Body mass index as a determinant for metabolic-related changes in resistant hypertension

Índice de massa corporal como fator determinante de alterações metabólicas na hipertensão arterial

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ABSTRACT

BACKGROUND AND OBJECTIVE: Obesity is a common feature of resistant arterial hypertension (RHTN) and it is considered a strong risk factor for the lack of blood pressure control. Moreover, increased aldosterone levels have been associated with impaired glucose metabolism and may interact with adipose tissue deregulating inflammatory adipokines such as leptin. This study aimed to verify the influence of obesity in aldosterone and leptin plasma levels as well as in markers of glucose metabolism in RHTN subjects. **METHODS**: Ninety-one resistant hypertensive patients were divided into two subgroups by the mean body mass index (BMI): (i) a more obese (OBS, N=41, BMI>31.5kg/m^2) and (ii) a leaner group (LNR, N=50, BMI<31.5kg/m^2). We determined body composition by bioimpedance (BIA 450). Fasting glucose, glycated hemoglobin (HbA1c) as well as aldosterone (radioimmunoassay) and leptin (enzyme immunoassay) levels were also evaluated. **RESULTS**: OBS subgroup showed altered glucose metabolism by fasting glucose (129±48 vs. 107±32mg/dL, p=0.04) and glycated hemoglobin (7.6±2.3 vs. 6.8±1.9%, p=0.03). Plasma aldosterone (137.9±102.0 vs. 92.6±67.9pg/ml, p=0.03) as well as leptin levels (24.4±17.2 vs. 36.4±23.5ng/ml, p=0.01) were also higher in OBS compared with LNR group. Multiple linear regression indicated that glucose level is independently associated with obesity in RHTN patients. **CONCLUSIONS**: Our findings demonstrated that a greater body mass index may be determinant for deregulating glucose metabolism as well as aldosterone and leptin levels in resistant hypertensive subjects.

Keywords: Body mass index; Hypertension; Blood pressure monitoring, ambulatory; Obesity; Diabetes mellitus; Leptin; Aldosterone

RESUMO

JUSTIFICATIVA E OBJETIVO: A obesidade é uma característica comum da hipertensão arterial resistente (HAR) e é considerado um forte fator de risco para a falta de controle da pressão arterial. Além disso, o aumento dos níveis de aldosterona tem sido associado ao prejuízo do metabolismo da glicose e pode interagir com o tecido adiposo desregulando adipocinas inflamatórias, tais como a leptina. Este estudo teve como objetivo verificar a influência da obesidade nos níveis plasmáticos de aldosterona e leptina, bem como nos marcadores do metabolismo da glicose em indivíduos com hipertensão arterial resistente. **MÉTODOS:** Noventa e um pacientes foram divididos em dois subgrupos pela média de índice de massa corporal (IMC): (i) obesos (OBS, N=41, IMC>31,5kg/m^2) e (ii) não obesos (nOBS, N=50, IMC<31,5kg/m^2). Nós determinamos a composição corporal por bioimpedância (BIA 450). A glicemia de jejum, a hemoglobina glicada (HbA1c), bem como os níveis plasmáticos de aldosterona (radioimunoensaio) e leptina (ensaio imunoenzimático) também foram avaliados. **RESULTADOS:** O subgrupo OBS apresentou o metabolismo da glicose alterado pela glicemia de jejum (129±48 *vs.* 107±32mg/dL, p=0,04) e hemoglobina glicada (7,6±2,3 *vs.* 6,8±1,9%, p=0,03). Os níveis de aldosterona (137,9±102,0 *vs.* 92,6±67,9pg/ml, p=0,03), assim como os de leptina (24,4±17,2 *vs.* 36,4±23,5ng/ml, p=0,01) também estavam mais elevados em OBS quando comparados ao grupo nOBS. A análise de regressão linear múltipla indicou que o nível de glicose foi independentemente associado à obesidade em pacientes hipertensão arterial resistente. **Conclusões:** Nossos resultados demonstraram que o índice de massa corporal pode ser determinante para desregular o metabolismo da glicose, bem como os níveis de aldosterona e leptina em indivíduos hipertensos resistentes.

