ORIGINAL ARTICLE

Nocturnal but not Diurnal Hypertension Is Associated to Insulin Resistance Markers in Subjects With Normal or Mildly Elevated Office Blood Pressure

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OBJECTIVE
The aim was to evaluate the relationships among insulin resistance markers and nocturnal and diurnal hypertension in normotensive or mildly untreated hypertensive adults.

METHODS
The study was performed in both female and male adults referred to the Cardiometabolic Unit of the Hospital San Martín, La Plata, Argentina, in order to perform an ambulatory blood pressure measurement (ABPM) for the evaluation of a possible hypertensive disorder. The population was stratified according to their ABPM in: 1—presence or absence of diurnal hypertension and 2—presence or absence of nocturnal hypertension; both conditions were analyzed separately. Fasting plasma insulin (FPI), homeostasis model assessment of insulin resistance (HOMA-IR), and triglycerides (TG)/high-density lipoprotein cholesterol (HDL-C) ratio were used as surrogate markers of insulin resistance and compared among subjects with vs. without diurnal or nocturnal hypertension.

RESULTS
One hundred and five patients, 55 women, 47 (11) years old, and 50 men, 44 (16) years old, were included. Diurnal and nocturnal hypertension were found in 60% and 64% of the sample, respectively. There were no significant differences among the levels of insulin resistance markers between individuals with or without diurnal hypertension. In contrast, individuals with nocturnal hypertension were more insulin resistant irrespectively of whether they were evaluated using FPI ($P = 0.016$), HOMA-IR ($P = 0.019$), or TG/HDL-C ratio ($P = 0.011$); FPI differences remained significant after adjustment for sex, age, and obesity indicators ($P = 0.032$).

CONCLUSIONS
Nocturnal but not diurnal hypertension was related to higher levels of 3 insulin resistance markers in normotensive and untreated mildly hypertensive adults; this relationship seems partially independent of obesity.

Keywords: ambulatory blood pressure monitoring; blood pressure; diurnal hypertension; hypertension; insulin resistance; nocturnal hypertension.

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Elevated blood pressure (BP) is a major independent risk factor for the development of cardiovascular disease, and its variation at day or night depends on a phenomenon called circadian rhythm. This BP variation (dipping phenomenon) consists in a decrease of mean nighttime BP of 10–20% from daytime BP and occurs as a normal physiologic change. However, these changes do not occur in some individuals. In a cohort study of the Spanish Society of Hypertension Ambulatory Blood Pressure Monitoring Registry, 35% of untreated patients and 40% of treated patients had no dipping pattern.[1] Subjects with a nondipping pattern had more hypertension-induced organ damage such as left ventricular hypertrophy, microalbuminuria, and reduced arterial compliance, and had worse prognosis in terms of cardiovascular events.[2,3]

Nocturnal hypertension is defined as BP >120/70 mm Hg at night.[4] Nocturnal hypertension is a frequently overlooked condition due to the limited use of ambulatory BP measurement (ABPM).[5] Although high nocturnal BP is sometimes accompanied by a nondipping pattern, they are not always present together and their significance could be different. While a nondipping profile reflects an inadequate mechanism of BP regulation, nocturnal BP represents the minimal BP levels that the subjects need for an adequate organ perfusion.[6] Consequently, absolute values of nocturnal BP could be a good opportunity to evaluate the relationships among BP and some physiological factors. Maintaining a high BP at night overloads the cardiovascular system with a negative impact on the heart and vascular structures.[6] Fagard *et al.*[7]

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assessed the prognostic significance of nighttime and daytime ambulatory BP by performing a meta-analysis in 3,468 hypertensive patients. Daytime and nighttime systolic BP predicted all-cause and cardiovascular mortality, coronary heart disease, and stroke. Nonetheless, when these BP were entered simultaneously into the models, nighttime BP predicted all outcomes, whereas daytime BP did not add prognostic precision. Remarkably, after adjustments, absolute nocturnal BP values were stronger predictors of cardiovascular disease than nondipping patterns.

Many factors were postulated as nocturnal hypertension producers. Some of these pathophysiological mechanisms, such as inflammation, nocturnal autonomic nervous system imbalance, and kidney limitations for sodium metabolism, are also states for insulin resistance/hiperinsulinemia.[8,9] Furthermore, in a study performed in obese children and adolescent, insulin resistance was associated to elevated nocturnal, but not daytime, BP.[10] The authors propose that the early increment of nocturnal BP associated to hiperinsulinemia in children and adolescent may be a harbinger of hypertension-related insulin resistance in adults.

