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Hypertension

Evaluation of Daily Blood Pressure Alteration in Subclinical Hypothyroidism

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Background: Subclinical hypothyroidism is the most common thyroid dysfunction in the general population. The relationship between overt thyroid dysfunction and hypertension is generally understood. Besides high blood pressure, non-dipper hypertension is known to increase cardiovascular risk. Our aim is to investigate daily blood pressure changes and the frequency of non-dipping patterns in patients with subclinical hypothyroidism.

Methods: Forty-nine patients without hypertension with subclinical hypothyroidism were compared with 50 healthy sex- and age-matched controls using ambulatory blood pressure monitoring.

Results: Thyroid-stimulating hormone (TSH) levels were significantly higher in the subclinic hypothyroidism group, and there was no difference between free triiodothyronine (FT3) and free thyroxine (FT4) levels which could be predicted as a result of the study design. Levels of mean diastolic, daytime diastolic, nighttime diastolic and nighttime systolic blood pressure were significantly higher in the subclinic hypothyroidism group (p = 0.001 for mean, daytime and nighttime diastolic and p = 0.01 for nighttime systolic). Diastolic non-dipping occurred more frequently in the subclinic hypothyroidism group [subclinical hypothyroidism group 24 patients (49%), control group 13 patients (26%), p = 0.01]. On multivariate analysis, subclinical hypothyroidism was independently associated with diastolic non-dipping (95% confidence interval 1.162-8.053, odds ratio 1.182, p = 0.024).

Conclusions: Our study found that both the frequency of diastolic non-dipping pattern and diastolic blood pressure increase with subclinical hypothyroidism. Therfore, it would appear that searching for non-dipping pattern can add valuable information for patients with subclinical hypothyroidism.

Key Words: Cardiovascular risk • Hypertension • Nondipping • Subclinical hypothyroidism

INTRODUCTION

Subclinical hypothyroidism is associated with increased cardiovascular disease,[1] and is defined as elevated serum thyroid-stimulating hormone (TSH) with normal levels of free thyroxine (FT4) and triiodothyronine (FT3).[2] Subclinical hypothyroidism is a more common disorder than overt hypothyroidism.[3] In the adult population, the prevalence of subclinical hypothyroidism ranges between 3-18%, and is particularly prevalent in women, elderly persons, and iodine insufficient populations.[4] Thyroid hormone relaxes vascular smooth muscle cells, thereby reducing peripheral vascular resistance.[5] In addition, sympathetic nervous system activation, increased arterial stiffness, a decrease in the rate of glomerular filtration, abnormalities of sodium metabolism and endothelial dysfunction may adversely affect the regulation of blood pressure (BP) in association with hypothyroidism.[6-8] Additionally, subclinical hypothyroidism has been reported to impair both left ventricular relaxation and systemic vascular resistance (SVR).[9]

Healthy, normotensive individuals exhibit a 10-20%

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nocturnal decrease in BP during the night. This decrease is subject to the influence of psychosocial, behavioral, and neurohumoral factors.[10] Non-dipping BP, defined as an average nighttime BP reduction less than 10% of the average daytime BP,[11] has been linked to target-organ damage, cerebrovascular accidents, and cardiovascular morbidity and mortality, both in hypertensive and normotensive individuals.[12,13] A relationship between hypothyroidism and non-dipping has been reported in normotensive patients,[14] but there is insufficient information regarding the relationship between subclinical hypothyroidism and non-dipping.

The aim of this study was to evaluate the effect of subclinical hypothyroidism on BP alteration, and on the development of a non-dipper blood pressure pattern in normotensive subjects.

MATERIALS AND METHODS

We enrolled 99 patients who applied to our cardiology outpatient clinic complaining of palpitation. Patients were divided into 2 groups: 49 patients with untreated subclinical hypothyroidism and 50 patients as the control group. Patients with hypertension, diabetes mellitus, severe obesity, renal disease, hepatic dysfunction, cardiac insufficiency, infections and acute inflammatory states, a history of alcohol abuse, and smokers were excluded. Subjects taking medications such as oral contraceptives or amiodarone, and those with any disease that might affect thyroid function or BP were excluded. The diagnosis of subclinical hypothyroidism was made after taking two TSH serum measurements with both measured levels above the normal upper range (4.0 mUI/ml), and FT4 within the normal range.[2] The euthyroid subjects had a negative history of thyroid diseases, with TSH and FT4 serum measurements within the normal range, and were normotensive with normal findings for the thyroid gland on physical examination.

