Blood pressure and its circadian pattern in obese and lean premenopausal women

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Abstract

Background. Obesity is frequently referred to as an independent risk factor for high blood pressure and hypertension is very prevalent among obese people. The aims of this study were: to compare office-based and 24 h blood pressure (BP) and its circadian pattern between lean and obese women; to study correlations between BP, insulin resistance (IR) and markers of subclinical inflammation/early atherosclerosis.

Material and methods. Eighty-eight lean and 107 otherwise healthy obese women were characterized for anthropometrics, BP (office-based determinations and 24 h ABPM) and for glucose, insulin, triglycerides, inteleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), high-sensitivity C reactive protein (hs-CRP), retinol-binding protein 4 (RBP-4), leptin, adiponectin, resistin, monocyte chemoattractant protein 1 (MCP-1), intercellular adhesion molecule 1 (ICAM-1), and vascular-cellular adhesion molecule 1 (VCAM-1). Insulin resistance was determined by homeostasis model assessment of insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), and McAuley indexes (also Matsuda in obese).

Results. Obese group presented higher office-based systolic/diastolic BP, systolic ambulatory blood pressure monitoring (ABPM), and more non-dippers. HOMA-IR and body fat was correlated to systolic (r2 = 0.176) and glucose to diastolic (p = 0.008; r = 0.256) ABPM. Age, QUICKI, and TNF-α was correlated with dipping (r2 = 0.172); adiponectin, age, BMI, and glucose to systolic (r2 = 0.226) and diastolic (r2 = 0.215) office-based BP. Concerning lean women, MCP-1 was associated with diastolic ABPM (p = 0.013; r = 0.267). Systolic office-based BP was associated with waist-to-hip ratio (p = 0.01; r = 0.273); this and RBP-4 was correlated with office-based diastolic BP (r2 = 0.12).

Conclusion. Although relatively healthy, obese women present higher BP than lean. Anthropometrics, IR, and fasting glucose all influence BP in obesity; additionally, IR is involved in non-dipping. No strong correlation exists between BP/dipping and subclinical inflammation in either group of women.

Key words: obesity; hypertension; cardiovascular diseases; dipping; subclinical inflammation

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Introduction

Obesity is frequently referred to as an independent risk factor for high blood pressure and hypertension is very prevalent among obese people [1]. Compared to lean individuals, the National Health and Nutrition Examination Survey III Study showed that the odds ratio for the presence of hypertension was 1.7 for overweight, 2.6 for class I obesity, 3.7 for class II obesity and 4.8 for class III obesity [2]. Being both obesity and hypertension independent cardiovascular risk factors, obese hypertensive patients represent very high-risk individuals [3]. In the presence of excessive fat mass, the dysfunctional adipose tissue produces higher levels of adipokines that may interfere at several steps of blood pressure control [4–7]. On the other hand adiponectin, an adipokine with reported beneficial effects on blood pressure lowering, is synthesized at lower levels [8–10]. Moreover, obesity is associated with a hyperactivation of the sympathetic nervous system, which contributes both to an increase in blood pressure and to the blockade of the normal nocturnal fall in blood pressure [5, 11–13]. The aim of this study was to compare classic office-based and 24h mean blood pressure and its circadian pattern between obese otherwise healthy and lean women without known history of hypertension. Secondarily, we aimed to study correlations of blood pressure, determined by the two methods, with insulin resistance, markers of subclinical inflammation and early atherosclerosis in each group of women.

Material and methods

Subjects

The obese group consisted in 107 obese Caucasian premenopausal women who attended the obesity outpatient clinic at the Curry Cabral Hospital — C.H.L.C. (Lisbon, Portugal). Their age ranged from 18 to 50 years old and their body mass index (BMI) was ≥ 30 kg/m^2. All of them referred less than 10% variation on their body weight in the previous year.

