

**Title:** Metabolic syndrome-related features in controlled and resistant hypertensive subjects

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## **ABSTRACT**

Metabolic syndrome (MetS) is widespread among hypertensive patients. In addition, clinical features and potential biomarkers associated with MetS in the presence of hypertension and resistant hypertension (RHTN) represent a great area of interest to investigate. The purpose of this study was to evaluate the prevalence of MetS and the clinical features associated with it in resistant and mild to moderate hypertensives. This cross-sectional study included 236 patients, (i) 129 mild to moderate hypertensive patients and (ii) 107 patients with RHTN. We determined BP measurements, bioimpedance parameters and adipokines levels. Microalbuminuria (MA), cardiac hypertrophy and arterial stiffness were also assessed. We found a prevalence of 73% in resistant and 60% in mild-to-moderate hypertensive patients. In a multiple regression analysis MA, leptin/adiponectin ratio (LAR) and RHTN were independently associated with the presence of MetS apart from potential confounders. Our findings suggest that the metabolic derangements present in MetS tend to develop early signs of end-organ damage with hormonal changes in hypertensive patients. Indeed, LAR may be useful as a reliable biomarker for identifying those who are at risk for developing MetS.

## **INTRODUCTION**

Metabolic Syndrome (MetS) is a cluster of metabolic abnormalities. Approximately a quarter of worldwide adult population has MetS making it an expressive public health challenge (1). Ever since the MetS was described in 1988 (2), several scientific organizations have attempted to formulate general definition for the syndrome. The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) in 2001 (3), and the revised version in 2005 (4) has become the most widely used definition, probably because it provides a relatively simple approach for diagnosing MetS with easily measurable risk factors.

The relationship between MetS and cardiovascular diseases is noteworthy (CVD) (5). In the largest meta-analysis comprising nearly one million patients, MetS, was associated with a 2-fold increase in risk of CVD, CV mortality, myocardial infarction and stroke, and a 1.5-fold increase in the risk of all-cause mortality (5). The negative prognostic impact of MetS was also observed in patients with hypertension (6-8). Studies have shown a high prevalence of hypertension-related asymptomatic organ damage in hypertensive patients with MetS, such as left ventricular hypertrophy (LVH), elevated urinary albumin excretion rate and arterial stiffness (9-12). The majority of these patients have shown a deregulated production of adipokines (13). Adiponectin, an adipokine with anti-atherogenesis activity, insulin sensitization, lipid oxidation enhancement, and vasodilatation functions (14) showed to be decreased in obese and subjects with essential (15) and resistant (16, 17) hypertension. In contrast, elevated leptin levels are associated with MetS, hypertension and atherosclerosis (18). On the other hand, there is few data regarding MetS, resistant hypertension and mild to moderate hypertension.

**AIMS** The present study aimed to evaluate the prevalence of MetS and the clinical features associated with it in resistant and mild to moderate hypertensive patients.

## **METHODS**

**Study population** In this cross-sectional study, 107 resistant (RHTN) and 129 mild to moderate hypertensive patients regularly followed at the Outpatient Specialized Resistant Hypertension Clinic and Hypertension Clinic of the University of Campinas (Campinas, Brazil) were enrolled, and classified into those with MetS (n=157) and without MetS (n=79). The diagnosis of "true" RHTN was done according to the American Heart Association Statement (19) defined by (1) high blood pressure (BP)