Blood was taken in the morning between 8-9 a.m., after the subjects fasted for 12 hours, Serum TSH, FT4 and FT3 were measured by immunochemiluminescent assays. The intra-assay coefficients of variation were 4.1%, and the inter-assay coefficients of variation for TSH were 7.6%. Serum parameters analysed were creatinine, blood glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG).

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice in the right arm using a standard mercury sphygmomanometer; the mean of the two BP readings was used for data analyses. Arterial BP $\geq$ 140/90 mmHg was considered an abnormal result requiring re-evaluation and exclusion from the protocol. Height and body weight were measured to calculate body mass index (BMI).

An Ambulatory Blood Pressure Monitor (CONTEC PM50, CONTEC MEDICAL SYSTEMS CO.,LTD; CHINA) was used for the ambulatory blood pressure monitor (ABPM). All subjects underwent 24-hour ABPM on a normal working day on their right arm, after which they were instructed to act and work normally. Patients were asked to record their sleeping and waking times, and these records were taken under consideration when making necessary calculations. BP measurements were performed at 15-minute periods between 7 am and 11 pm and at 30-minute periods between 11 pm and 7 am. In case of insufficient measurements (more than 10% of the measurements) or technical problems, the ABPM was repeated. BP fall was calculated in accordance with the formula BP fall = (BP daytime – BP nighttime)/BP daytime) $\times$ 100.[11] Systolic and diastolic BP fall were calculated seperately. BP fall with < 10% was considered as nondipping, whereas BP fall between $\geq$ 10% and < 20% was considered as dipping. Also, BP drop of $\geq$ 20% was considered as extreme dipping.

Ethics

All participants were 18 years of age or older, and who each gave their written informed consent to the study; additionally, this study was approved by the Institutional Ethical Committee, according to the Declaration of Helsinki.

Statistics

Continuous variables are presented as mean $\pm$ standard deviation (SD), and categorical variables are presented as percentages. A chi-square test was used to compare the differences between categorical variables. The independent samples *t*-test was used to compare continuous variables with normal distribution, and the Mann-Whitney U test was used to compare continuous variables without a normal distribution. Multiple logistic

regression analysis was used to identify the factors related to non-dipping pattern. p values of less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed utilizing SPSS software version 15.0 (SPSS, Chicago, IL, USA).

RESULTS

Forty-nine patients with subclinic hypothyroidism and 50 sex- and age-matched controls were included in the study. TG and LDL-C levels were significantly higher in the subclinical hypothyroidism group (p = 0.001 for TG and p = 0.02 for LDL). General patient characteristics are summarized in Table 1. In fact, HDL-C levels were significantly lower in the subclinical hypothyroidism group (p = 0.001). TSH levels were significantly higher in the subclinical hypothyroidism group, and there was no difference between FT3 and FT4 levels, as can be predicted as a result of the study design. The range of TSH levels was 4.2 to 23 mUI/ml in the subclinic hypothyroidism group, and 1.1 to 4 mUI/ml in the control group. Thirty-nine (79.5%) patients had elevated anithyroid peroxidase and/or antithyroglobulin levels, and autoimmune thyroiditis was the most common cause of subclinical hypothyroidism in the study population. The mean BMI of the subclinic hypothyroidism group was higher than in the control group (p = 0.02). Mean age, gender, and fasting blood glucose levels were not significantly different between the groups.

Table 1. General characteristics

	SH group (N = 49)	Control group (N = 50)	p
Gender (female) (n, %)	31 (63.3%)	30 (60.0%)	0.738
Age (years)	48.4 ± 8.1	49.0 ± 7.9	0.678
FBS (mg/dl)	89.4 ± 12.7	85.1 ± 11.5	0.080
TG (mg/dl)	162.4 ± 49.1	127.0 ± 35.2	0.001
LDL (mg/dl)	100.9 ± 31.5	88.5 ± 19.4	0.020
HDL (mg/dl)	44.0 ± 6	50.0 ± 7.8	0.001
FT3 (pg/ml)	2.8 ± 0.4	2.6 ± 0.5	0.130
FT4 (ng/dl)	0.9 ± 0.1	1.04 ± 0.1	0.090
TSH (mUI/ml)	10.0 ± 5.1	2.9 ± 0.9	0.001
BMI (kg/m^2)	26.3 ± 2.3	25.3 ± 1.9	0.020
Mean SBP (mmHg)	115.4 ± 6.3	114.5 ± 5.7	0.470
Mean DBP (mmHg)	69.9 ± 4	64.5 ± 6.1	0.001
Daytime SBP (mmHg)	122.4 ± 5.5	120.5 ± 6.0	0.120
Daytime DBP (mmHg)	73.8 ± 4.7	69 ± 6.1	0.001
Nighttime SBP (mmHg)	107.2 ± 7.4	103.7 ± 7.2	0.010
Nighttime DBP (mmHg)	63.2 ± 5.4	57.2 ± 5.7	0.001
Systolic dipping (n,%)	33 (67.3%)	39 (78.0%)	0.230
Diastolic dipping (n,%)	25 (51.0%)	37 (74.0%)	0.010
Any dipping (n, %)	40 (81.6%)	46 (92%)	0.127

BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood sugar; FT3, triiodothyronine; FT4, free thyroxine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SH, subclinic hypothyroidism; TG, triglyceride; TSH, thyroid-stimulating hormone.

When we looked at the ABPM results, 83 (83.8%) patients had a dipping pattern, and 3 (3.03%) patients had an extreme dipping pattern (BP fall ≥ 20%). Only 13 of the study group was non-dipper. Mean diastolic, daytime diastolic, nightime diastolic, and nightime systolic BP were significantly higher in the subclinic hypothyroidism group (p = 0.001 for mean, daytime, and nighttime diastolic and p = 0.01 for nighttime systolic). Diastolic non-dipping was significantly more frequent in the subclinic hypothyroidism group (p = 0.01) (Table 1).

We searched for factors affecting diastolic dipping (Table 2). Age, gender, laboratory findings and BMI were not significantly different between diastolic dippers and non-dippers. Mean diastolic and nighttime diastolic BP were significantly higher for the diastolic non-dippers (p = 0.01 for mean diastolic pressures and p = 0.001 for

Table 2. Characteristics of diastolic dippers and non-dippers

	Diastolic dipper (N = 62)	Diastolic nondipper (N = 37)	p
Age (years)	48.5 ± 7.7	49.1 ± 8.4	0.690
Gender (female)	38 (61.3%)	23 (62.2%)	0.930
BG (mg/dl)	87.8 ± 12.1	86.3 ± 12.6	0.560
TG (mg/dl)	140.5 ± 47.3	151.3 ± 43.4	0.260
LDL-C (mg/dl)	98.1 ± 25	88.8 ± 28.8	0.090
HDL-C (mg/dl)	47.6 ± 7.1	46.0 ± 8.4	0.300
BMI (kg/m^2)	25.7 ± 2.2	25.9 ± 2.0	0.560
Mean DBP (mmHg)	66.0 ± 5.4	69.0 ± 6.0	0.010
Day DBP (mmHg)	70.9 ± 5.4	72.1 ± 6.6	0.240
Night DBP (mmHg)	58.2 ± 5.2	63.6 ± 6.5	0.001
Mean SBP (mmHg)	114.23 ± 6.04	116.35 ± 5.85	0.09
Day SBP (mmHg)	121 ± 5.31	122.32 ± 6.60	0.277
Night SBP (mmHg)	104.05 ± 7.62	107.86 ± 6.48	0.013

BG, blood glucose; BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglyceride.

nighttime diastolic pressures). There was no significant difference in daytime diastolic BP between diastolic dippers and non-dippers.

Logistic regression analysis was performed to determine the independent predictors of the diastolic non-dipping pattern, including subclinical hypothyroidism, age, gender, TSH, and mean diastolic pressure. Multiple logistic regression analysis data revealed that age, gender and mean diastolic pressure were not independent associating factors of diastolic non-dipping pattern (Table 3). In this analysis, subclinic hypothyroidism was the only independent predictor of diastolic non-dipping pattern [95% confidence interval (CI) 1.162-8.053, odds ratio (OR) 1.182, p = 0.024].

Table 3. Multiple logistic regression analysis to identify the factors related to diastolic non-dipping pattern

	OR	CI (95%)	p
Age (years)	1.019	0.934-1.042	0.638
Female gender	0.981	0.400-2.405	0.967
Mean DBP (mmHG)	0.934	0.858-1.017	0.116
SH	1.182	1.162-8.053	0.024

CI, confidence interval; DBP, diastolic blood pressure; OR, odds ratio; SH, subclinical hypothyroidism.

