143,5 ± 16,8 *#
ADBP (mm Hg)	74,4 ± 9,5	74,3 ± 6,2	88,5 ± 9,4 *#	87,5 ± 14,4 *#
A-HR (bpm)	76,2 ± 8,4	83,1 ± 9,7 *	80,9 ± 10,9	85,9 ± 9,3 *
SSBP (mm Hg)	107,5 ± 9,9	108,9 ± 8,4	124,7 ± 11,9 *#	133,8 ± 14,8 *#
SDBP (mm Hg)	63,3 ± 7,7	62,3 ± 5,8	76,7 ± 8,4 *#	75,3 ± 11,8 *#
Sleep-HR (bpm)	66,5 ± 8,8	70,6 ± 9,6	67,9 ± 9,3	74,7 ± 8,4 *‡
Nocturnal dip < 10% (%)	31%	50%	60%	67%

** p<0.05 vs NT-NO; # p<0.05 vs NT-OB; ‡ p<0.05 vs HT-NO; § p=0.05 vs NT-OB. O-SBP/O-DBP - office systolic/diastolic blood pressure measure; O-HR - office heart rate; ASBP - awake systolic blood pressure; ADBP - awake diastolic blood pressure; SSBP - sleep systolic blood pressure; SDBP - sleep diastolic blood pressure.*

Table 3 - Echocardiographic and electrocardiographic parameters according to the groups

	NT-NO	NT-OB	HT-NO	HT-OB
LA (mm)	30.9 ± 3.3	35.6 ± 4.0 *	33.7 ± 3.4 *	35.7 ± 5.2 *
AO (mm)	30.4 ± 2.4	30.1 ± 2.2	31.1 ± 3.2	33.4 ± 4.0 *#
IVSTd (mm)	8.2 ± 1.7	10.1 ± 1.5 *	9.6 ± 1.2 *	10.1 ± 1.1 *
LVPWd (mm)	8.7 ± 1.9	10.1 ± 3.8	9.2 ± 1.2	9.8 ± 1.3
IVSTd/LVPWd	0.9 ± 0.12	1.0 ± 0.2 *	1.0 ± 0.1 *	1.0 ± 0.1 *
LVDD (mm)	43.6 ± 2.8	45.6 ± 4.3	44.6 ± 3.9	46.0 ± 4.7
LVM (g)	122.4 ± 24.0	167.7 ± 48.2 *	152.8 ± 36.7 *	173.4 ± 43.6 *
LVMI (g/m²)	78.6 ± 13.8	91.4 ± 23.4	94.0 ± 22.9	91.4 ± 20.5
LVM/height (g/m)	78.4 ± 15.5	107.2 ± 30.7 *	95.8 ± 22.3 *	109.1 ± 26.0 *
E wave/A wave	1.4 ± 0.6	1.2 ± 0.3	1.1 ± 0.4	0.8 ± 0.1 *#‡
EF (%)	0.66 ± 0.06	0.66 ± 0.06	0.66 ± 0.07	0.67 ± 0.07
PR interval (ms)	145.9 ± 18.0	155.6 ± 18.8	155.3 ± 20.7	164.3 ± 11.6 *
QTc (s)	0.38 ± 0.03	0.39 ± 0.03	0.39 ± 0.02	0.40 ± 0.02 *

** p< 0.05 vs NT-NO; # p< 0.05 vs NT-OB; ‡ p< 0.05 vs HT-NO. LA - left atrial diameter; AO - aorta diameter; IVSTd - diastolic interventricular septum thickness; LVPWd - diastolic left ventricular posterior wall thickness; LVDD - left ventricular diastolic diameter; LVM - left ventricular mass; LVMI - left ventricular mass index; LVM/height - left ventricular mass by height; EF - ejection fraction.*

Plasma insulin values two hours after glucose load were higher in the HT-NO and HT-OB groups (49.9 ± 25.3 and 127.5 ± 73.0 μU/ml), compared with NT-NO and NT-OB groups (34.7 ± 27.3 and 86.8 ± 42.7 μU/ml), respectively. The HT-NO group showed a tendency towards higher blood glucose level (111.9 ± 27.4 *vs* 87.1 ± 29.0 mg/dl; p = 0.057) at 2h-OGTT than the NT-NO group.

