

Ambulatory Blood Pressure Monitoring in Normotensive Patients with Subclinical Hypothyroidism

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Abstract

Background: Overt hypothyroidism is associated with elevation of diastolic blood pressure; however the association of subclinical hypothyroidism (SH) with arterial blood pressure (ABP) alteration is unknown.

Objective: The aim of the present study was to evaluate ambulatory blood pressure monitoring (ABPM), over 24 hours, in normotensive patients with SH in comparison to euthyroid (EU) normotensive individuals.

Methods: A cross-sectional study was performed with 50 participants (SH=30 and EU=20) that did not differ regarding risk factors for hypertension. The ABPM was carried out with a Dynamapa™ monitor, using the oscillometric method validated by AAMI (Association for the Advancement of Medical Instrumentation) and by the BHS (British Hypertension Society).

Results: The mean serum TSH and FT4 were respectively $6.9 \pm 2.2 \mu\text{UI/ml}$ and $1.1 \pm 0.2 \text{ ng/dl}$ in SH patients. Although there was no difference in the mean values of systolic and diastolic blood pressure between the two groups, there was a positive correlation between the mean values of diastolic blood pressure (DBP) and serum TSH levels in SH patients ($r:0.477$; $p = 0.004$). These correlations were detected at daytime ($r:0.498$; $p = 0.002$) and sleep-time ($r:0.322$; $p = 0.032$) measurements.

Conclusion: The blood pressure was not different between patients with or without SH; however, the results suggest that the progression of subclinical hypothyroidism to higher levels of TSH may increase the cardiovascular risk by increasing diastolic blood pressure. (Arq Bras Cardiol 2010;94(6) : 756-762)

Key words: Hypothyroidism; blood pressure; blood pressure monitoring, ambulatory.

Introduction

Subclinical hypothyroidism (SH) is defined as an elevation in serum thyroid-stimulating hormone (TSH) levels with normal circulating free thyroid hormone levels (FT4 and FT3)^{1,2}. The prevalence in the general population is 1 to 10% according to different studies³⁻⁷.

Thyroid hormone has many effects on cardiovascular hemodynamics, such as heart rate, cardiac output, systemic vascular resistance and blood pressure^{8,9}. Factors affecting peripheral resistance or cardiac output can be involved in the control of blood pressure, affecting the basic equation blood pressure = cardiac output x peripheral resistance¹⁰. Thyroid hormone has an effect on peripheral vascular smooth muscle by T3 converted from T4 via types 1 and 2 deiodinases and the presence of the latter has been detected in aortic

media of rats¹¹. Experiments involving aortic endothelial and vascular smooth muscle cells revealed relaxation in response to exposure to T3 and further suggested that T3 acted directly on vascular smooth cells to cause vascular relaxation. There is a correlation between thyroid hormones and systemic vascular resistance (SVR) and thyroid hormone deficiency leads to increased SVR¹². Hypothyroidism is associated with decreased endothelium-dependent vasodilatation and animal studies have proposed that the thyroid status alters the capacity for both formation and response to nitric oxide. Endothelial dysfunction in patients with SH may result from reduction in nitric oxide availability, with resultant impairment of flow-mediated vasodilatation^{12,13}.

Overt hypothyroidism results in high systemic vascular resistance with a consequent rise in diastolic blood pressure¹⁴⁻¹⁷. Whether SH is associated with arterial blood pressure (ABP) alteration is unknown. Blood pressure measurement by the traditional method of obtaining a few readings through the auscultatory technique is characterized by too much variability. The reasons for this variability include a poor technique by the examiner, the "white-coat" effect (the transient elevation of blood pressure in a medical setting) and the inherent variability of blood pressure¹⁸. Ambulatory blood pressure monitoring

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(ABPM) enables blood pressure to be measured during sleep and permits the evaluation of circadian patterns of blood pressure¹⁹. The present study evaluated arterial blood pressure, by ambulatory blood pressure monitoring (ABPM) over 24 hours, in normotensive patients with SH and compared the results to euthyroid normotensive controls.