Descritores: Índice de massa corporal; Hipertensão; Monitorização ambulatorial da pressão arterial; Obesidade; Diabetes mellitus; Leptina; Aldosterona

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INTRODUCTION

Resistant hypertension (RHTN) was defined to identify subjects at high cardiovascular risk with persistently high blood pressure (BP)[1]. Resistant hypertensive patients are those (i) who have BP above the target levels (≥140x90mmHg) despite the concurrent use of three or more classes of antihypertensive drugs in optimal doses, one being a diuretic, or (ii) who can achieve BP control with the use of four or more agents[1].

According to Framingham cohort study, obesity is one of the main risk factors for the lack of BP control, with great impact on resistance to antihypertensive treatment[1,2]. About one third of obese patients have poor BP control compared to patients with body mass index (BMI)<25kg/m^2[2]. Hence, obesity can be associated with more severe hypertension, with patients requiring more medications to effectively control BP than those who were of normal weight[3].

The pathophysiological mechanisms of obesity-induced arterial hypertension (HTN) are complex and not fully elucidated, but have been associated with impaired sodium excretion, increased activity of the sympathetic nervous system and activation of the renin-angiotensin-aldosterone system (RAAS)[1,4-6]. The hyperaldosteronism, as well as obesity, is associated with clinical and biochemical features of RHTN[7]. The aldosterone hormone promotes insulin resistance and participates in deregulation of inflammatory adipokines, such as leptin, from adipose tissue[8], resulting in systemic inflammation and glucose intolerance[9,10].

It is well documented that leptin influences the BP levels and insulin sensitivity by regulating sympathetic nerve activity in both thermogenic brown adipose tissue and in the kidney, which may result in RAAS stimulation[11,12]. This proinflammatory adipokine was also related to cardiovascular damage in obese resistant hypertensive subjects[8]. Although emerging data suggest that obesity, aldosterone excess and leptin levels may interact to have an important role in the pathophysiology of RHTN[7,8], some questions are still unknown. This study aimed to verify the influence of obesity in aldosterone and leptin plasma levels as well as in markers of glucose metabolism in RHTN subjects.

METHODS

Study Population

Ninety-one patients followed at Outpatient Resistant Hypertension Clinic Hospital of the Faculty of Medical Sciences, Universidade Estadual de Campinas (FCM/UNICAMP, Campinas, Brazil) were included and categorized into two subgroups by the mean BMI: (i) a more obese group with BMI>31.5kg/m^2 (OBS, N=41) and (ii) a leaner group with BMI<31.5kg/m^2 (LNR, N=50). The inclusion of patients was performed only after a six-month period of clinical follow-up, and exclusion of secondary causes of hypertension (pheochromocytoma, coarctation of aorta, primary aldosteronism, Cushing's syndrome and renal artery stenosis) and pseudoresistance by Ambulatory Blood Pressure Monitoring (ABPM) and pill count assessment (screening for white coat hypertension and non-drug adherence, respectively).

The inclusion criteria were subjects older than 35 years diagnosed with "true" RHTN according to the Guidelines of the American Heart Association[1]. Patients with symptomatic ischemic heart, liver or renal diseases or history of stroke or peripheral vascular disease were excluded.

This cross-sectional study was approved by the Research Ethics Committee of FCM/UNICAMP (approval no. 222/2011) and it was conducted in accordance with the Declaration of Helsinki. All patients signed an informed consent before participation in the study.

Office blood pressure measurement

The office systolic (SBP) and diastolic (DBP) blood pressures were measured in the right arm using a validated digital sphygmomanometer (HEM-907XL, Omron Heathcare Inc., Japan).

Ambulatory Blood Pressure Monitoring (ABPM)

The ABPM is essential for the diagnosis of true resistant hypertension, since it avoids misleading diagnoses of white coat hypertension. The measures of SBP and DBP were obtained by SPACELABS 24h-ABPM monitoring (Washington, USA) according to the Guidelines of the European Society of Hypertension. Patients were instructed to keep their routine activities and write symptoms in a personal diary.

Biochemical tests

The routine biochemical exams such as fasting glucose and glycated hemoglobin (HbA1c) were assessed. Plasma aldosterone levels were determined by radioimmunoassay (RIA) and plasma leptin by enzyme-linked immunosorbent assay (ELISA) kit. The intra- and interassay coefficients of variation were below 4.8% for leptin kits.