ECG analysis showed that QRS intervals were similar in all four groups, whereas PR and QTc intervals were longer in the HT-OB than in the NT-NO group (Table 3).

Multiple linear regression analysis, with LVM/height as the dependent variable, and with age, BMI, fasting glucose, 2h- blood glucose, 2h- plasma insulin, VF, awake and sleep systolic BP (SBP) as independent variables, showed that only age, fasting glucose and BMI were determinants of LVM/height (R^2=0.59; p<0.05; Backward).

Positive correlations were found between sleep systolic blood pressure (SSBP) and 2h- plasma insulin levels ($r = 0.38$; $p = 0.01$) and between sleep heart rate and 2h- blood glucose values (0.43; $p < 0.01$).

Mean values of LVM/height and E/A ratio in the groups are shown in Figures 1 and 2.

Discussion

Obesity and arterial hypertension are classical components of the metabolic syndrome[2,3,8,18,19]. Some authors have shown an association between obesity, as well as arterial hypertension, and left ventricular hypertrophy, increasing cardiovascular risk[10,16,19].

Hyperinsulinemia has been considered the link between obesity, arterial hypertension and type 2 diabetes through increases in adrenergic tonus and in renal sodium reabsorption[2,18,20-23].

In our study, mean systolic and diastolic blood pressures were higher in hypertensive obese women than in hypertensive non-obese women, and these differences were also associated with increased heart rate during sleep and higher plasma insulin levels. In addition, a reduced nocturnal blood pressure fall was observed in hypertensive obese patients, and a positive

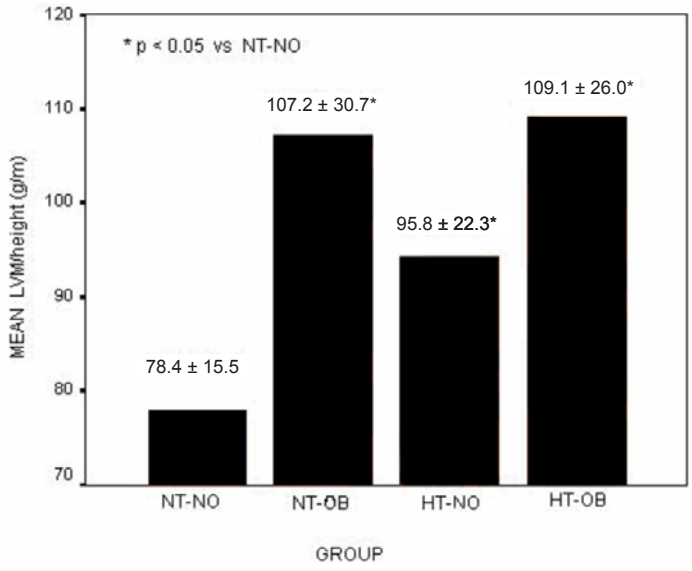

Fig. 1 - *Mean LVM/height in the groups.*

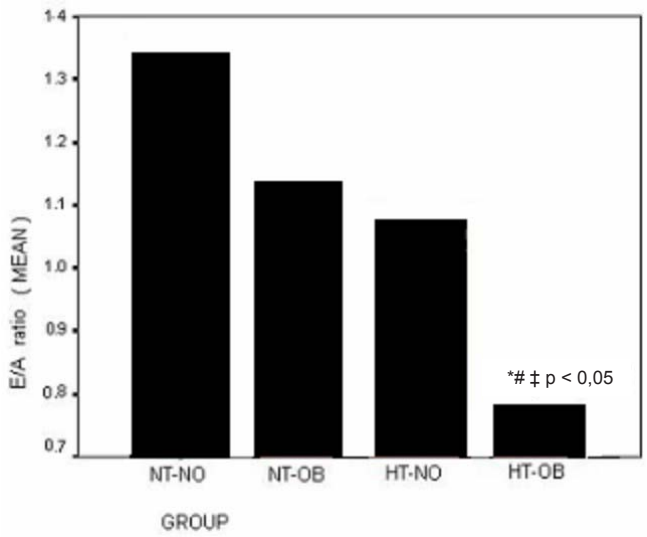

Fig. 2 - *Mean E/A ratio in the groups. * $p < 0.05$ vs NT-NO; # $p < 0.05$ vs NT-OB; ‡ $p < 0.05$ vs HT-NO.*