Methods

Thirty patients with SH (29 women and 1 men) and twenty euthyroid subjects (18 women and 2 men) were recruited from the outpatient clinic of the Clementino Fraga Filho University Hospital (HUCFF) of the Federal University of Rio de Janeiro (UFRJ). To be enrolled, SH patients had to have two TSH serum measurements, within a minimum interval period of six weeks, with both measured levels above the normal upper range (4.0 mUI/ml), and free thyroxine (FT4) within the normal range (0.9-1.8 ng/dl). All participants were eighteen years or older and gave their written informed consent to the study, which was approved by the Institutional Ethical Committee, according to the Declaration of Helsinki. Subjects on drug treatment or those with any disease which might affect thyroid function or blood pressure were excluded. Patients undergoing treatment for hypertension and those with BMI³ 30 kg/m² or with a diagnosis of diabetes mellitus were also excluded. To evaluate only SH patients with mild thyroid disease, we excluded patients with serum TSH levels higher than three times the upper reference range (> 12.0 mUI/ml). There is more evidence in the literature about the negative consequences of serum TSH levels > 10.0 mUI/ml in SH; however, the upper reference range of different laboratory methods may vary between 4.0 and 5.5 mUI/ml¹.

The euthyroid subjects had a negative history of thyroid diseases and normal evaluation of the thyroid gland on palpation and a serum measurement of TSH and FT4 within the normal range (0.4-4.0mUI/ml and 0.9-1.8 ng/dl) with no antithyroid peroxidase antibodies (TPO-Ab) in serum.

Fasting samples of venous blood were collected in the morning, from the antecubital vein of the participants. Serum TSH, FT4 and TPO-Ab were measured by immunochemiluminescent assays (DPC - Diagnostic Products Corporation/ Immulite 2000™). Reference ranges for TSH and FT4 were respectively 0.4-4.0 mUI/ml and 0.9-1.8 ng/dl. Levels of TPO-Ab > 35 UI/ml were considered positive. The intra-assay coefficients of variation were 3.8-12.5%, 4.4-7.5% and 4.3-5.6% for TSH, FT4 and TPO-Ab, respectively. The coefficients of variation between assays were 4.6-12.5%, 4.8-9.0% and 7.8-10.5%, respectively. Serum total cholesterol, HDL-cholesterol and triglycerides were measured by immunoenzymatic methods (Dimension™; Dade Behring S.A.). The low-density lipoprotein cholesterol (LDL-c) levels were calculated by Friedewald's formula ($LDL = CT - (HDL + TG/5)$).

BP was measured three times in every participant during the clinic visit, by a physician responsible for the study, using a mercury sphygmomanometer. A BP \geq 140 / 90 mmHg was considered an abnormal result requiring reevaluation and exclusion from the protocol.

The ABPM was performed with a DYNAMAP monitor, using the oscillometric method validated by the AAMI (Association

for the Advancement of Medical Instrumentation) and by the BHS (British Hypertension Society). The measurements were carried out at 15-minute intervals during the day and 30-minute intervals at night. Mean values of SBP, DBP and mean BP (MBP) were recorded in every reading throughout the 24-h interval. The difference between the mean BP during daytime and night-time was calculated. The nocturnal dipping in systolic, diastolic and mean BP was also expressed as the percentage of mean daytime BP values. Patients were classified as dippers or non-dippers when night-time MBP fall was \geq 10% or < 10% respectively. The results were interpreted according to The Seventh Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure and individuals with a diagnosis of hypertension were excluded²⁰.

Statistical analysis

Results were expressed as the mean \pm SD and were compared between two groups using the Student *t*-test, for normally distributed data, and the Mann-Whitney test for non-parametric data. The SH group was also evaluated according to serum TSH levels. Patients in the first SH group had serum TSH levels that did not reach two-fold the upper reference limit of serum TSH and that in the second group presented higher serum TSH levels, to a maximum of 12.0 mUI/ml. The comparisons between the three groups (Euthyroidism vs SH patients with serum TSH levels > 4.0-8.0 mUI/ml vs SH patients with serum TSH >8.0mUI/ml) were performed by Kruskal Wallis or ANOVA test. The correlations between two continuous variables were assessed by Pearson's or Spearman's correlation, according to the distributions patterns (normal or not normal). The χ^2 test or the Fisher exact test compared the proportions of qualitative variables in the two groups. A ROC curve was created to detect which level of serum TSH had better sensitivity and specificity to be associated with higher levels of diastolic blood pressure. A *p* value < 0.05 was considered statistically significant.