levels despite the use of at least three antihypertensive agents of different classes or (2) controlled BP after the use of four or more drugs. Ideally, one of the three agents should be a diuretic and all agents should be prescribed at optimal doses. Mild to moderate hypertensive subjects were defined in accordance to the 2013 ESH guidelines (20). Diagnosis of MetS was determined according to the criteria proposed by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) in 2001 (3), and revised in 2005 (4), as the presence of at least three of the following criteria: (i) waist circumference  $\geq 88$ cm for women or  $\geq 102$ cm for men, (ii) HDL-cholesterol  $< 50$  mg/dL for women or 40mg/dL for men, (iii) triglycerides  $\geq 150$  mg/dL (or in current use of fibrate), (iv) cutoff BP values of  $\geq 130/85$ mmHg (or current antihypertensive treatment), and (v) fasting glucose  $\geq 100$ mg/dL (or current treatment for type 2 diabetes). This study was approved by the Research Ethics Committee of the Faculty of Medical Sciences at University of Campinas (Campinas, Brazil; Approval n. 188.161). All patients provided written informed consent form before participation, and the study was carried out according to the ethical principles for medical research involving human subjects of the World Medical Association (Declaration of Helsinki).

**Bioimpedance** Fat-free mass (FFM), fat mass (FM), total body water (TBW) and basal metabolic rate (BMR) were determined by bioimpedance device Bioimpedance Analyser 450 (Biodynamics Corporation, Seattle, USA).

**Office and Ambulatory BP measurements** Office systolic BP (SBP) and diastolic BP (DBP) were evaluated at approximately 08:00 a.m. in the right arm using a validated digital sphygmomanometer (HEM-907XL, OMRON Healthcare Inc., Bannockburn, IL, USA) (21). The 24-h ABPM measurements were performed with a validated automatic device (Spacelabs 90217, Spacelabs Inc, Redmon, WA, USA), and measurements were taken every 20min. Both office and ambulatory BP measurements were performed according to 2013 ESH guidelines (20).

**Biochemical measurements** The values between 30 and 300 mg/g of urine albumin/creatinine ratio grouped the patients as having microalbuminuria (MA) for comparisons of early renal damage. Plasma concentrations of adiponectin and leptin (R&D Systems, Minneapolis, USA) were determined by ELISA and aldosterone (Immunotech SAS, Marseille, France) by chemiluminescence, according to the manufacturer's instructions.

**Pulse wave velocity** Arterial stiffness was determined by pulse wave velocity (PWV), in meters per second (m/s), dividing the distance between the right carotid and femoral arteries by the pulse transit time through these two sites of interest. We used the Sphygmocor device (AtCor Medical, USA), synchronized with the electrocardiogram. The patients were considered as having arterial rigidity if  $PWV \geq 10$ m/s, for comparisons of vascular damage (22)

**Echocardiography** The left ventricular (LV) measurements were performed according to the recommendations of the American Society of Echocardiography using two-dimensional M-mode echocardiography (23). Examinations were performed by an echocardiography expert and reviewed by one blinded investigator, following standard technique, using a cardio-vascular ultrasound machine (Siemens Acuson CV70, Munich, Bavaria, Germany) with a multi-frequency sector transducer (2-4 MHz). We calculated LV mass index (LVMI), and considered those with  $LVMI > 95$ g/m<sup>2</sup> (females) and  $> 115$ g/m<sup>2</sup> (males) as having left ventricular hypertrophy (LVH).

**Statistical analyses** For continuous variables we calculated the mean and standard deviation or median (Q1, Q3 percentiles), according to normal distribution, measured by the Kolmogorov-Smirnov test. Comparisons between groups were performed using Student's t or Mann-Whitney test. A logistic regression model was applied to determine association of clinical variables with the presence of MetS, apart from potential confounders. A significance level of  $\alpha = 0.05$  was adopted.

## RESULTS

Baseline characteristics of hypertensive subjects with and without MetS are shown in table 1. We found a MetS prevalence of 66% in all hypertensive population. Neither

office and ambulatory BP levels nor the proportion of patients with uncontrolled office BP (>140/90mmHg) were different between groups. The patients with MetS showed a higher prevalence of MA compared to their counterparts (Table 1). The medication use was similar between groups, except for the calcium channel blockers and antidiabetics that were higher in MetS group. Adiponectin levels were significantly lower in patients with MetS, while leptin demonstrated to be increased in those patients, compared to the subjects without MetS (Table 2). Finally, the multiple logistic regression revealed that MA, leptin/adiponectin ratio and resistance to antihypertensive treatment were independently associated with the presence of MetS (Table 3).