Although some early studies supported this notions,[11] others did not.[12] Furthermore, to the best of our knowledge, the relationships among insulin resistance and nocturnal vs. diurnal BP has not been extensively evaluated in normotensive or mildly untreated hypertensive adults. In consequence, the aim of this study was to evaluate the relationships among insulin resistance markers and nocturnal and diurnal hypertension.

MATERIAL AND METHODS

The sample consisted of adults of both sexes, aged 18–85, referred to the Cardiometabolic Unit of the Hospital San Martín, La Plata, Argentina—a specialized hypertension centre—enrolled to perform an ABPM for the evaluation of a possible hypertensive disorder. Written informed consent was obtained from all participants. In order to define office BP, a specially trained nurse performed 3 BP measurements with a validated automatic oscillometric BP monitors (OMRON HEM 705 CP), appropriate arm sleeves, a previous 5 minutes resting period and in seated position, with the arm at heart level. Office BP was defined as an average of 3 determinations. Individuals with a previous diagnosis of cardiovascular disease, hypertension or diabetes, office BP ≥160/100 mm Hg or taking antihypertensive drugs were excluded. On the same day, an ABPM was initiated with a Spacelabs 90207. Measurements were scheduled every 15 minutes during the day and every 20 minutes at night. Only ABPM with ≥70% of successful measurements and at least 1 record per hour were considered valid. In order to evaluate quality of habitual nocturnal resting, the usual sleep duration, loud snoring, and daytime sleepiness were investigated. Also, at the end of the monitoring session, the participants filled a questionnaire focused on the quality of sleep during the overnight BP monitoring. The questionnaire included the hour of retiring, the hour of rising, the perceived duration of sleep, and the difference in sleep duration compared to the usual (ie, in the absence of ABP monitoring) scored as: 1—usual, 2—< 2 hours less than usual, and 3—> 2 hours less than usual.

Night and day period, defined taking into account the patient's diary, were analyzed separately. Hypertension during daily activities was defined as day ABPM ≥135/85 mm Hg; nocturnal hypertension was defined as ABPM during night rest ≥120/70 mm Hg.

Weight was determined with subjects wearing light clothing and no shoes. Height was also measured without shoes, using a metallic metric tape, and body mass index (BMI) was calculated with the formula weight (kg)/height^2 (m). Waist circumference was measured with a relaxed abdomen using a metallic metric tape on a horizontal plane above the iliac crest; neck circumference was measured on the middle of the neck, between the mid-cervical spine and the superior line of the cricothyroid membrane in a standing position. Metabolic assessment was performed under fasting conditions in the early morning. Peripheral blood samples were obtained to measure concentrations of plasma glucose, total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and fasting plasma insulin (FPI). Low-density lipoprotein cholesterol was estimated by the Friedewald formula.[13] FPI concentrations were determined using immunoassay of paramagnetic microparticles (Ultrasensitive insulin Acces Beckman Coulter, dynamic range: 0.03–300 μIU/ml, sensitivity: 0.03 μIU/ml precision: <10% coefficient of variation). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the formula [FPI (μU/ml) × glucose (mg/dl/18)/22.5].[14]

The experimental population was dichotomously classified according to their ABPM in: 1—presence or absence of diurnal hypertension and 2—presence or absence of nocturnal hypertension; both conditions were analyzed separately. Values for age, heart rate, BP, BMI, total cholesterol, HDL-C and low-density lipoprotein cholesterol, and glucose were compared between subjects with vs. without diurnal or nocturnal hypertension using Student "t" test for independent samples. This procedure produces 2 tests of the difference between the 2 groups. One test assumes that the variances of the 2 groups are equal and a in a second test equal variances are not assumed. This assumption is tested by the Levene statistic and the proper *P* values are selected.

FPI, HOMA-IR, and TG/HDL-C were used as surrogates markers of insulin resistance and compared between subjects with vs. without diurnal or nocturnal hypertension. Since insulin resistance is associated to obesity, covariance analysis (univariate general lineal model) including BMI, waist circumference, and neck circumference as covariates, was performed to control the differences among these parameters. Finally, since some subjects had both nocturnal and diurnal hypertension, a further comparison between subjects with isolated diurnal hypertension vs. isolated nocturnal hypertension was performed.

All significant tests were 2-tailed, and *P* values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS (SPSS, Chicago, IL).