Results

Twenty euthyroid subjects and thirty SH patients were included in the study. The presence of TPO-Ab was detected in twenty-one SH patients. Both study groups had similar means of age and BMI (Table 1). Patients and controls were well-matched for gender, race, current smoking, sedentary lifestyle, menopausal status, family history of hypertension and levels of total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides. Mean serum TSH levels were $6.9 \pm 2.2 \mu\text{UI/ml}$ (range 4.15 to 11.8 $\mu\text{UI/ml}$) in SH patients and $1.48 \pm 0.6 \mu\text{UI/ml}$ in controls. FT4 levels were significantly lower in SH patients, although they were within the normal range (1.1 vs 1.25 ng/dl, *p* = 0,001). Clinic blood pressure was similar in both groups (Table 1).

There was no difference in mean systolic and diastolic blood pressure loads during daytime, night-time and 24-h between SH and euthyroid patients (Table 2). Moreover, when SH patients were evaluated according to serum TSH levels, the studied groups demonstrated similar aspects of blood pressure parameters at the ABPM (Table 2). There were no

Table 1 - Demographic characteristics of the participants

	Subclinical hypothyroidism (n = 30)	Euthyroidism (n = 20)
Age (years)	47.7 ± 10.7	45.0 ± 8.4
BMI (kg/m ²)	24.5 ± 4.0	25.1 ± 3.0
Over weight** (%)	46.7	52.6
Total cholesterol (mg/dl)	195.0 ± 34.8	194.8 ± 34.1
HDL-c (mg/dl)	53.5 ± 11.1	48.5 ± 12.7
LDL-c (mg/dl)	126.6 ± 49.8	125.3 ± 29.6
Triglycerides (mg/dl)	109.3 ± 74.9	125.7 ± 95.2
TSH (mUI/ml)*	6.9 ± 2.19	1.48 ± 0.62
FT4 (ng/dl)*	1.10 ± 0.18	1.25 ± 0.17
Ambulatory SBP (mmHg)	113.0 ± 16.2	116.5 ± 13.0
Ambulatory DBP (mmHg)	70.5 ± 10.7	74.6 ± 8.6

All p values between the two groups were > 0.10 except for TSH and FT4. *p value < 0.01. ** BMI² 25.0 and < 30.0 kg/m².

statistical differences in the frequencies of dippers between the groups; however, the nocturnal dipping in DBP (higher than 10%) occurred in 60% of SH and 80.0% of the control group (p = 0.131). SBP nocturnal dipping occurred in 70 and 71% of patients and controls, respectively (p = 0.941).

When evaluating the SH group, we observed that serum TSH levels were positively correlated with mean values of diastolic blood pressure at daytime (r_s:0.498; p = 0.002) and sleep-time (r_s:0.322; p = 0.032) as showed in figures 1 and 2. There was a positive correlation between the mean 24-h values of diastolic blood pressure (DBP) and serum TSH levels

in SH patients (r: 0.477; p = 0.004). There was no association between TSH and SBP or nocturnal BP dipping (the correlation indexes were < 0.100, with p values > 0.100). The mean dipping in nocturnal ABP was 15.8 ± 0.06% in the control group, 14.5 ± 0.07% in the SH group with serum TSH levels bellow 8.0 μUI/ml and 13.0 ± 0.07 μUI/ml in the SH patients with serum TSH > 8.0-12.0 μUI/ml (p = 0.591).

The ROC curve demonstrated that the cutoff value for serum TSH best associated with day-time and night-time DBP elevations was 3.15 mUI/ml (100% sensitivity and specificity). When evaluating day-time DBP, the area under the curve was 0.795 for a value greater than 70 mmHg of this state variable and 0.568 for a value of 80 mmHg (Figure 3). The area under the curve was 0.821 for a value > 70 mmHg of night-time blood pressure.