The control group consisted in 88 healthy Caucasian premenopausal women, who either attended to a routine health check or belonged to the health care staff of Curry Cabral Hospital — C.H.L.C. They were aged from 18 to 50 years old, body mass index (BMI) from 18,5 to 24,9 kg/m^2, and referring less than 10% variation on their body weight in the previous year.

No woman was pregnant or had been pregnant in the precedent 12 months. We considered only women without previous diagnosis of any acute/chronic health conditions (except obesity for the obese group), namely previous diagnosis of hypertension. No woman was on any pharmacological regimen (except for oral contraceptives) or took any sporadic drug in the previous 7 days.

The study was conducted following the approval of the institutional scientific and ethical boards accordingly to the standards of the Declaration of Helsinki. Additionally, an informed consent was signed by all participants.

Clinical evaluation

Each woman was characterized for total body weight, BMI, waist and hip circumferences, and waist-to-hip ratio. The total body fat mass (absolute and percentage of body weight) was assessed by bioelectrical impedance (Tanita TBF-300A˚, Tanita Europe B.V., Hoofddorp, The Netherlands).

Office-based blood pressure was assessed by the mean value of 2 determinations at the left arm, in the standard recommended conditions with a 5 minutes interval, using an electronic device with appropriated sized cuffs (CASMED˚ 740 monitor, CAS Medical Systems Inc, Branford, CT, USA). Women were classified as hypertensive if the mean values were ≥ 140 mm Hg for systolic or ≥ 90 mm Hg for diastolic blood pressure.

ABPM was performed during a 24 h period, in a regular day, with registrations every 30 minutes during daytime (from 07:00 am to 11:00 pm) and every hour for the night-time (from 11:00 pm to 07:00 am) with a portable electronic device (SpaceLabs 90207˚ monitor, SpaceLabs Healthcare, Issaquah, WA, USA) and appropriated sized cuffs. The device established the mean values of systolic and diastolic blood pressure for daytime, night-time and the overall 24h period. Women were classified as hypertensive if mean values were ≥ 130/80 mm Hg for the overall 24h, ≥ 135/85 mm Hg for the daytime or ≥ 120/70 mm Hg for the night-time periods accordingly to the European Society of Hypertension and European Society of Cardiology criteria [11]. They were considered as dippers if a ≥ 10% decrease in mean night-time blood pressure occurred compared to mean daytime blood pressure.

Women answered a small questionnaire regarding smoking status, use of oral contraceptives and the existence of diagnosed hypertension among first degree relatives.

Blood sample collection and measurements

After a period of 10h fasting, a venous blood sample was collected from obese and lean women for assessment of glucose, insulin, triglycerides, interleu-

kin 6 (IL-6), tumor necrosis factor alpha (TNF-α), high-sensitivity C-reactive protein (hs-CRP), retinol-binding protein 4 (RBP-4), leptin, adiponectin, resistin, monocyte chemoattractant protein 1 (MCP-1), intercellular adhesion molecule 1 (ICAM-1), and vascular-cellular adhesion molecule 1 (VCAM-1). Additionally, a classic 75 g oral glucose tolerance test was performed with blood samples collected after 30, 60, 90, and 120 minutes for the assessment of glucose and insulin. Serum samples were obtained by low-speed centrifugation, stored at a –80°C ultra-freezer, and thawed just before each assay.

Glucose and triglycerides were determined by automated chemistry analyzer (Vitros® 5,1 FS Chemistry System, Ortho-Clinical Diagnosis Inc, Rochester, NY, USA) and hs-CRP concentration by a nephelometer system using CardioPhase® hsCRP assay (Siemens Healthcare Diagnostics Inc, Tarrytown, NY, USA). Leptinemia was assessed by radioimmunoassay technique (EMD Millipore Corporation, Billerica, MA, USA). Insulinemia was determined by a chemiluminescent immunometric technique (IMMULITE® 2000 Immunoassay System, Siemens Healthcare Diagnostics Inc, Tarrytown, NY, USA). Serum IL-6, TNF-α, RBP-4, adiponectin, resistin, MCP-1, ICAM-1, and VCAM-1 concentrations were all measured by enzyme-linked immunosorbent assay following the manufacturer's instructions (R&D Systems Inc., Minneapolis, MN, USA). Insulin resistance/sensitivity was assessed by the application of four mathematical equations as follows:

- homeostasis model assessment of insulin resistance (HOMA-IR) using the formula: fasting insulin in µU/mL × fasting glucose in mg/dL/405;

- quantitative insulin sensitivity check index (QUICKI): 1/[log(fasting insulin in µU/mL) + log(fasting glucose in mg/dL)];
- McAuley index (for assessment of insulin sensitivity): exp[2.63 – 0.28 × log(fasting insulin in µU/mL – 0.31 × log(fasting triglycerides in mg/dl/87.72];
- Matsuda formula (also an index of insulin sensitivity): 10.000/SqRt[fasting insulin in µU/mL × fasting glucose in mg/dL × mean (insulin at 0, 30, 60, 90, and 120 min in µU/mL) × mean (glucose at 0, 30, 60, 90, and 120 min in mg/dL].

Statistical analysis

Data are reported as mean ± SD. Comparisons between groups were made by t-Student test. The interactions between non-continuous parameters were analyzed by χ^2 test.

Simple associations were tested by Spearman r test and multiple regression analysis was carried out by the use of a forward stepwise model. A p value < 0.05 was considered statistically significant. All determinations were performed using SPSS software, version 18.0 (IBM Corporation, Armonk, NY, USA).

Results

The characterization of obese and lean groups is depicted in Table 1. In the obese group, office-based systolic blood pressure was significantly correlated to systolic blood pressure values obtained by ABPM in daytime (p < 0.001; r = 0.539), night-time (p < 0.001; r = 0.386) and 24h period (p < 0.001; r = 0.561). Identical results were observed between mean diastolic blood pressure at the office and in

Table 1. Characteristics of lean and obese women (mean ± SD)

	Lean women	Obese women	p value
N	88	107	
Age (years)	33.8 ± 8.4	34.5 ± 8.3	0.561
BMI [kg/m²]	21.5 ± 1.7	43.5 ± 7.5	< 0.001
Total body weight [kg]	56.0 ± 5.3	111.2 ± 20.8	< 0.001
Total body fat [kg]	14.2 ± 3.6	53.7 ± 14.5	< 0.001
Percentage of body fat (%)	25.0 ± 4.7	47.7 ± 5.1	< 0.001
Waist circumference [cm]	71.9 ± 6.0	117.3 ± 14.3	< 0.001
Hip circumference [cm]	97.6 ± 4.6	134.0 ± 12.6	< 0.001
Waist-to-hip ratio	0.74 ± 0.05	0.88 ± 0.08	< 0.001
Office systolic BP [mm Hg]	108.6 ± 12.1	124.7 ± 16.3	< 0.001
Office diastolic BP [mm Hg]	69.3 ± 9.7	79.5 ± 10.3	< 0.001

Table 1. Characteristics of lean and obese women (mean ± SD)