RESULTS

The initial enrolment included 122 subjects without history of diabetes who were not taking antihypertensive drugs; during the evaluation period 2 individuals with BP

≥160/100 mm Hg and 1 with glucose levels >126 mg/dl were excluded. One hundred and five patients, 55 women, 47 (11) years old, and 50 men, 44 (16) years old (P = 0.153), had valid day and night ABPM and completed all the laboratory data necessary for the present study. There were no significant differences in terms of age (P = 0.364), BMI (P = 0.344), and office BP (P = 0.324 and P = 0.909 for systolic and diastolic, respectively) between individuals that completed the study and those who did not. Characteristics of the sample are shown in Table 1.

There were not significant differences in the usual duration of the sleep among individuals with vs. without nocturnal hypertension, 6.9 (1.3) vs. 6.8 (1.1) h, P = 0.490. Furthermore, the prevalence of snoring (60.9% vs. 64.9%, P = 0.695) and daytime sleepiness (29.7% vs. 37.8%, P = 0.400) were similar in both groups. The distribution of perceived sleep duration in terms of difference from usual was: usual 78.7%, <2 hours less than usual 14.8%, and >2 hours less than usual 5.5%. Diurnal and nocturnal hypertension were found in 60% and 64% of the sample, respectively. There were no significant differences in terms of age, office BP, BMI, waist circumference, neck circumference, and clinic chemistry values among individuals with vs. without diurnal hypertension (Table 2). These findings were similar when the comparison was made between subjects with vs. without nocturnal hypertension except for TG, which was significantly higher in those with nocturnal hypertension. Remarkably, there were no significant differences in obesity markers (Table 2).

There were no significant differences in the levels of insulin resistance surrogates (FPI, HOMA-IR, and TG/HDL-C ratio) between individuals with or without diurnal hypertension. In contrast, individuals with nocturnal hypertension were more insulin resistant irrespectively of whether they were evaluated using FPI, HOMA-IR, or TG/HDL-C ratio (Table 3). Higher FPI concentrations in this group remained significant after adjustment for sex, age, and obesity indicators. Moreover, obesity adjusted differences in HOMA-IR values had marginal significance.

Individuals with isolated nocturnal hypertension, compared to those with isolated diurnal hypertension, had significantly higher levels of FPI (P = 0.015), HOMA-IR (P = 0.010), and TG/HDL-C ratio (P = 0.038) and these differences remained significant after adjustment for sex, age, and obesity indicators (P values 0.033, 0.013, 0.015, respectively). The comparisons of FPI levels between individuals with vs. without diurnal hypertension (i), with vs. without nocturnal hypertension (ii), and with isolated diurnal vs. isolated nocturnal hypertension (iii) can be seen in Figure 1.

DISCUSSION

Our study shows that nocturnal but not diurnal hypertension was related to higher levels of 3 insulin resistance

Table 1. Demographic and metabolic characteristics of the study population

	Women (n = 55)	Men (n = 50)	
	Mean (SD)	Mean (SD)	P*
Age (years)	48 (11)	44 (16)	0.161
BMI (kg/m^2)	30.0 (5.0)	29.0 (4.6)	0.327
Waist circumference (cm)	94 (17)	100 (14)	0.058
Neck circumference (cm)	37 (2)	43 (10)	<0.001
Systolic office BP (mm Hg)	125 (20)	135 (10)	<0.001
Diastolic office BP (mm Hg)	79 (14)	84 (9)	0.050
Diurnal systolic ABPM (mm Hg)	130 (8)	134 (7)	0.007
Diurnal diastolic ABPM (mm Hg)	83 (8)	86 (7)	0.047
Nocturnal systolic ABPM (mm Hg)	117 (11)	120 (8)	0.142
Nocturnal diastolic ABPM (mm Hg)	69 (9)	72 (8)	0.175
Creatinine (mg/dl)	0.8 (0.1)	0.9 (0.1)	<0.001
Uric acid (mg/dl)	4.1 (1.1)	5.5 (1.1)	<0.001
Glucose (mg/dl)	91 (10)	96 (12)	0.021
Total cholesterol (mg/dl)	191 (35)	187 (29)	0.619
LDL-C (mg/dl)	121 (31)	120 (24)	0.904
HDL-C (mg/dl)	46 (11)	39 (7)	<0.001
Triglicerydes (mg/dl)	122 (54)	149 (87)	0.064
FPI (μU/ml)	7.0 (4.9)	6.9 (4.8)	0.899

Abbreviations: ABPM, ambulatory blood pressure monitoring; BMI, body mass index; BP, blood pressure; FPI, fasting plasma insulin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

P*: independent samples "t" test.

