Original Article

Does Treatment of Either Hypothyroidy or Hyperthyroidy Affect Diurnal Blood Pressure

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Abstract

Objective: Thyroid hormone has well recognized effects on the cardiovascular system. The purpose of this study was to define the influence of treatment of either hypothyroidism and hyperthyroidism on the values and circadial variations of arterial blood pressure measured by ambulatory blood pressure monitoring.

Material and Methods: The study was carried out on 30 hypothyroidic and 30 hyperthyroidic patients without hypertension and 46 healthy participants. First, all the parameters of the groups, then blood pressure values obtained by ambulatory blood pressure monitoring before and after treatment (thyroid hormone replacement with levothyroxine and antithyroid treatment either with propylthyrouracil or metimazole) were compared. For statistical examinations, Shapiro-Wilk, one-way analysis of variance, Kruskal Wallis, post-hoc Tukey, and Wilcoxon Sign tests were used.

Results: In the hypothyroid group, 24-hour mean and diastolic blood pressure, daytime diastolic blood pressure, nighttime mean, systolic and diastolic blood pressures were higher than the control group ($P < 0.05$). After treatment, 24-hour, daytime and nighttime systolic and diastolic blood pressures diminished. Mean blood pressures diminished only in daytime and nighttime. In the hyperthyroid group, 24-hour average and daytime systolic, mean blood pressures, and all nighttime blood pressure values were higher than the control group ($P < 0.05$). After treatment, 24-hour and daytime systolic, mean blood pressures, all nighttime pressures diminished ($P < 0.05$).

Conclusion: Throughout 24 hours, in hypothyroidic patients especially higher diastolic and in hyperthyroidics especially higher systolic blood pressures were exhibited than euthyroid subjects. After treatment of these diseases, ambulatory blood pressure values decreased. Early control of thyroid dysfunctions may help to protect cardiovascular system from hazardous effects of thyroid dysfunctions and lower mortality and morbidity in these patients.

Keywords: Ambulatory blood pressure monitoring, hyperthyroidism, hypothyroidism

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Introduction

Thyroid hormones have many effects on the cardiovascular system.[1] Triiodothyronine (T3) stimulates transcription of sarcoplasmic reticulum calcium adenosine triphosphatase and increases the rate of myocardial diastolic relaxation and also the expression of myosin heavy chain α isoforms which enhanches systolic function. T3 affects expression of sodium potassium Na-K adenosine triphosphatase genes with α adrenergic receptors and also decreases inhibitory Gi-α concentration. T3 influences the heart rate, by increasing repolarization and depolarization of sinoatrial node. Thyroid hormones also affect diastolic ventricular function, lower peripheral vascular resistance and increase intravascular volume which contributes to the increase in cardiac output. Simply, thyroid hormones have positive inotropic and cronotropic effects on heart.

Hypothyroidism is an independent risk factor for heart failure, and can also cause it by altering blood lipids and accelerating atherosclerosis, stimulating myocardial fibrosis and vasoconstruction, reducing contractility, and impairing relaxation.[1–4] Hypothyroidism also leads to decreased cardiac output, narrow pulse pressure, and increased systemic vascular resistance.[5] The effects of hyperthyroidism on the cardiovascular system include increased cardiac output, contractility, tachycardia, widened pulse pressure, and decreased systemic vascular resistance.[1,5]

Ambulatory blood pressure monitoring (ABPM) is being increasingly recommended for routine clinical practice.[6–8] It may be particularly useful in evaluating the patient with variable blood pressure readings in the office, or the patient with wide discrepancies between the blood pressure readings at home and the clinician's office (i.e., "white coat" hypertension). ABPM and, in particular, nocturnal blood pressure readings, may also provide prognostic data.[9] A number of studies have suggested that the risk of hypertensive cardiovascular complications[10–13] and end organ damage[14–16] correlates more closely with 24-hour, daytime, or nighttime ambulatory blood pressure monitoring (ABPM) than with the office pressure.

There are few studies investigating long-term and circadian effects of thyroid hormone metabolism on blood pressure and heart rate. A limited number of studies about clinical hypothyroidism[17–23] and hypertyroidism[24–29] show that thyroid hormones contribute to the control of systemic arterial blood pressure homeostasis

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throughout the day. There are also few studies examining blood pressure variations before and after treatment of hypothyroidism or hyperthyroidism and no studies investigating the status of both thyroid hormones taken together.