Discussion

The present study suggests a possible association between higher diastolic BP levels and the progression of SH to higher serum TSH elevations. However, no differences were detected in the mean values of systolic or diastolic blood pressure in SH in comparison to euthyroid subjects.

Additionally, the results suggest that mild elevations of DBP, even in the normal range, may occur in response to increments in serum TSH above 3.15 mUI/ml in middle age patients. It is important to notice that patients included in the present study were normotensive subjects. The mechanisms by which serum elevations of TSH levels would cause higher blood pressure may be associated with minimal thyroid dysfunction and reduction of thyroid hormone action on the peripheral vasculature. Thyroid hormones act directly on vascular muscle cells, causing vasodilatation by reducing arteriolar resistance^{8,9}.

Table 2 - Characteristics of ABPM of the participants and the distribution according TSH levels in the SH subgroup

Measurements	Whole group		TSH < 8 mUI/ml	TSH > 8 mUI/ml
	Subclinical hypothyroidism (n = 30)	Euthyroidism (n = 20)	Subclinical hypothyroidism (n = 22)	Subclinical hypothyroidism (n = 8)
Mean SBP* (24h)	109.5 ± 8.2	111.1 ± 8.5	109.2 ± 8.7	110.4 ± 6.8
Mean DBP* (24h)	68.7 ± 5.3	70.2 ± 4.1	68.2 ± 5.7	70.0 ± 4.3
Mean daytime SBP*	113.7 ± 8.6	116.2 ± 8.1	113.2 ± 8.9	115.0 ± 7.8
Mean daytime DBP*	71.5 ± 5.8	73.7 ± 3.7	71.0 ± 6.4	72.8 ± 4.6
Mean night-time SBP*	99.0 ± 9.3	100.7 ± 10.4	98.6 ± 9.9	100.0 ± 7.6
Mean night-time DBP*	61.2 ± 5.7	62.1 ± 5.46	60.5 ± 5.8	63.1 ± 5.1
Mean diastolic ABP nocturnal dipping	14.1 ± 0.07%	15.8 ± 0.06%	14.5 ± 0.07	13.0 ± 0.07
Mean systolic ABP nocturnal dipping	13.5 ± 0.05	12.8 ± 0.06	12.7 ± 0.07	13.1 ± 0.06
Systolic nocturnal dipping (%/ n of participants in the group)	70% / 21	70% / 14	68.2% / 15	75% / 6
Diastolic nocturnal dipping (%/ n of participants in the group)	60% / 18	80% / 16	59.1 / 13	62.5 / 5

All p values were > 0.10 in the comparison among the three groups (euthyroidism vs SH patients with serum TSH levels > 4.0-8.0 mUI/ml vs SH patients with serum TSH > 8.0 mUI/ml) and in the comparisons between the different groups.