Bioimpedance

Variables fat-free mass (FFM), fat mass (FM), total body water (TBW) and basal metabolic rate (BMR) were determined by the device Bioimpedance Analyser 450 (Biodynamics Corporation, Seattle, USA). Briefly, the method is based on tetrapolar bioelectrical impedance (electrodes on feet and hands) to assess body composition (mass and body fluids). The measurements were performed according to the manufacturer's instructions with the patient after overnight fasting, instructed to avoid the practice of physical activity and smoking prior to the exam.

Statistical analyses

The variables were expressed as mean and standard deviation and compared using the Student's t-test or Mann-Whitney test, according to the data distribution. Correlation analyses (by Pearson or Spearman tests) and a multiple linear regression analysis were performed to evaluate the association of the variables of interest to the presence of obesity. The level of significance accepted was α=0.05.

RESULTS

The general characteristics of the subgroups according to BMI categorization are listed in table 1. There were no differences regarding age, gender and race among the studied subgroups. Still, office BP and ABPM levels were similar, except for diastolic ABPM, which was lower in the OBS subgroup. Bioimpedance body composition variables were in agreement with categorization of subgroups by BMI as shown in figure 1.

The subgroups did not differ the use of antihypertensive drugs (table 2). Furthermore, the proportion of statin therapy (45.8% vs. 55.6%), glucose-lowering drugs (33.3% vs. 55.6%) and insulin use (10.4% vs. 20.0%) did not differ among subjects in the leaner group and the obese group, respectively.

The patients in the OBS subgroup showed altered glucose metabolism, determined by higher levels of fasting glucose (129±48 *vs*. 107±32mg/dL, p=0.04, figure 2A) and glycated hemoglobin (7.6±2.3 *vs*. 6.8±1.9%, p=0.03, figure 2B). Plasma aldosterone (137.9±102.0 *vs*. 92.6±67.9pg/ml, p=0.03, figure 2C) as well as leptin levels (24.4±17.2 *vs*. 36.4±23.5ng/ml, p=0.01, figure 2D) were also higher in OBS when compared to LNR subgroup. Correlation analyses demonstrated that BMI (r=0.33, p=0.006; r=0.29, p=0.01; r=0.32, p=0.002) and FM (r=0.32, p=0.03; r=0.26, p=0.04; r=0.40, p=0.003) were positively associated with fasting glucose, glycated hemoglobin and leptin levels, respectively. Finally, as shown in table 3, multiple linear regression indicated that only glucose level is independently associated with obesity in RHTN patients, adjusted for age, gender and race.

Table 1. General characteristics of RHTN subgroups

	BMI<31.5 (n=50)	BMI>31.5 (n=41)
Age (years)	59.4±12.9	59.5±7.1
Gender (M/F)	20/30	12/29
Race (W/nW)	23/27	20/21
BMI (Kg/m²)	27.1±2.8	36.8±3.6
SBP office (mmHg)	146.4±23.4	146.3±21.1
DBP office (mmHg)	84.7±17.1	85.6±13.1
PP office (mmHg)	62.1±18.6	61.7±15.1
SBP ABPM (mmHg)	133.2±16.6	130.0±21.5
DBP ABPM (mmHg)	80.4±11.2	75.11±15.3*
PP ABPM (mmHg)	52.8±11.5	54.8±11.2
Urea (mg/dL)	34.4±10.7	38.4±16.4
Creatinine (mg/dL)	1.0±0.3	1.2±0.7
Clear Creat (mL/min/1,73m²)	76.0±45.4	85.3±32.1
Total cholesterol (mg/dL)	198.6±49.5	201.2±45.6
HDL-c (mg/dL)	47.7±17.2	45.1±10.6
LDL-c (mg/dL)	122.5±34.4	119.7±39.7
Triglycerides (mg/dL)	157.1±84.1	182.2±91.0
Plasma sodium (mEq/L)	141.4±2.1	141.3±2.2
Plasma potassium (mEq/L)	4.7±1.1	4.4±0.7
Microalbuminuria (mg/g)	37.1±56.6	38.0±72.4

Values expressed as mean±SD. M: male; F: female; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; ABPM: Ambulatory blood pressure monitoring; Clear Creat: creatinine clearance; HDL-c: cholesterol high density lipoprotein; LDL-c: cholesterol low density lipoprotein. * p<0.05.