With regard to these findings, we decided to examine the daily variations of blood pressure by ambulatory blood pressure monitoring in patients with hypothyroidism or hyperthyroidism and compare their results with control subjects and with the values after their thyroid hormone levels were normalized.

Materials and Methods

Patients

This is an experimental non-randomized clinical study. A total of 60 patients without hypertension [53 female (88.30%), 7 male (11.7%)], 30 hypothyroid [26 female (86.7%), 4 male (13.3%)] and 30 hyperthyroid [27 female (90.0%), 3 male (10.0%)] patients aged 22 – 70 years, were recruited from the outpatient Clinic of Ankara Dışkapı Yıldırım Beyazıt Education and Research Hospital from January 2006 to April 2007. Fourty-six age- and sex-matched healthy individuals admitted to outpatient Clinic of Ankara Dışkapı Yıldırım Beyazıt Education and Research Hospital with non-specific complaints and no disease found on physical and laboratory examinations [39 female (84.8%), 7 male (15.2%)] were chosen as the control group.

Our exclusion criteria were having hypertension, heart failure, congenital cardiac disease, valvular and, atherosclerotic heart disease, active infection or a systemic disease (renal, gastro-intestinal, hepatobiliary, hematological, oncological, neurological disease) and women suspected of pregnancy. We excluded patients once diagnosed with a thyroid disease and treated for it who now had an endocrinological disease except thyroid disease. We did not include individuals with subclinical hypothyroidism (TSH levels ≥ 5.0 μIU/mL and fT4 levels between 0.8 – 1.9 ng/dL), hyperthyroidism (TSH levels ≤ 0.35 μIU/mL and fT4 levels between 0.8 – 1.9 ng/dL), central hypothyroidism (TSH levels ≤ 0.35 μIU/mL and fT4 levels ≤ 0.8 ng/dL), or central hyperthyroidism (TSH levels ≥ 5.0 μIU/mL and fT4 levels ≥ 1.9 ng/dL). We also excluded individulas who smoked.

In our laboratory, the reference ranges for TSH were between 0.35 – 5.0 μIU/mL, for fT4 between 0.35 – 1.9 ng/dL and for fT3 2.3 – 4.2 pg/mL. Hypothyroidism was defined as TSH levels ≥ 5.0 μIU/mL and fT4 levels ≤ 0.8 ng/dL, and hyperthyroidism was defined as TSH levels ≤ 0.35 μIU/mL and fT4 levels ≥ 1.9 ng/dL.

After detailed physical examination, body weight and height of all subjects were measured. We calculated body mass index (BMI) as weight in kilograms divided by the square of height in meters (kg/m^2).

Systolic and diastolic blood pressures were measured after a 5-minute rest in the semi-sitting position with a sphygmomanometer. Blood pressure was measured at least three times on the right upper arm, and the mean was used in the analyses. Patients who were taking antihypertensive drugs or patients with measured mean blood pressure levels ≥ 140/90 mmHg were diagnosed as having hypertension (HTA) and excluded from the study.[30]

Blood was drawn after 12 hour of overnight fasting, at 08.30 for fasting plasma glucose (FPG), serum total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C), triglyceride (TG), creatinine, albumin levels and free triiodothyronin (fT3), free thyroxin (fT4), thyroid stimulating hormone (TSH), as well as whole blood count and platelet counts.

We formed three groups; Group I, Control group; Group II, Hypothyroid patients; and Group III, Hyperthyroid patients. Electrocardiograms (ECG) of all the individuals were recorded. The ABPM device was applied twice in the patient groups before thyroid hormone replacement with levothyroxine (1.4 – 1.8 μg/kg) or antithyroid treatment either with propylthyrouracil (100-450 mg/day) or metimazole (10 – 45 mg/day) orally without β-blockers were started and after normal thyroid hormone levels were reached. ABPM was applied once in the control group. We followed our patients with montly controls and obtained normal thyroid hormone levels in 1 – 3 months in hypothyroids and 3 – 8 months in hyperthyroids. Normal thyroid hormone levels were defined as TSH levels between 0.35 – 5.0 μIU/mL and fT4 levels between 0.8 – 1.9 ng/dL.