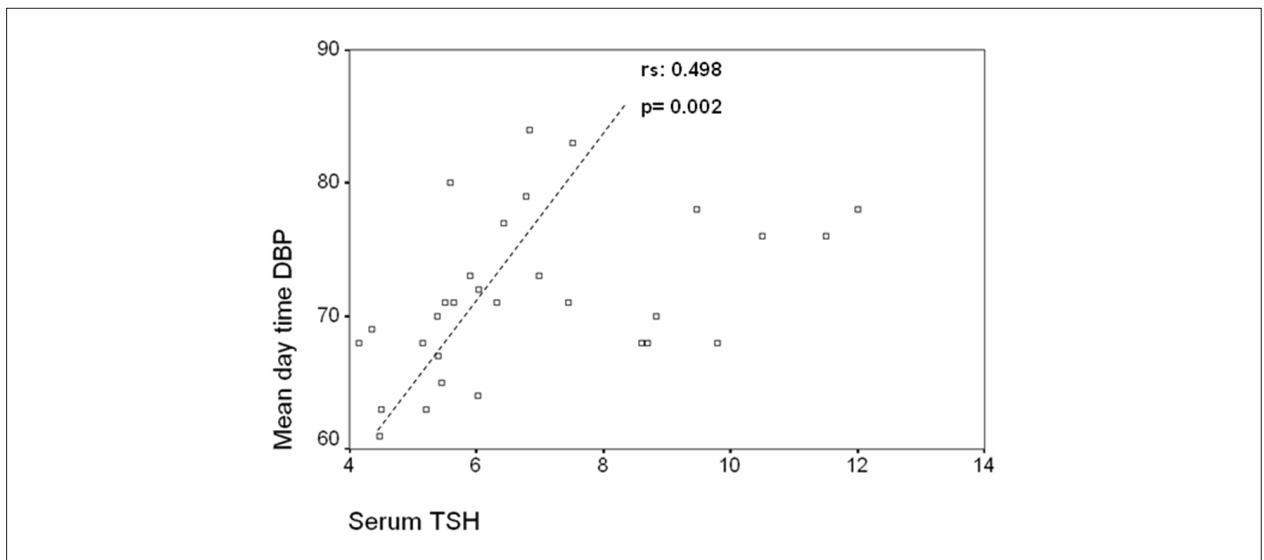


Figure 1 - Dispersion graph between mean daytime DBP and serum TSH levels in SH participants. DBP - diastolic blood pressure.

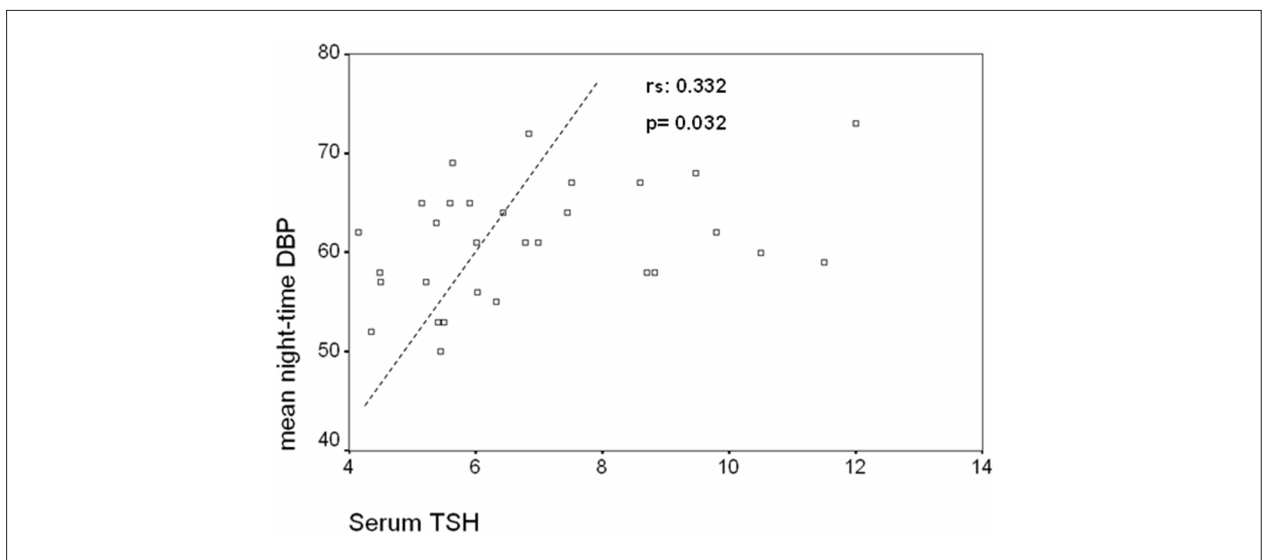


Figure 2 - Dispersion graph between mean night-time DBP and serum TSH levels in SH participants. DBP - diastolic blood pressure.

A special feature of the present study was the evaluation by ABPM over a 24-hour period, not only by casual BP measurement. Previous studies differ in their results about cardiovascular aspects of SH, since many of them had diverse variable definitions of disease states and inclusion criteria. Hypothyroidism may be a predictor of higher cardiovascular target-organ damage, as it has been associated with higher mean 24-h systolic blood pressure, 24-h pulse pressure and 24-h systolic blood pressure variability²¹. A recent study demonstrated that non-dipper hypertensive patients had lower serum FT3 levels than dipper patients and that FT3 was an independent predictor of non-dipper hypertension. Despite the exclusion of SH patients, the mean serum TSH of non-dippers was 3.5 ± 5.0 mIU/ml²².