Table 2. Comparison of the characteristics of individuals with vs. without diurnal hypertension and with vs. without nocturnal hypertension, both defined using ambulatory blood pressure monitoring (ABPM)

	Diurnal hypertension			Nocturnal hypertension		
	No (*n* = 42)	Yes (*n* = 63)	*P**	No (*n* = 38)	Yes (*n* = 67)	*P**
Age (years)	46 (13)	47 (14)	0.661	46 (13)	47 (14)	0.775
BMI (kg/m^2)	30.5 (4.7)	28.9 (4.9)	0.90	28.9 (4.8)	29.9 (4.9)	0.340
Waist circumference (cm)	97 (13)	97 (18)	0.819	96 (10)	98 (19)	0.553
Neck circumference (cm)	41 (11)	39 (4)	0.438	38 (3)	41 (9)	0.119
Office heart rate (beats/min)	73 (16)	74 (20)	0.719	75 (12)	73 (21)	0.729
Systolic office BP (mm Hg)	126 (12)	132 (20)	0.130	128 (12)	131 (20)	0.337
Diastolic office BP (mm Hg)	78 (9)	83 (13)	0.021	79 (8)	83 (13)	0.097
Diurnal heart rate (beats/min)	76 (10)	80 (9)	0.043	78 (11)	79 (9)	0.654
Diurnal systolic ABPM (mm Hg)	125 (5)	137 (6)	<0.001	128 (8)	134 (7)	<0.001
Diurnal diastolic ABPM (mm Hg)	78 (5)	89 (6)	<0.001	80 (6)	87 (7)	<0.001
Nocturnal heart rate (beats/min)	65 (8)	68 (9)	0.149	65 (10)	68 (8)	0.178
Nocturnal systolic ABPM (mm Hg)	113 (8)	122 (9)	<0.001	110 (7)	123 (7)	<0.001
Nocturnal diastolic ABPM (mm Hg)	65 (6)	74 (8)	<0.001	63 (5)	75 (7)	<0.001
Creatinine (mg/dl)	0.8 (0.2)	0.8 (0.2)	0.620	0.8 (0.2)	0.8 (0.1)	0.674
Uric acid (mg/dl)	4.8 (1.5)	4.7 (1.1)	0.853	4.5 (1.4)	4.8 (1.2)	0.270
Glucose (mg/dl)	94 (11)	94 (11)	0.902	92 (10)	94 (12)	0.376
Total cholesterol (mg/dl)	192 (34)	187 (31)	0.479	193 (33)	187 (31)	0.396
LDL-C (mg/dl)	124 (29)	118 (26)	0.300	126 (28)	117 (27)	0.102
HDL-C (mg/dl)	44 (12)	42 (8)	0.264	44 (11)	42 (9)	0.276
Triglicerydes (mg/dl)	123 (51)	142 (84)	0.155	112 (50)	147 (81)	0.008

Variables expressed as mean and SD. Abbreviations: BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

*P**: independent samples "t" test.

Table 3. Comparison of the markers of insulin resistance between individuals with vs. without diurnal hypertension and with vs. without nocturnal hypertension

	Diurnal hypertension				Nocturnal hypertension			
	No (*n* = 42)	Yes (*n* = 63)			No (*n* = 38)	Yes (*n* = 67)		
	Mean (SD)	Mean (SD)	*P**	*P***	Mean (SD)	Mean (SD)	*P**	*P***
FPI (μU/ml)	6.8 (3.4)	7.0 (5.6)	0.803	0.431	5.7 (2.6)	7.7 (5.6)	0.016	0.032
HOMA-IR	1.6 (0.8)	1.7 (1.5)	0.667	0.424	1.3 (0.7)	1.8 (1.5)	0.019	0.058
TG/HDL-C ratio	3.1 (1.6)	3.7 (2.6)	0.209	0.376	2.8 (1.5)	3.8 (2.5)	0.011	0.198

Abbreviations: FPI, fasting plasma insulin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglycerides.