In the study, a Schiller BR-102 ossilometric ABPM device was used. Blood pressure and heart rate (HR) values were recorded every 30 minutes during the daytime (awake) and every 60 minutes during nighttime (asleep). These blood pressures were recorded on the device, and the average day or night blood pressures were determined from the data by a computer. Daytime period was arranged between 08.00 and 23.00 and nighttime between 23.00 and 08.00.

Average systolic blood pressure (SBP) and diastolic blood pressure (DBP), mean blood pressure (MBP) and heart rate (HR) values were recorded by the device. Maximum, mean, minimum SBP and DBP, HR values were calculated separately for 24 hours, in daytime and nighttime periods. Circadian rhythm was calculated by extracting the level of a day parameter from the same parameter measured by night. Nocturnal fall was determined by calculating the nocturnal fall of the parameter as the percentage of the day (Day-night difference x100 /day measurement). If the nocturnal fall of SBP was ≥ 10%, it was classified as dipper, and ≤ 10% was classified as non-dipper.

Approval for the study was granted by the ethical commitee of Ankara Dışkapı Yıldırım Beyazıt Education and Research Hospital on 01.12.2006 under number 04419.

This study was performed according to the 2008 Helsinki decleration. The local ethics comittee approved this study and all the subjects gave written informed consent.

Laboratory methods

Plasma glucose, TC, and TG concentrations were determined by enzymocalorimetric spectrophotometric method in a Roche/Hitachi molecular PP autoanalyser. Creatinine was examined with Beckman Coulter AU2700, and blood count with ROCHE Sysmex SE 9000 automatic blood count device and fT3, fT4, TSH with BAYER ACS 180 device by chemoluminessance method.

Statistical analysis

Calculations were performed using SPSS version 15.0. For the dispersion of constantly measured variables, the Shapiro Wilk test was used to determine normal distribution. Descriptive statistics were expressed as mean ± SD for constantly measured variables and as observation number or % for qualitative variables. To evaluate statistically significant difference in constantly measured variables of the groups, one-way analysis of variance (One-way ANOVA) or the Kruskal-Wallis test were used. Where the ANOVA or the Kruskal Wallis test results were found to be significant,

post-hoc Tukey and Kruskal-Wallis multiple comparison tests were used respectively in order to determine the group or groups causing the significant difference.

We used dependent *t*-test or Wilcoxon Sign test for investigating statistically significant differences between beginning and after treatment values in thyroid function tests, BMI and blood pressure measurements in hypothyroid and hyperthyroid groups. For categoric comparisons, the Pearson-Chi square test was used.

Results

A total of 60 patients and 46 controls in 3 different groups were recruited for the study. Demographic and laboratory parameters of all the groups and their comparisons are shown in Table 1.

Difference of age and sex between the groups were non-significant. SBP and HR of hyperthyroid group was higher than those of control and hypothyroid patients (both $P < 0.05$ and both $P < 0.001$, respectively). fT3 and fT4 levels of hyperthyroid group was higher than those of control and hypothyroid patients (both $P < 0.01$). TSH levels of the hypothyroid group was higher than control and hyperthyroid patients (both $P < 0.01$). When TSH levels of control and hyperthyroid groups were compared, they were significantly higher in the control group ($P < 0.01$). As for albumin levels, they were lower in the hypothyroid group than both control and hyperthyroid groups ($P < 0.001$).

In Table 2, the results of ambulatory blood pressure monitorisation before treatment are demonstrated. Concerning 24 hour measurements, SBP in the hyperthyroid group was higher than that of other groups ($P < 0.001$ and $P < 0.032$). In the hypothyroid group, DBP was higher than the levels of control group ($P < 0.006$). MBPs of the hypothyroid and hyperthyroid groups were higher than the control group ($P < 0.01$ and $P < 0.001$). HR was higher in hyperthyroid patients than other groups ($P < 0.01$ both) and in the control group compared to the hypothyroid group ($P < 0.01$).