To our knowledge, this is the first study to evaluate BP by ABPM in a group of SH patients with strict inclusion criteria, to minimize possible confounding variables in the BP variability. SH group was matched to controls for HBP risk factors, to avoid possible interference of factors independently associated with an increased BP level. Previous studies evaluated the usual measurement of BP with a mercury or aneroid sphygmomanometer, which can be influenced by the examiner's technique, white-coat effect (the transient, but variable elevation of BP in a medical setting), and the inherent variability of BP. Ambulatory blood pressure monitoring (ABPM) provides information about BP during daily activities and sleep, is not affected by these influences and is warranted for the evaluation of "white-coat" hypertension^{18,19}.

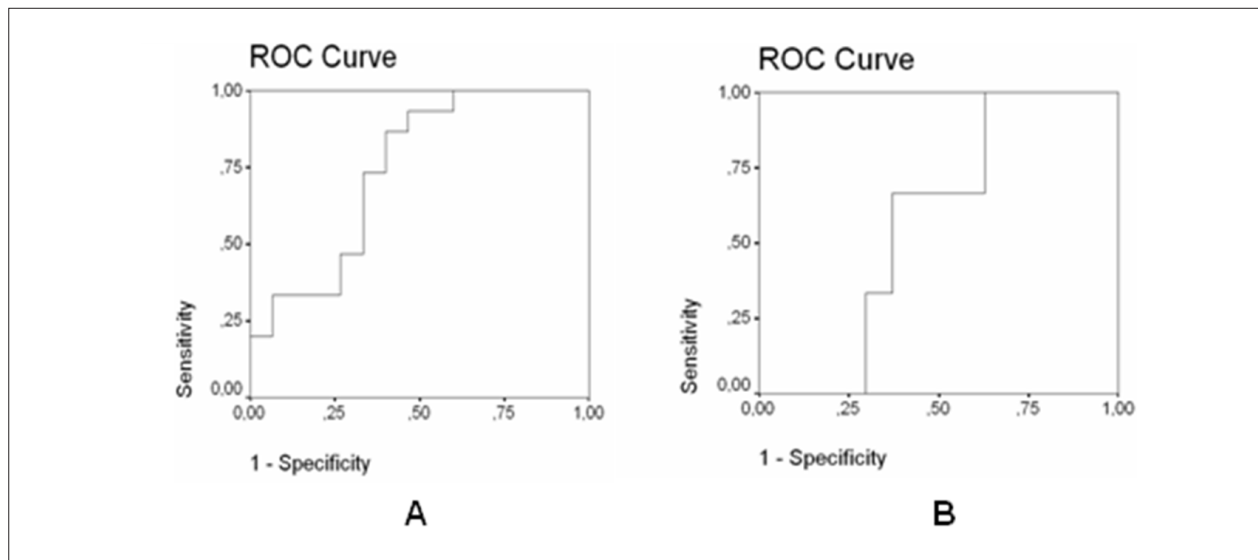


Figure 3 - ROC curves testing the variable TSH and the state variable "day-time diastolic blood pressure". The sensitivity and the specificity were 100% for serum TSH = 3.15 μ UI/ml. A - DBP higher than 70 mmHg (area under the curve = 0.795); B - DBP higher than 80 mmHg (area under the curve = 0.568).

The discrepancies in the results evaluating blood pressure in subjects with SH may reflect selection bias arising from clinic-based design and lack of information about hypertension risk factors of the participants. In the Whickham survey, SH women with mean serum TSH > 6.0 mU/ml had higher mean blood pressure than controls, but the results were not adjusted for age⁷.

Luboshitzky et al²³ studied 57 female patients with SH and detected higher diastolic blood pressure when compared to controls²³. Their patients had higher TSH levels than the ones in the present study ($10.0 \pm 4.0 \mu$ U/ml) and included participants with hypertension. The percentage of patients with high blood pressure, borderline elevated cholesterol, total cholesterol/HDL-c and triglyceride levels was significantly higher than in controls.