*P**: unadjusted, *P*****: adjusted for age, sex, BMI, and waist and neck circumference.

markers (FPI, HOMA-IR, and TG/HDL-C ratio) in normotensive and mildly hypertensive adults at office. The results are in concert with previous reports of a positive relationship between insulin resistance and nocturnal hypertension in obese children and adolescents.[10]

Obesity, high levels of FPI, HOMA-IR, TG, and low levels of HDL-C during childhood and adolescence are related to the subsequent development of hypertension during adulthood.[15] Although insulin resistance and obesity are strongly related, a recently published study[16] showed that insulin resistance has a synergistic effect on the obesity-hypertension association in young adults, indicating that the role of adiposity in the development of hypertension is modified by insulin resistance. Thus, excessive adiposity and high levels of insulin resistance markers in childhood and adverse longitudinal changes through young adulthood characterize the early natural history of hypertension.

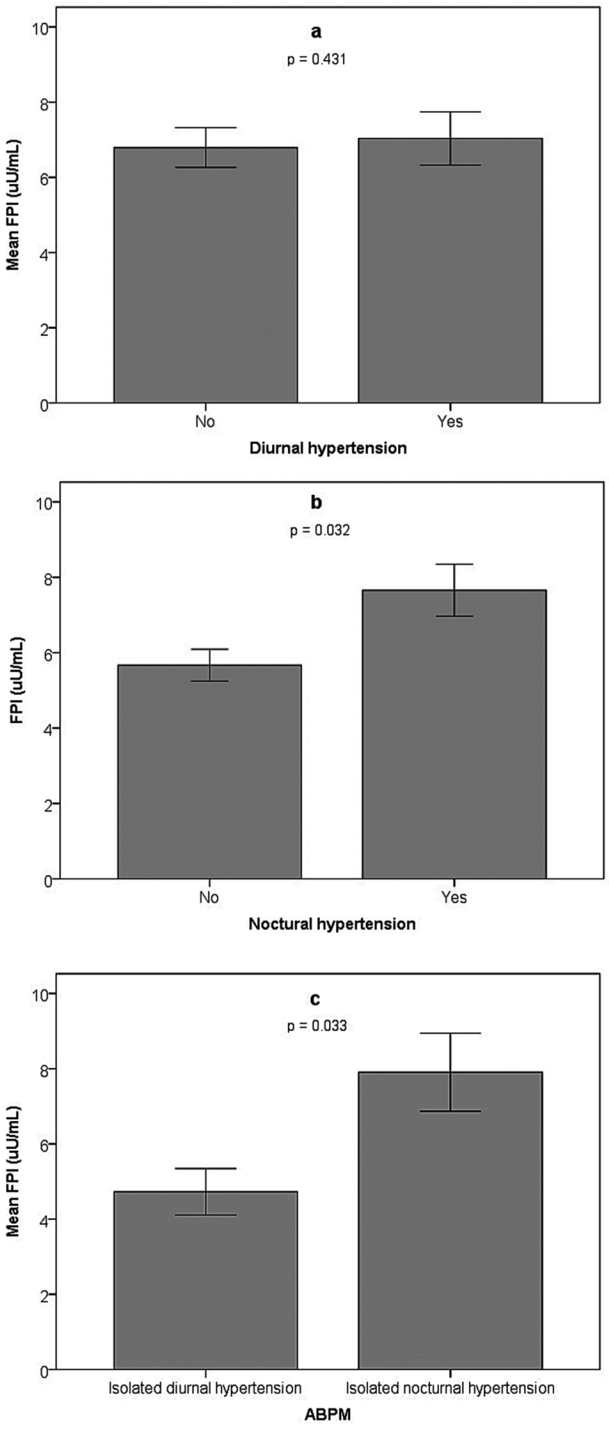

Figure 1. Comparison of FPI levels (mean ± SE) between individuals with vs. without diurnal hypertension (**a**), with vs. without nocturnal hypertension (**b**), and isolated diurnal vs, isolated nocturnal hypertension (**c**); *P* values are adjusted for sex, age, BMI, and neck and waist circumference. Abbreviations: ABPM, ambulatory blood pressure monitoring; BMI, body mass index; FPI, fasting plasma insulin.

In this context, Lurbe *et al.*[10] have suggested that the early increment of nocturnal BP and heart rate associated to hyperinsulinemia may be a harbinger of hypertension in the adult life and may contribute to a heightened cardiovascular risk. However, data analyzing the relationship between insulin resistance and nocturnal hypertension in adults is scanty and yields conflicting results. Most of the studies have analyzed nocturnal BP changes using the dipping pattern and not the absolute values of BP during nocturnal rest, and/or were focused on patients with hypertension and some comorbidities such as diabetes, renal disease, and obstructive sleep apnea.[17,18] Remarkably, in a study performed in uncomplicated and untreated hypertensive individuals, nocturnal hypertension was more frequent than nondipping patterns. Furthermore, it was associated to organ damage, independently of dipping/nondipping status and it was more reproducible than the dipping patterns.[19] Consequently, some of the previously published studies could not be appropriate to evaluate the early relationships among the values of nocturnal BP and insulin resistance. In contrast, our study focused on nocturnal hypertension and was performed in nondiabetic adults, without neither known cardiovascular disease nor markedly elevated BP, and clearly shows the relationships between nocturnal BP and insulin resistance.