Then we illustrated daytime and nighttime measurements. As daytime measurements were concerned, in hyperthyroid patients, SBP and in hypothyroid patients, DBP were higher than those in the control group (all ($P < 0.01$). In hyperthyroid patients, MBP and HR were higher than those of both the control and hypothyroid groups (all $P < 0.01$). As for night measurements, SBPs of the hyperthyroid patients were higher than SBP of other groups, and SBPs of the hypothyroid patients were higher than SBP of control group (all $P < 0.01$). DBPs of the hypothyroid patients were higher than DBP of both control and hyperthyroid groups, and DBPs of the hyperthyroid patients were higher than DBP of the control group (all $P < 0.01$). Both hypothyroid and hyperthyroid groups had statistically higher MBP levels than the control group (all $P < 0.01$). HR of the hyperthyroid group was higher than HR of the other two groups (all $P < 0.01$).

As circadian rhythm was concerned, only MBP levels were different; MBPs of hypothyroid patients were lower than the MBP of other groups (all $P < 0.01$). As nocturnal fall was concerned, fall in DBP of the hypothyroid group was smaller than control and hyperthyroid groups (both $P < 0.01$). Nocturnal fall of MBP was smaller in hypothyroid patients than control and hyperthyroid groups (both $P < 0.01$). No difference was observed in other parameters.

In hypothyroid patients, we monitored ambulatory blood pressure before and after treatment, as illustrated in Table 3 with thyroid

Table 1. Characteristics of all the groups

	GroupI/Control (n=46)	GroupII/Hypothyroid (n=30)	GroupIII/Hyperthyroid (n=30)
Age(year)	42.0 ± 12.8	37.0 ± 9.5	36.1 ± 11.5
Women, n(%)	39 (84.8%)	27 (90%)	26 (86%)
BMI	26.3 ± 4.4	26.9 ± 4.5	25.7 ± 2.6
SBP (mmHg)	120.8 ± 7.6	122.8 ± 8.7[c]	125.7 ± 7.7[b]
DBP (mmHg)	78.5 ± 6.3	81.9 ± 7.3	79.7 ± 6.3
HR (beat/min)	83.2 ± 8.2	83.6 ± 8.3[c]	93.2 ± 9.8[b]
fT3 (pmol/L)	2.4 ± 0.4[a]	3.0 ± 1.0[c]	9.4 ± 4.7[b]
fT4 (pmol/L)	1.4 ± 0.4[a]	0.5 ± 0.2[c]	4.4 ± 2.4[b]
TSH (mU/L)	1.9 ± 0.6[a]	8.1 ± 2.4[c]	0.1 ± 0.09[b]
FBG (mg/dl)	90.2 ± 8.4	88.8 ± 8.0	89.8 ± 9.8
T.Chol (mg/dl)	211.8 ± 64.0	192.2 ± 44.4	187.5 ± 32.3
TG (mg/dl)	117.8 ± 63.8	146.1 ± 78.7	105.2 ± 29.4
Creatinine (mg/dl)	0.8 ± 0.1	0.7 ± 0.1	0.7 ± 0.2
Albumin (g/dl)	4.7 ± 0.3[a]	4.0 ± 0.2[c]	4.7 ± 0.4
Hb (g/dl)	13.4 ± 1.0	12.9 ± 0.9	13.4 ± 0.9
MPV	8.4 ± 0.2	8.6 ± 0.6	8.4 ± 0.5
MCV	83.8 ± 2.7	83.6 ± 7.1	85.4 ± 3.1
Leucocyte count	7556.5 ± 1044.0	6933.3 ± 1187.0	7476.6 ± 1223.0
Trombocyte count	250239.0 ± 49577	251700.0 ± 84501.0	313533.0 ± 66550.0

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; fT3: Free triiodothyronin; fT4: Free thyroxin; TSH: Thyroid stimulating hormone; FBG: Fasting blood glucose; T.Chol: Total cholesterol; TG: Triglyceride; Hb: Hemoglobin; MPV: Mean Platelet volume; MCV: Mean corpuscular volume; Data are presented as mean ± SD; [a]the difference between Group I and II is statistically significant ($P < 0.05$); [b]the difference between Group I and III is statistically significant ($P < 0.05$); [c]the difference between Group II and III is statistically significant ($P < 0.05$)