Faber et al²⁴ found a decrease in systemic vascular resistance and in the mean arterial pressure with LT-4 replacement among 16 women (mean age 60 years) with SH and mean serum TSH = 17.1 mU/l²⁴. Nagasaki et al²⁵ also demonstrated that SH patients exhibited increased DBP, in a group of elderly patients (65.2 ± 2.6 years old), with lower serum HDL cholesterol levels²⁵. Owen et al²⁶ found higher DBP in 19 female subjects with SH in comparison to 10 euthyroid controls and BP reduction after LT4 treatment in SH, but the patients had significantly higher total cholesterol and LDL levels than the euthyroid subjects²⁶.

Some studies have also aimed at evaluating the association between higher levels of TSH and hypertension in euthyroid patients. A recent large population-based study, including 5,872 patients, reported a familial aggregation of high-normal TSH levels in hypertensive families²⁷. Guimieak et al²⁸ reported lower serum FT4 and higher TSH level in 194 euthyroid hypertensive individuals when compared with 90 euthyroid normotensive individuals (TSH 1.7 ± 0.9 mU/ml versus 1.5 ± 0.8 mU/ml), but hypertensive subjects were older and had higher BMI than normotensive subjects, and others factors that

could influence BP were not evaluated, such as dyslipidemia²⁸.

The absence of higher levels of ABP in SH in comparison to euthyroid subjects demonstrated in the present study is consistent with data from a cross-sectional study of 2,033 participants carried out by Walsh et al²⁹, who showed that mean SBP, DBP and the prevalence of hypertension did not differ significantly between SH (n = 82) and euthyroid subjects (n = 1,591). However, differently from our study, they did not demonstrate that an increase in serum TSH > 10.0 mU/ml was associated with any increase in systolic or diastolic BP²⁹.

Similarly, Kvetny et al³⁰ did not find a significant difference in BP when comparing 249 subjects with SH (mean TSH = 3.7 mU/ml) and 963 euthyroid subjects³⁰. In the Rotterdam study, no difference in was detected regarding BP between 124 women with mild SH (mean TSH 6.6 mU/ml) and 931 euthyroid women³¹. It is noteworthy the fact that the participants were older than those included in the aforementioned studies (69.0 ± 7.9 years). Results from a large prospective cohort study with 496 participants with SH (mean TSH = 6.67 mU/ml) and 2,639 euthyroid controls, did not demonstrate a higher prevalence of hypertension³². These two last studies differ from the present study, as the mean age of the participants was > 65 years. Biondi et al³³, studied 26 subjects with SH (mean serum TSH = 8.6 mU/ml) and 30 euthyroid controls and found similar BP and SVR, but patients were younger (36 ± 12 years) in comparison to the present study³³. Monzani et al³⁴ did not observe higher BP in a group of 20 SH individuals when compared to 20 younger controls (34.3 ± 12.3 years) and with lower mean TSH (5.4 ± 2.4 mU/ml)³⁴. Arem et al³⁵, studying 8 patients with SH before and after thyroxine treatment, found no change in BP (serum TSH = 14.8 ± 9.5 mU/ml)³⁵.

A limitation of the present study is the small sample size from a non-population database, but the analysis of different confounding variables that were similar between the groups and the strict exclusion criteria minimized these characteristics.

The inclusion of SH patients with only mild serum TSH elevations is important, as this group of patients corresponds to the majority of SH patients in the general population and the absence of consensus about the association between SH and cardiovascular disease is specially present in this subgroup of SH patients.

The absence of higher levels of blood pressure in SH can be justified by the mild presentation of SH and the absence of other confounding variables in the group, such as the presence of hypertension risk factors. However, the positive correlation between serum TSH levels and diastolic blood pressure may represent a higher cardiovascular risk associated to subclinical hypothyroidism. These data should be confirmed in further large population studies and through the assessment of potential benefits with LT-4 replacement

in randomized trials.

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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