DISCUSSION

This present study showed that obese resistant hypertensive patients (BMI>31.5kg/m²) had higher fasting glucose as well as HbA1c levels, which may reflect the impact of obesity in deregulation of glucose metabolism in these individuals. In addition, fasting blood glucose was strongly and independently associated with obesity - represented by increased BMI. In fact, obesity is a strong predisposing factor for the development of type 2 diabetes[13]. This relationship may be explained by the association of obesity with low-grade inflammation, characterized by higher levels of circulating proinflammatory cytokines and fatty acids, which induces insulin resistance by interfering in the normal insulin function and causing β-cell dysfunction[14,15]. Indeed, the β-cell failure may be partly due to genetic factors and partly due to acquired factors. Among the acquired factors, the prolonged exposure of pancreatic β-cells to high levels of glucose and lipids may contribute to oxidative stress and high rates of β-cells apoptosis[16,17].

The OBS subgroup showed greater hormonal change due to the higher plasma levels of aldosterone and leptin when compared to the counterparts. The effects of aldosterone are mediated by the mineralocorticoid receptor (MR), which acts on the salt homeostasis and BP regulation in epithelial target tissues. Those receptors have also been identified stimulating non-classical signaling pathways of aldosterone, particularly on the adipose tissue, which mediate the adipogenesis and proinflammatory process[10]. In this context, MR activation may arise as a causative factor in several pathological conditions, including insulin resistance and obesity[18]. Obesity and increased aldosterone may be linked, because adipose tissue releases soluble factors that stimulate adrenal aldosterone secretion[19]. In turn, active MR on adipocytes promotes proinflammatory cytokines expression, which causes reduced insulin receptor expression and impaired insulin-induced glucose uptake[19]. Moreover, improvement in insulin sensitivity has been closely associated with decreases in skeletal muscle NADPH oxidase activity – as well as the levels of reactive oxygen species – and with greater mitochondrial structure integrity[20]. Thus, the MR antagonists, besides the current use to treat patients with RHTN, emerge as a potential pharmacological strategy to reverse metabolic outcomes involved in RHTN disease[21,22] and downregulate proinflammatory adipokines, such as leptin[11].

In addition, leptin – secreted from the peripheral adipose tissue – reaching the brain can activate neural pathways that increase the renal sympathetic nervous system. This will result in RAAS stimulation leading to increases in sodium retention, volume expansion and BP levels[11,12]. As obesity may result in chronic hyperleptinemia, it is possible to associated leptin levels with the RHTN pathophysiology[8].