DISCUSSION

This study has revealed that levels of mean diastolic, daytime diastolic, nighttime diastolic and nighttime systolic blood pressure are higher in normotensive patients with subclinical hypothyroidism than in healthy euthyroid subjects. Additionally, the number of diastolic non-dippers was significantly higher in patients with subclinical hypothyroidism than in the control group, even though all of them are normotensive.

A number of studies have suggested that the risk of hypertensive cardiovascular complications correlates more closely with 24-hour, daytime, or nighttime ABPM than with the BP measured in the office.[15,16] Thyroid hormone plays a role in blood pressure homeostasis. The increase of systemic vascular resistance may be the main mechanism causing hypertension in clinical hypothyroidism patients.[17] The prevalence of hypertension in the subclinical hypothyroidism group has been suggested to be higher than that in the normal control group.[18] Even though TSH was in the normal range, there was a linear increase in SBP and DBP correlating with increasing serum TSH levels, and the prevalence of hypertension also increased.[19] The only study ever published on this topic, Marcia et al., reported a slightly higher BP in patients with normotansive subclinical hypothyroidism than in the controls, but it did not reach clinical significance.[20] In our study, we demonstrated significantly higher mean, daytime and nighttime DBP, and nighttime SBP in subclinical hypothyroidism patients by including more patients. DBP may vary directly with serum TSH levels over the entire spectrum of thyroid disease.[6] Overt hypothyroidism is associated with increased SVR, decreased cardiac contractility, and decreased cardiac output.[21] These complications may be the result of diastolic hypertension in hypothyroid patients.[18] Elevated diastolic BP in subclinical hypothyroidism patients has been shown in prior studies, but these were done with patients who already had hypertension or with older patients.[18,22] Our study is the first study that showed elevated DBP in normotensive subclinical hypothyroidism patients compared to age- and sex-matched controls. Increasing trend of DBP may have become statistically significant with increasing number of patients in our study.

The relationship between non-dipping and cardiovascular accidents and end-organ damage is well-known.[13,23] Hormones affecting BP such as cortisol, cathecolamines and renin are also thought to be affecting non-dipping.[24] Some studies had demonstrated that thyroid disfunction affects these hormones.[25,26] Another hypothesis on the mechanism of non-dipping is an inequilibrium between the sympathic and parasympathic systems.[23] The upregulation of sensitivity of the sympathic system due to TSH and declines in vascular relaxation can lead to non-dipping.[5] TSH induces increased sodium reuptake from the kidneys, and sodium sensitivity of patients with non-dipping can play a role in its pathophysiology.[7] A previous 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.[26] In a recent study, the number of non-dippers was found to be significantly higher in the group involving patients with overt hypothyroid and subclinical hypothyroidism compared to healthy euthyroid individuals.[27] Only one study attempted to measure the dipping frequency in sub-

clinical hypothyroidism patients compared to controls, but the difference did not reach clinical significance, probably because of the limited number of patients. In our study we included more patients and found that diastolic non-dipping was significantly higher in the subclinical hypothyroidism patients. This result was independent of other risk factors that may influence blood pressure, such as gender and age.

An essential limitation of thyroid dysfunction studies is that the time of onset of thyroid pathology in patients with subclinical hypothyroidism is not precisely known. The time required for the development of abnormalities of blood pressure and lipid levels is difficult to detect. Therefore, prospective studies with a large number of patients are needed to detect the effect of subclinical hypothyroidism on hypertension and other cardiovascular risk factors such as dyslipidemia and inflammation. Another limitation of our investigation was that it was based upon data provided by a single center, with a small number of patients. Also, ABPM was only performed once, which was another study limitation. In experimental and clinical studies, reductions of mean arterial pressure and systemic vascular resistance with levothyroxine supplementation in subclinical hypothyroidism have been shown.[28-30] However, there have been no studies investigating the effect of levothyroxine supplementation on daily blood pressure patterns. Therefore, prospective studies are needed to investigate the relationship between levothyroxine supplementation in subclinical hypothyroidism and changes in blood pressure patterns.

CONCLUSIONS

Although within normal BP limits, patients with subclinical hypothyroidism had significantly higher DBP than the controls, and the prevalence of diastolic non-dipping was significantly higher in the subclinical hypothyroidism group. Cardiovascular effects of thyroid dysfunction are based on dyslipidemia, but BP effects also seem to be important as well.

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