	Lean women	Obese women	p value
ABPM systolic BP in 24h [mm Hg]	115.9 ± 9.6	121.0 ± 9.1	< 0.001
ABPM diastolic BP in 24h [mm Hg]	72.5 ± 7.2	72.6 ± 6.7	0.889
ABPM systolic BP in daytime [mm Hg]	119.2 ± 9.6	124.0 ± 9.7	0.001
ABPM diastolic BP in daytime [mm Hg]	75.9 ± 7.2	75.9 ± 7.5	0.973
ABPM systolic BP in night-time [mm Hg]	106.6 ± 10.6	112.4 ± 11.0	< 0.001
ABPM diastolic BP in night-time [mm Hg]	62.7 ± 7.6	63.6 ± 8.2	0.447
Fasting glucose [mg/dL]	81.0 ± 7.2	93.3 ± 29.2	< 0.001
Fasting insulin [μUI/mL]	5.9 ± 3.8	17.7 ± 11.4	< 0.001
Triglycerides [mg/dL]	79.8 ± 29.7	120.6 ± 78.3	< 0.001
Interleukin-6 [pg/mL]	1.39 ± 1.33	2.38 ± 1.66	< 0.001
TNF-α [pg/mL]	1.31 ± 0.81	1.38 ± 0.89	0.579
High-sensitivity C reactive protein [mg/dL]	0.22 ± 0.31	0.96 ± 0.76	< 0.001
RBP-4 [ng/mL]	41.3 ± 12.5	34.2 ± 16.4	0.001
Leptin [ng/mL]	10.5 ± 5.8	36.8 ± 14.9	< 0.001
Adiponectin [μg/mL]	12.3 ± 5.1	6.9 ± 3.3	< 0.001
Resistin [ng/mL]	19.2 ± 10.7	19.2 ± 9.6	0.99
MCP-1 [pg/mL]	324.7 ± 102.2	374.5 ± 129.6	0.003
ICAM-1 [ng/mL]	228.1 ± 54.2	245.8 ± 72.8	0.061
VCAM-1 [ng/mL]	506.7 ± 182.6	496.9 ± 186.1	0.714
HOMA-IR	1.18 ± 0.76	4.31 ± 3.56	< 0.001
QUICKI	0.17 ± 0.02	0.14 ± 0.01	< 0.001
McAuley index	9.50 ± 1.96	6.4 ± 1.7	< 0.001
Matsuda formula	ND	3.92 ± 2.79	–
Women on oral contraceptives (%)	50.0 (44/88)	46.7 (50/107)	0.649
Current smokers (%)	35.2 (31/88)	12.1 (13/107)	< 0.001
Diagnosed hypertension in first degree relatives (%)	55.7 (44/79)*	54.1 (46/85)*	0.839

ND — not determined; BMI — body mass index; ABPM — ambulatory blood pressure monitoring; TNF-α — tumor necrosis factor alpha; hs-CRP — high-sensitivity C reactive protein RBP-4 — retinol-binding protein 4; MCP-1 — monocyte chemoattractant protein 1; ICAM-1 — intercellular adhesion molecule 1; VCAM-1 — vascular-cellular adhesion molecule 1; HOMA-IR — homeostasis model assessment of insulin resistance; QUICKI — quantitative insulin sensitivity check index

*Data concerning to the presence/absence of diagnosed hypertension in first degree relatives could not be obtained in 9 lean and in 22 obese women

ABPM in daytime (p < 0.001; r = 0.717), night-time (p = 0.002; r = 0.295) and 24h period (p < 0.001; r = 0.43). Also in obese women, there was a significant inverse association of age with insulin resistance determined by HOMA-IR (p = 0.042; r = –0.197) and a trend for the inverse correlation with BMI (p = 0.056; r = –0.186); age was directly associated with all insulin sensitivity indexes: QUICKI (p = 0.009; r = 0.253), McAuley index (p = 0.007; r = 0.261), and Matsuda formula (p = 0.01; r = 0.248).

Less strong correlations were observed in the lean women between office-based systolic blood pressure and systolic blood pressure by ABPM in daytime (p = 0.001; r = 0.359), night-time (p = 0.015; r = 0.26) and 24h period (p = 0.002; r = 0.327). The same was observed concerning association of diastolic office-based blood pressure and diastolic ABPM mean values in daytime (p = 0.009; r = 0.278), night-time (p = 0.013; r = 0.264) and 24h (p = 0.015; r = 0.258).

For both groups of women, the association between office-based blood pressure and 24h values in ABPM for systolic and diastolic blood pressure is exposed graphically in Figures 1 and 2, respectively.