Miomi *et al.*,[20] in a recently published study performed in young normotensive women with polycystic ovary syndrome, found that nighttime systolic and diastolic BP were significantly higher in obese insulin resistant women compared to noninsulin resistant obese women. Remarkably, all of these studies have compared the values of nocturnal BP between individuals defined categorically as insulin resistant or not. In contrast, we used a somewhat different approach. Based on current recommendations,[21] our sample was divided as having or not nocturnal hypertension and the differences in FPI, HOMA-IR, and TG/HDL-C levels were analyzed as continuous variables. Using this approach, individuals with nocturnal hypertension had clearly the highest values of all insulin resistant surrogates. The overactivity of the sympathetic nervous system could work as a link between hiperinsulinemia and higher values of nocturnal BP.[8] However, no differences in the heart rate were found between individuals with vs. without nocturnal hypertension in this study.

Obesity, associated or not to obstructive sleep apnea, could be a link between insulin resistance and nocturnal hypertension. However, our data suggest that the effect of insulin resistance/hiperinsulinemia on nocturnal BP could be partially independent of obesity. First, as Table 2 shows, there are no differences in BMI, waist circumference, or neck circumference between individuals with vs. without nocturnal hypertension. Additionally, higher FPI levels observed in subjects with nocturnal hypertension remained significant after the adjustment for these obesity parameters.

Since a polysomnography was not performed, we cannot discard obstructive sleep apnea. Indeed, the sample had a high prevalence of habitual snoring and daytime sleepiness, probably related to overweight and obesity (mean BMI ~30 kg/m^2, Table 2). However, the usual duration of the sleep and percentages of habitual snoring and daytime sleepiness were similar in individuals with vs. without nocturnal hypertension.

There are several limitations of this study that must be acknowledged. Firstly, specific measurements of insulin action were not performed. Since direct measurements of muscular

uptake of glucose are neither practical nor widely available, several approaches to estimate insulin resistance have been proposed and surrogate markers are commonly used in the clinical setting. In our study, we evaluated the insulin resistance level using 3 validated surrogates: FPI, HOMA-IR, and TG/HDL-C. Supporting this notion, Abbasi *et al.* have shown, in 758 apparently healthy nondiabetic individuals, that HOMA-IR and FPI correlated significantly and in a similar degree with steady-state plasma glucose concentration during the insulin suppression test.[22] Furthermore, McLaughlin *et al.* have communicated significant correlations between steady-state plasma glucose and TG/HDL-C and between steady-state plasma glucose and FPI.[23] Thus, we believe that the level of insulin resistance was reasonably estimated in our study. Secondly, the results are based on one BP monitoring only. However, in a study performed on >650 never-treated hypertensive subjects in which 2 consecutive ABPM were performed, the reproducibility of nocturnal hypertension was >70%, remarkably higher than nondipping pattern. Furthermore, a variable pattern (as they changed their profile from one to the other ABPM session) was observed in <10% of the subjects.[19] Thirdly, sleep deprivation induced by cuff inflations during overnight BP monitoring might interfere with the interpretations of our results. However, Verdecchia *et al.*[24] showed that the independent prognostic value of nighttime BP for total cardiovascular end points disappeared only when perceived sleep deprivation >2 hours. In our study ~95% of subjects reported a sleep duration perceived as usual, or <2 hours less than the usual. Consequently, it seems unlikely for the results to be substantially modified by changes in the usual pattern of nocturnal rest. Finally, the sample is relatively small and biased since the individuals included were referred to a specialized diagnostic center in order to perform an ABPM for a possible hypertensive disorder. This later issue could explain the high prevalence of abnormal ABPM. Nonetheless, our data support the use of ABPM in this specific population (subjects with normal or mildly elevated office BP) since the finding of nocturnal hypertension (combined or isolated) suggests an unfavorable cardiometabolic profile.

In conclusion, despite these limitations our results support the hypothesis regarding nocturnal hypertension as an early manifestation of hypertension-related insulin resistance in adults.

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DISCLOSURE

The authors declared no conflict of interest.

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