## **DISCUSSION**

Our main findings suggest that MA, high leptin levels and low adiponectin levels (demonstrated by leptin/adiponectin ratio) are associated with the presence of MetS in hypertensive population, apart from potential confounders. Also, resistance to antihypertensive treatment is strongly associated with MetS. The high prevalence of these coexisting conditions – hypertension and MetS (10-12) – may explain the increased prevalence of hypertension-related target organ damage (TOD), such as elevated urinary albumin excretion (9-12). Additionally, this early renal organ damage may in part explain the increased CV risk conferred by MetS in hypertensive patients, since this marker of TOD is a well-known predictor of CV events (24, 25). In this sense, the identification and treatment of risk factors for cardiovascular and renal diseases, as well as an early detection of hypertension-related TOD may directly affect the prognosis of hypertensive patients with MetS (26).

Our finding of increased MA in hypertensive patients with MetS is supported by previous studies (9, 12, 25, 27, 28). The common underlying mechanisms that may explain increased MA in patients with MetS include factors such as: (i) overactivation of the renin-angiotensin system; (ii) increase in oxidative stress and (iii) inflammation (29, 30). In addition, the presence of MA may reflect on progressive endothelial and vascular dysfunction (31). It is worth to mention that we found no difference in BP levels between the groups. Thus, in our cross-sectional study MA is probably associated with other components that comprise MetS. Another hypothesis is that the greater use of calcium channel blockers (CCB) by hypertensive patients with MetS could have resulted in BP control, but not in avoiding early renal damage, in agreement with several studies (32). Another point to be mentioned is that despite of the greater use of antidiabetic drugs by patients with MetS, HbA1c remained higher in this group. On the other hand, studies (33-36) have consistently shown that levels of HbA1c <7% are associated with a reduced risk of structural and clinical manifestations of diabetic nephropathy in patients with diabetes type 1 and type 2. For instance, the U.K. Prospective Diabetes Study (UKPDS) demonstrated about 30% risk reduction for the development of microalbuminuria in the group intensively treated for hyperglycemia (HbA1c of 7%)(34).

Hypoadiponectinemia and hyperleptinemia is commonly found in hypertensive and obese patients. Previous studies have shown an inverse association between adiponectin levels and low-grade albuminuria in essential (15) and resistant hypertensive patients (16, 17). Similarly in experimental studies, adiponectin knockout rats have higher levels of albuminuria (twice above normal values), and after replacement of the protein, albuminuria returned to its normal levels (37). Hyperleptinemia is also an independent risk factor for coronary artery disease (38) and strong predictor of acute myocardial infarction. Besides that, leptin acts as a powerful sympathostimulator, associated with increased blood pressure and tachycardia, which consequently contributes to obesity-related hypertension and kidney damage (39-42). Furthermore, a study has supported that the leptin/adiponectin ratio (LAR) is more beneficial than either alone for the diagnosis of MetS (43). The use of LAR has the potential to assess insulin sensitivity and metabolic syndrome in the non-fasting state, since the difference between adiponectin and leptin tends to be small in the fasting versus postprandial state (44). Our study showed that LAR was independently

associated with the presence of MetS. There are several studies that relate MetS to various cytokines and adipokines, but no biomarker is currently used in clinical practice to help in predicting and establishing MetS in individuals. Therefore, the deregulated adipokine levels (LAR) might be an important tool for diagnosis, prognosis or even early detection of MetS in the high-risk hypertensive population, although these associations should be tested. This approach may also guide a better rational therapeutic approach and risk management, since adipokines are altered after lifestyle modifications and medications. Specifically, a study has shown serum increase of adiponectin in diabetic hypertensive patients who were using valsartan (45). Further, a study showed that the use of bromocriptine – a potent agonist at dopamine D2 receptors – lowers circadian leptin concentrations in obese women (46).