Hypertension based on office measurements of blood pressure was more prevalent among obese women (Tab. 2), but that difference was not observed on ambulatory blood pressure monitoring (Tab. 3). Likewise, no difference between obese and lean groups was observed if we considered ABPM criteria for hypertension in daytime (16.8% *vs.* 15.9%), night-time
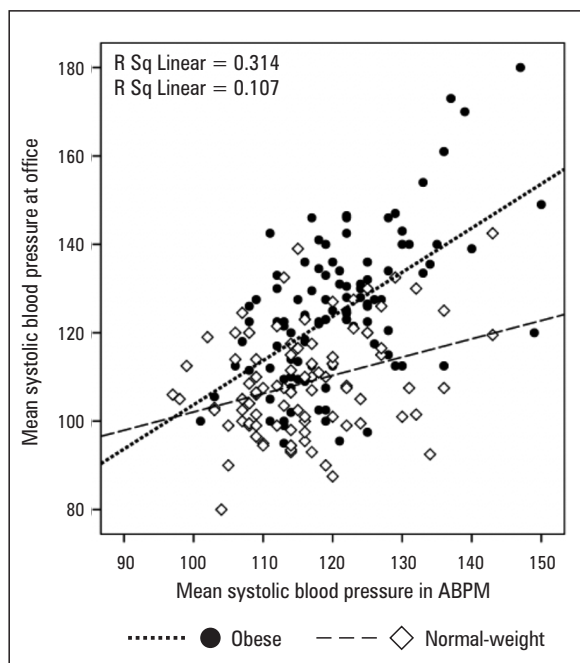
Figure 1. Correlation of mean systolic office-based blood pressure and mean values in 24 h ambulatory blood pressure monitoring, in obese and normal-weight women
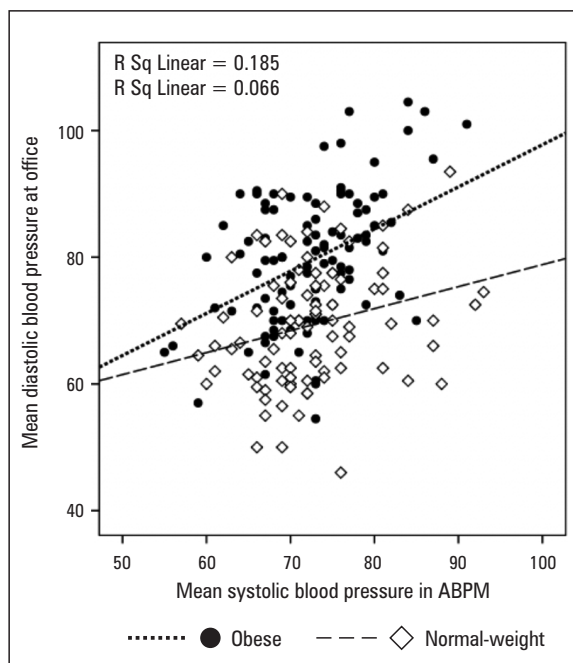

Figure 2. Correlation of mean diastolic office-based blood pressure and mean values in 24 h ambulatory blood pressure monitoring, in obese and normal-weight women

Table 2. Obese and lean women meeting criteria for hypertension by office-based blood pressure

p < 0.001		Office-based blood pressure criteria for hypertension		Total
		Yes	No	
Group	Obese women	28 (26.2%)	79 (73.8%)	107 (100%)
	Lean women	3 (3.4%)	85 (96.6%)	88 (100%)
	Total	31 (15.9%)	164 (84.1%)	195 (100%)

Table 3. Obese and lean women meeting criteria for hypertension by ambulatory blood pressure monitoring

p = 0.199		Ambulatory blood pressure monitoring criteria for hypertension		Total
		Yes	No	
Group	Obese women	41 (38.3%)	66 (61.7%)	107 (100%)
	Lean women	26 (29.5%)	62 (70.5%)	88 (100%)
	Total	67 (34.4%)	128 (65.6%)	195 (100%)

(31.1% *vs.* 27.6%) and 24h (19.6% *vs.* 18.2%) periods separately. When comparing those diagnosed for hypertension by office-based measurements with those based on ABPM, different populations were found (Tab. 4). That was also true if we compared office-based hypertensive women with those with daytime (p < 0.001), night-time (p = 0.012) and 24h (p < 0.001) criteria for hypertension.