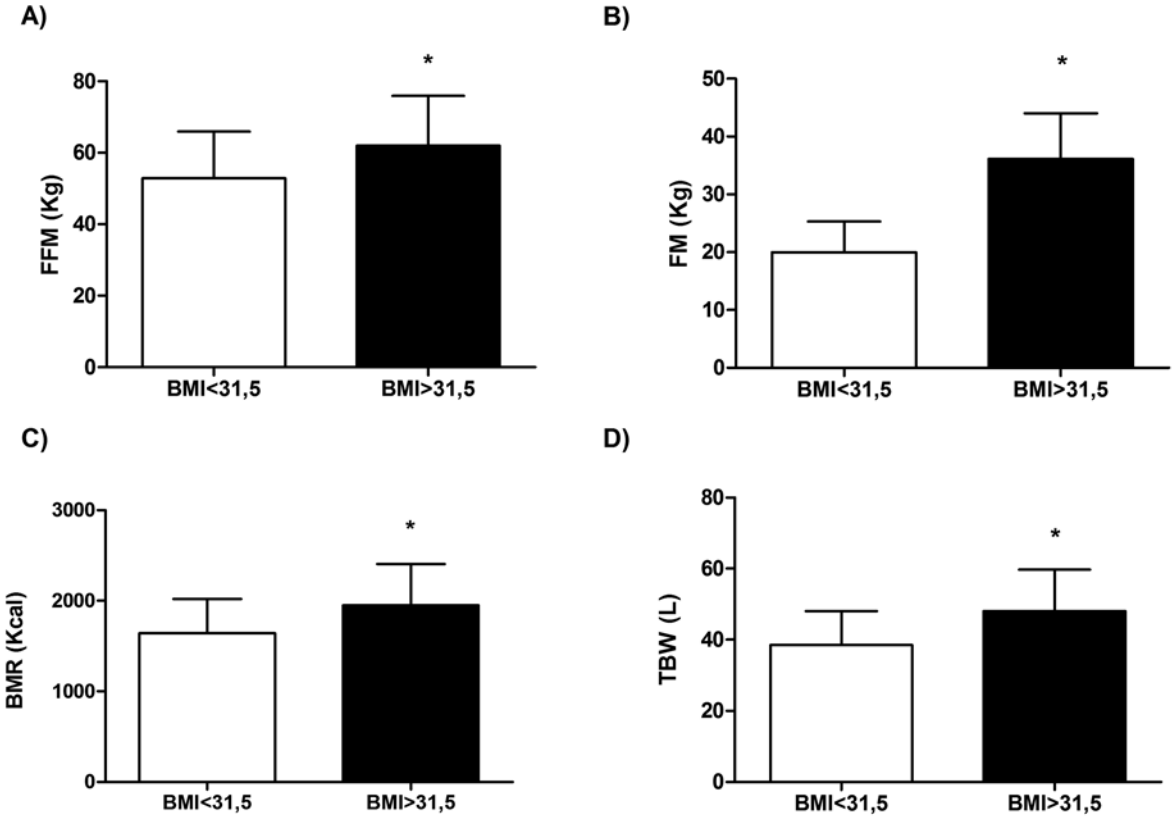

Figure 1. Bioimpedance parameters in RHTN subgroups according to the categorization of BMI (FFM: fat-free mass; FM: fat mass; BMR: basal metabolic rate; TBW: total body water).

Table 2. Proportion of antihypertensive drugs use for the RHTN subgroups

Anti-HT drugs, n (%)	BMI<31,5 (n=50)	BMI>31,5 (n=41)
Diuretic	47 (93,8%)	38 (91,7%)
Spironolactone	20 (39,6%)	18 (42,7%)
Beta-blockers	35 (70,8%)	31 (75,0%)
ACE	21 (41,7%)	15 (36,1%)
ARB	26 (52,1%)	26 (63,9%)
CCB	44 (87,5%)	38 (91,7%)
Centrally acting-drugs	14 (27,1%)	9 (22,2%)

Values expressed as mean±SD. ACE: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor antagonists; CCB: calcium channel blockers.

Finally, the parameters of bioimpedance in agreement with the literature[23], demonstrated that obese individuals have higher FFM, FM, BMR and TBW. A recent study has showed that the FFM and FM contribute almost equally to the BMI variation, being this contribution caused by common genetic as well as shared environmental and metabolic factors[24]. BMI is an index current used in clinical practice as an easy indirect parameter of obesity. Although the parameters of bioimpedance may offer a better description of adiposity of an individual[25], the BMI categorization has been associated with metabolic changes in our subjects, supporting the measurement of this parameter of great interest. On the other hand, the bioelectrical impedance method can be more appreciated in the clinical management of RHTN population, since it may better predict cardiovascular risk[26].

Some limitations to our study should be mentioned. This study enrolled a small number of RHTN patients. The 24-hour urinary aldosterone excretion rate test was not performed, although this assay could help assess patients with changes in aldosterone physiology. Some antihypertensive drugs may reduce expression of proinflammatory factors reversing obesity-related changes[27]. Despite that, those possible sources of interferences did not affect our findings, since subgroups had similar proportion of antihypertensive agents use. Furthermore, due to ethical issues RHTN individuals must not be assessed withdrawing the antihypertensive drugs. Because this study was cross-sectional, causal inferences cannot be made. However, our findings support a possible link of metabolic diseases such as obesity, diabetes and resistant hypertension.