The prevalence of MetS has been increasing worldwide (47), and it is higher in hypertensive patients than in general population (8, 9, 11, 48). In our study, we found a considerable prevalence of MetS in all hypertensive subjects (66%), but a prevalence of 73% in resistant and 60% in mild-to-moderate hypertensive patients. Similar data have been reported in the Global Cardiometabolic Risk Profile in Patients with hypertension disease (GOOD) study (49), in which 58% of essential hypertensive patients had MetS. Indeed, other similar study also indicated a high proportion of resistant hypertension among patients with MetS (50). This high prevalence may be explained by the older age of the population in the studies, since prevalence of MetS is highly age-dependent (1). In our study, RHTN was associated with MetS independently of potential confounders. The metabolic derangements associated with MetS promote alterations in the vasculature and the kidney that might lead to RHTN and CKD (51). Furthermore, the increased renal impairment in the patients with MetS is probably linked directly to the underlying condition of prior hypertension of these patients (52). In this context, our findings highlighted the importance of improving strategies to prevent cardiovascular and renal outcomes. Still, it points out that not only RHTN patients require a close clinical attention, but also mild to moderate hypertensive subjects, who demonstrated a high prevalence of MetS as well as RHTN patients.

Finally, pharmacological approaches should be carried out in order to improve obesity (e.g. orlistat, bariatric surgery), dyslipidemia (e.g. statins, ezetimibe, fibrates, omega-3-polyunsaturated), hyperglycemia (e.g. metformin, glucagon-like peptide-1-agonists, dipeptidyl peptidase-4-inhibitors) and hypertension (e.g. angiotensin converting enzyme inhibitors, angiotensin II receptor blockers,  $\alpha$ -antagonists, thiazide-type diuretic, spironolactone) (52) for renal protection. However, the cornerstone of treating MetS remains lifestyle modification (4, 53), which mainly involves healthy diet, aerobic exercise, and behavioral counseling. To date, current guidelines do not specifically address the management of hypertension in the patient with MetS. However, considering the increased risk of developing diabetes in these patients, it seems reasonable that the first consideration in antihypertensive treatment is to be focused on the inhibition of the renin-angiotensin system with either angiotensin converting enzyme or angiotensin II receptor inhibitions (54, 55). There has been increasing interest in combination strategies of antihypertensive agents in RHTN patients with MetS to reduce the pill burden. In the TRINITY study, the triple-combination therapy with olmesartan, amlodipine and hydrochlorothiazide provides higher BP reductions and enabled greater proportions of participants to reach BP goal without any increase in adverse effects when compared to the dual-combination in obese hypertensive patients (56). Future works are still needed to define the best antihypertensive therapy in this group of high-risk patients.

In summary, our study showed that MetS is significantly associated with MA, RHTN and adipokines levels. These findings suggest that hypertensive patients with MetS tend to develop early manifestations of end-organ damage with metabolic/hormonal changes, culminating in increased cardiovascular risk and renal impairment. Early diagnosis of MetS in hypertensive patients may enable more accurate prediction of adverse cardiovascular events and renal impairment and could implement more

efficient strategies in terms of primary prevention. Besides that, prompt identification of MetS in resistant hypertensive patients allows modification of multiple risk factors that promote resistance to antihypertensive therapy, as well as guide the treatment to individual components of the syndrome. Thus, targeted treatment to individual components of the syndrome along with weight loss and lifestyle modifications can prevent the development of resistance to antihypertensive treatment, as well as contribute to effective therapy in resistant hypertensive patients with MetS. Given the alterations that MetS confers on RHTN, future clinical trials can begin to address this important topic. Once the syndrome is identified, lifestyle changes and a different therapeutic approach can enhance the prognosis of the disease. Indeed, further studies on LAR in a larger hypertensive population with MetS is needed to assess whether this marker is sensitive and specific for identifying those who are at risk for developing MetS. The LAR could provide a relatively easy, minimally-invasive mean for early MetS diagnosis and, consequently, decreasing the chance of maladaptive effects that this syndrome causes.