Non-dipper pattern of blood pressure variation was more prevalent in obese than in lean women

Table 4. Comparison of hypertensive groups by office-based and ambulatory blood pressure monitoring considering only obese women and both groups together

		Ambulatory blood pressure monitoring criteria for hypertension		Total
		Yes	**No**	**Total**
Obese women (p = 0.005)				
Office-based blood pressure criteria for hypertension	Yes	17 (15.9%)	11 (10.3%)	28 (26.2%)
	No	24 (22.4%)	55 (51.4%)	79 (73.8%)
	Total	41 (38.3%)	66 (61.7%)	107 (100%)
Both groups together (p = 0.001)				
Office-based blood pressure criteria for hypertension	Yes	19 (9.8%)	12 (6.1%)	31 (15.9%)
	No	48 (24.6%)	116 (59.5%)	164 (84.1%)
	Total	67 (34.4%)	128 (65.6%)	195 (100%)

(39.6% *vs.* 24.1%; p = 0.022). Considering each group of women, the prevalence of non-dippers was lower in those who fitted the criteria for night-time hypertension than in those who did not, either in obese (p = 0.001) or in lean women (p = 0.018).

In obese women several direct correlations exist between blood pressure, insulin resistance and some markers of subclinical inflammation or atherogenesis. Moreover, some particular inverse correlations were present between some of those parameters and the degree of nocturnal fall in blood pressure. By a stepwise multiple regression analysis HOMA-IR and body fat percentage were found to be independently associated to 24 h (r^2 = 0.176) and daytime (r^2 = 0.111) systolic blood pressure; HOMA-IR and waist circumference were independently associated with night-time systolic blood pressure (r^2 = 0.202). Fasting glucose was associated with daytime (p = 0.039; r = 0.199) and 24h diastolic blood pressure (p = 0.008; r = 0.256). Night-time diastolic blood pressure was correlated with HOMA-IR (p = 0.003; r = 0.286) and QUICKI (p = 0.017; r = –0.231). By a stepwise multiple regression analysis, it was shown that TNF-α levels (inversely), age and QUICKI (directly) were all independently correlated with the dipping phenomenon (r^2 = 0.172). Adiponectin circulating levels (inversely), age, BMI, and fasting glucose (directly) were all independently correlated to systolic (r^2 = 0.226) and diastolic (r^2 = 0.215) office-based blood pressure.

By contrast, among lean women an independent association exists between MCP-1 circulating levels and diastolic blood pressure in daytime (p = 0.013; r = 0.269) and 24h period (p = 0.013; r = 0.267) ABPM. Systolic office-based blood pressure was associated with waist-to-hip ratio (p = 0.01; r = 0.273); waist-to-hip ratio and RBP-4 circulating levels were independently associated with diastolic office-based blood pressure (r^2 = 0.12). In this group of women, no association was found for the dipping phenomenon with any of the parameters considered in this study.

Discussion

As classically described, obesity is associated with high blood pressure [1, 2]. That was also shown in this study for office-based systolic and diastolic blood pressure and for systolic blood pressure in all periods considered in ABPM. Although a high correlation was present between office-based and ABPM, it was found a significant difference in hypertension prevalence between obese and lean women for office-based criteria but not for ABPM criteria. In concordance to these data, we confirmed that the group of women diagnosed with hypertension by one criterion does not fit in the hypertension definition by the other. For the definition of daytime and night-time we considered fixed schedules. One possibility for the dissimilarity between criteria could be the fact that some women had daytime-like activities over 11:00 pm or before 07:00 am. If it would be the case, mean night-time blood pressure values would be expected to increase

leading to a higher prevalence of night-time hypertension and exaggerating hypertension rates based in ABPM [15]. Nevertheless, that explanation does not appear to fit; if we compared women with office-based hypertension with those with hypertension criteria based on daytime, the difference was even greater (p < 0.001) than if we compared with those with night-time hypertension (p = 0.012).