In conclusion, our findings showed that higher BMI may be determinant in deregulating glucose metabolism as well as aldosterone and leptin levels in resistant hypertensive subjects. Those outcomes support that an intensive lifestyle change is crucial trying to revert metabolic disorders and achieve BP

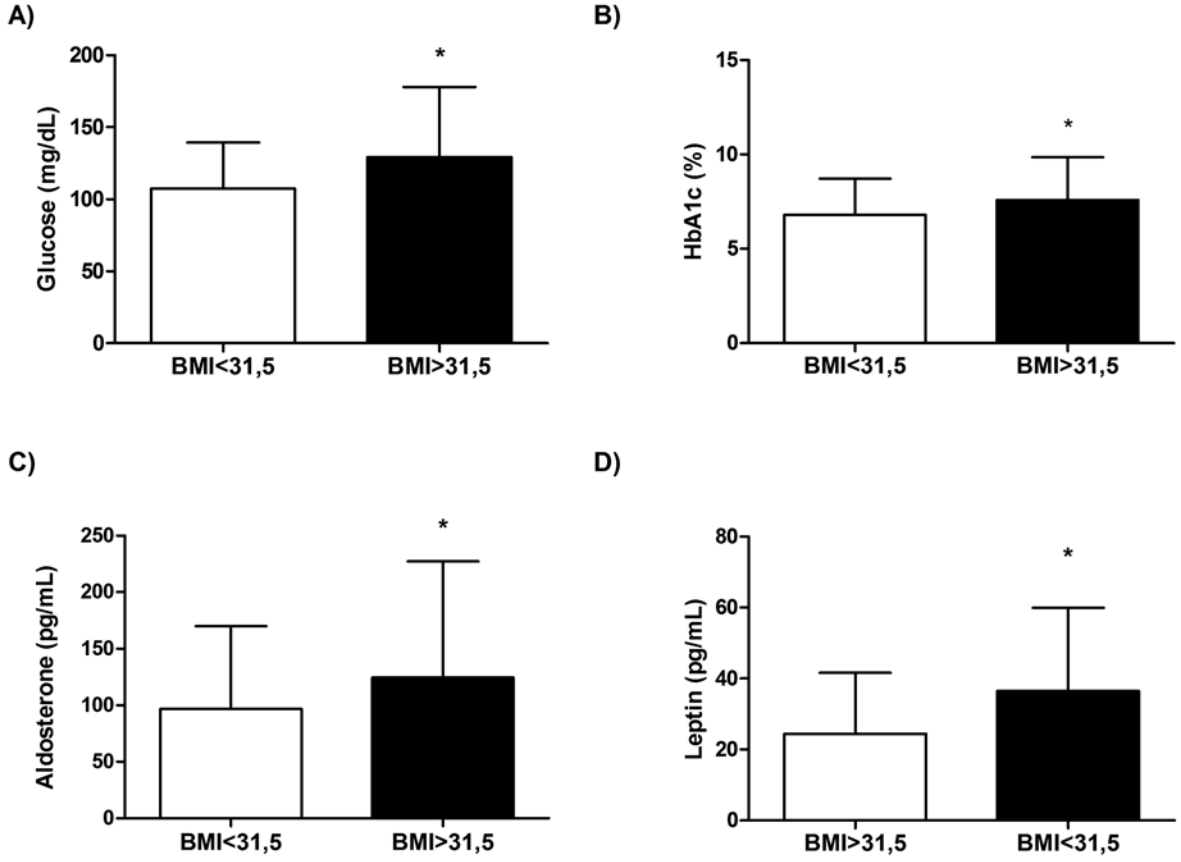

Figure 2. Hormonal and metabolic parameters in RHTN subgroups according to the categorization of BMI (HbA1c: glycated hemoglobin).

Table 3. Multiple linear regression for the presence of obesity in RHTN subgroups*

Variable	β coefficient	SE	*P*
Glucose	0.05	0.02	0,003
Aldosterone	0.01	0.01	0,21
Leptin	0.0001	$5x10^{-5}$	0,31

*Also adjusted for age, gender and race.

control[28, 29]. Moreover, the RHTN-related disorders such as diabetes[30] must also be focused. Indeed, this may reflect a worse prognosis of those obese subjects, although this hypothesis should be tested using prospective studies with a larger RHTN population.

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