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**Table 1. General characteristics of hypertensive patients with and without metabolic syndrome**

	Patients with MetS (n=157)	Patients without MetS (n=79)	p-value
<b>Clinical data</b>			
Age (years)	63 (56 – 70)	65 (56 – 71)	0.39
White race (%)	122 (77)	52 (65)	0.05
Female gender (%)	106 (67)	47 (59)	0.23
BMI (kg/m <sup>2</sup> )	31 (27 – 34)	26 (23 – 28)	<0.01
WC (cm)	100 ±13	89 ±12	<0.01
FFM (Kg)	54 (46 – 62)	52 (44 – 63)	0.13
FM (Kg)	24 (19 – 31)	17 (13 – 23)	<0.01
TBW (%)	74 (72 – 75)	73 (72 – 75)	0.03
BMR (cal/day)	1672 (1436 – 1947)	1616 (1369 – 1954)	0.23
Office SBP(mmHg)	142 (134 – 150)	146 (132 – 154)	0.39
Office DBP(mmHg)	82 (75 – 89)	82 (80 – 88)	0.44
Office HR (bpm)	67 (61 – 76)	64 (58 – 72)	0.01
24h-ABPM SBP(mmHg)	128 (118 – 139)	129 (118 – 136)	0.78
24h-ABPM DBP(mmHg)	77(70 – 81)	78 (70 – 86)	0.28
ABPM HR (bpm)	64±14	64±13	0.94
Uncontrolled office BP (%)	96 (61)	48 (60)	0.97
<b>TODs</b>			
MA≥30(mg.g <sup>-1</sup> ), n (%)	31 (20)	3 (4)	<0.01
PWV≥10(m.s <sup>-1</sup> ), n (%)	68 (43)	35 (44)	0.94
LVH, n (%)	83 (53)	44 (55)	0.96

Abbreviations: BMI, body mass index; WC, waist circumference; FFM, fat free mass; FM, fat mass; TBW, total body water; BMR, basal metabolic rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; ABPM, ambulatory blood pressure monitoring; LVH, left ventricular hypertrophy; MA, microalbuminuria; PWV, pulse wave velocity.

**Table 2. Biochemical parameters of hypertensive patients with and without metabolic syndrome**

	Patients with MetS (n=157)	Patients without MetS (n=79)	p-value
Leptin (ng.mL <sup>-1</sup> )	21.0 (14.40–41.60)	15.70 (6.30–33.20)	<0.01
Adiponectin (µg.dL <sup>-1</sup> )	5.30 (2.60– 7.80)	7.50 (3.80 – 11.90)	<0.01
LAR	4.81 (2.14 – 10.80)	2.22 (1.10 – 5.20)	<0.01
LAR > 3.72, n (%)	85 (54)	24 (30)	<0.01

Values are expressed as mean ± standard deviation or median (1st, 3rd quartiles), according to data distribution. Abbreviations: MetS, metabolic syndrome; LAR, leptin adiponectin ratio.

**Table 3. Multiple logistic regression for the presence of MetS\***

	Odds ratio	95% CI	p-value
LAR>3.7	4.13	1.38 – 12.34	0.01
HR (bpm)	0.97	0.92 – 1.03	0.39
MA>30 (mg.g <sup>-1</sup> )	8.51	1.53 – 47.14	0.01
hs-CRP (mg.dL <sup>-1</sup> )	2.92	0.83 – 10.19	0.09
RHTN	3.75	1.09 – 12.92	0.03

\*Also adjusted for age, gender and race. Abbreviations: MetS, metabolic syndrome; hs-CRP, high-sensitivity c-reactive protein; HR, heart rate; MA, microalbuminuria; RHTN, resistant hypertension; LAR>3.7, leptin adiponectin ratio>3.7 (the cutoff value was determined by median value).

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