All the factors that were independently associated with office-based blood pressure values in obese women (i.e. age, BMI, fasting glucose, and adiponectin), and that explains more than one fifth of its variation, are in line with previous reports in the literature [5, 16–18]. Also based on ABPM, it was shown a direct association of systolic blood pressure with anthropometrics. The net association between fasting glucose levels and diastolic blood pressure is concordant with the close relationship that exists between hypertension and glucose intolerance states. Hypertension is more prevalent in individuals with type 2 diabetes and intermediate hyperglycemia and these conditions are more prevalent among individuals diagnosed with hypertension [17–19]. Independently from anthropometrics, insulin resistance was also directly associated with blood pressure values in obese women. This is in line with the evidence of insulin resistance *per se* as a contributing factor for hypertension. There are several mechanistic explanations for the association between insulin resistance and blood pressure increase; one of those mechanisms involves sympathetic activation. [20]. The greater sympathetic activity in insulin resistant women would explain the higher night-time blood pressure values and the non-dipping pattern observed. Non-dippers have also been reported to be more prevalent in conditions characterized by insulin resistance [21].

The inverse independent association of TNF-α with the dipping status would be expected in the context of a higher atherogenic-related subclinical inflammation state [22]. Assuming non-dipper status as a cardiovascular risk factor it would be logical to find higher levels of several atherogenic markers, but it was not the case. Another possible explanation for the inverse association of TNF-α with dipping phenomenon could be through induction of insulin resistance [23]. Nevertheless, that association is independent of insulin sensitivity and no association could be found between TNF-α and insulin resistance indexes in this study. On the other hand, TNF-α itself could have some direct effect on vasculature inducing endothelial dysfunction and a decrease in nitric oxide synthesis as previously demonstrated in rats [24, 25].

Aging is characterized by an increase in sympathetic activity [26]. However, in this study it was found an inverse association between age and dipping in obese women. It is true that there was a trend for the inverse correlation of age with BMI and that age was directly associated with insulin sensitivity. Nevertheless, the association of age with the dipping status was independent of those two parameters. For the inclusion criteria only women without any known health condition (other than obesity) were accepted. The age ranged from 18 to 50 years old but it was especially difficult to find obese women above the age of 35 (and a more prolonged history of obesity) with no known comorbidities. Perhaps those older obese women selected belong to the so-called relatively benign obesity or metabolically healthy but obese individuals, i.e. those with obesity but without the metabolic and cardiovascular risks as expected for the degree of excessive body fat [27, 28].

Opposite to the obese group, in lean women all the above associations were missing. That could be the case because most of the parameters shown to be associated with blood pressure parameters in the obese group were lower in lean women. Thus there was still no deleterious involvement on blood pressure control. One exception was anthropometry, confirming that it exerts an effect on blood pressure even in the absence of excessive body fat mass.

Although an association exists between mean blood pressure levels in ABPM and those obtained by standard measurement in the office setting, whether we use one or the other for the diagnosis of hypertension we are identifying different groups of women. In obese women, anthropometrics and insulin resistance are main determinants of blood pressure in ABPM. Age, anthropometrics, fasting glucose, and adiponectin circulating levels all influence office-based blood pressure levels, explaining a little more than 20% of it. On the other hand, age, insulin resistance and TNF-α levels are all independent determinants of blood pressure fall during night-time. Even though assuming a lower cardiovascular risk compared to the classic obesity, metabolically healthy but obese women present higher blood pressure (essentially systolic blood pressure). However, no strong correlation exists between blood pressure or the dipping phenomenon and subclinical inflammation or markers of atherosclerosis activity either in lean or in metabolically healthy but obese women.

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