correlation was found between insulin levels and sleep SBP values. These results suggest that high sympathetic activity, which could be influenced by hyperinsulinemia, contributes to increase blood pressure during the night and to reduce the blood pressure falls that usually occur during sleep.

This reduced nocturnal blood pressure fall has been shown to be associated with left ventricular hypertrophy in hypertensive patients[8]. Although in our study no difference was found in LVM/height between normotensive and hypertensive obese patients, we can not exclude totally the participation of sympathetic activity in the determination of ventricular mass, since 76% of the hypertensive obese patients were on antihypertensive therapy up to seven days before our evaluation. In normotensive obese women, evidence of a small increase in adrenergic activity, which could also be suffering influence from hyperinsulinemia, was found in the higher office blood pressure values and awake heart rate, when compared to normotensive non-obese group. This adrenergic hyperactivity, in association with expanded blood volume usually found in obese individuals, could also be contributing to increase LVM. In addition to increases in sympathetic drive and blood volume expansion, increases in blood glucose levels could also be favoring increases in left ventricular mass in the two groups of obese women, as reported previously[24]. Possible mechanisms to explain this relationship are: 1) direct action of serum glucose on myocytes, leading to cellular changes and hypertrophy; 2) hyperactivity of the renin-angiotensin system and 3) changes in the extracellular matrix[25-28].

In contrast to our findings in obese women, no evidence of increased sympathetic activity could be demonstrated in hypertensive non-obese women, who also showed mild changes in plasma insulin levels when compared to normotensive non-obese women. Thus, no relationship could be demonstrated in this hypertensive group between hyperinsulinemia and increased left ventricular mass, as has been shown previously[29].

However, in addition to blood pressure elevation in this group, higher blood glucose levels were found after oral glucose load. This reflects a certain degree of peripheral insulin resistance that may have contributed to increased LVM.

The diagnosis of cardiac hypertrophy is a controversial point. Several studies have used left ventricular mass by corporal surface (LVMI), while some authors suggested the correction of cardiac mass by height (LVM/height)[8,12,13]. Obese subjects may show an underestimated left ventricular mass because of excess weight when LVMI is used for the diagnosis of LVH[11,12,14]. As we have reported before, LVM/height seems to be a more appropriate index for this purpose[8]. Although it has been reported that obese patients usually show changes in left ventricular geometry, which characterize eccentric cardiac hypertrophy, and hypertensive non-obese patients show changes which characterize concentric hypertrophy, in our study no differences in left ventricular geometry were detected among the two obese groups and the hypertensive non-obese group. Thus, in this study, the results have shown that isolated obesity or isolated hypertension may have similar impact on left ventricular mass, although antihypertensive therapy could have attenuated the effects of hypertension on cardiac structure.

Hypertension superimposed on obesity may, however, interfere with left diastolic function, as we observed in the hypertensive obese women. This possibly reflects the presence of more severe cardiac muscle abnormalities, in result of the association of high blood pressure with metabolic and hormonal changes induced by insulin resistance. Cardiac muscle conduction abnormalities may be observed as a consequence. This may explain the increases in PR and QTc intervals that we observed in the electrocardiogram of hypertensive obese patients.

Conclusion

Our results indicate that hypertension and central obesity are causes of left ventricular hypertrophy through increases in sympathetic activity and blood pressure, and the metabolic and hormonal abnormalities that characterize insulin resistance. The association of obesity and arterial hypertension results in increased probability of left ventricular diastolic dysfunction and abnormalities in cardiac conduction properties.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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