Table 2. The results of ambulatory blood pressure monitoring

	Group I/ Control	GroupII/ Hypothyroid	GroupIII/ Hyperthyroid
24 h measurement			
SBP (mmHg)	111.4 ± 8.7	114.6 ± 9.2[c]	120.0 ± 6.1[b]
DBP (mmHg)	70.5 ± 5.6[a]	75.1 ± 7.0	72.3 ± 6.1
MBP (mmHg)	84.7 ± 6.5[a]	88.1 ± 8.7	90.3 ± 8.1[b]
Heart rate (beat/min)	75.6 ± 100.7[a]	72.5 ± 5.4[c]	85.0 ± 8.4[b]
Daytime			
SBP (mmHg)	115.9 ± 8.8	116.7 ± 9.6	121.7 ± 9.0[b]
DBP (mmHg)	75.0 ± 5.71[a]	79.1 ± 7.2	77.2 ± 6.3
MBP (mmHg)	88.8 ± 6.9	91.1 ± 10.1[c]	95.5 ± 7.9[b]
Heart rate (beat/min)	82.2 ± 9.5	80.6 ± 8.8[c]	90.1 ± 8.11[b]
Nighttime			
SBP (mmHg)	102.4 ± 9,5[a]	107.7 ± 11.8[c]	109.8 ± 7.4[b]
DBP (mmHg)	62.0 ± 6.4[a]	70.1 ± 10.2[c]	64.1 ± 5.4[b]
MBP (mmHg)	76.0 ± 7.3[a]	82.8 ± 10.6	82.2 ± 8.5[b]
Heart rate (beat/min)	67.3 ± 9.2	66.1 ± 8.5[c]	77.4 ± 8.9[b]
Circadian Rythm			
SBP (mmHg)	13.4 ± 6.0	9.0 ± 11.5	13.9 ± 5.7
DBP (mmHg)	13.0 ± 5.0	9.1 ± 10.9	13.1 ± 5.0
MBP (mmHg)	12.8 ± 7.0[a]	8.3 ± 10.8[c]	13.3 ± 5.9
Heart rate (beat/min)	12.9 ± 6.5	10.5 ± 10.7	12.7 ± 5.7
Nocturnal Fall			
SBP (%)	11.6 ± 4.8	7.4 ± 9.6	9.6 ± 4.4
DBP (%)	17.3 ± 6.2[a]	10.9 ± 13.3[c]	16.8 ± 6.0[b]
MBP (%)	14.2 ± 7.8[a]	8.5 ± 11.4[c]	13.8 ± 6.2[b]
Heart rate (%)	15.9 ± 7.9	12.2 ± 13.2	14.0 ± 6.2

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MBP: Mean blood pressure; Data are presented as mean ± SD; [a]the difference between Group I and II is statistically significant ($P < 0.05$); [b]the difference between Group I and III is statistically significant ($P < 0.05$); [c]the difference between Group II and III is statistically significant ($P < 0.05$).

Table 3. Results of thyroid function tests, body mass index and ambulatory blood pressure monitoring in hypothyroid patients before and after treatment

Variable	Before treatment	After treatment	*P*
fT3 (pmol/L)	3.8 ± 1.0	2.9 ± 0.7	**0.222**
fT4 (pmol/L)	0.5 ± 0.2	1.4 ± 0.1	**0.001**
TSH (mU/L)	8.1 ± 2.4	2.6 ± 0.3	**0.001**
BMI (kg/m2)	26.9 ± 4.9	25.0 ± 3.6	**0.010**
24 h measurement			
SBP (mmHg)	114.6 ± 9.2	109.0 ± 7.4	**0.001**
DBP (mmHg)	75.1 ± 7.0	71.7 ± 6.3	**0.010**
MBP (mmHg)	88.1 ± 8.7	85.9 ± 6.5	**0.340**
Heart rate (beat/min)	72.5 ± 5.4	78.4 ± 7.3	**0.010**
Daytime			
SBP (mmHg)	116.7 ± 9.6	112.7 ± 7.1	**0.001**
DBP (mmHg)	79.1 ± 7.2	76.8 ± 6.5	**0.050**
MBP (mmHg)	91.1 ± 10.1	88.2 ± 8.1	**0.050**
Heart rate (beat/min)	80.6 ± 8.8	84.2 ± 8.0	**0.001**
Nighttime			
SBP (mmHg)	107.7 ± 11.8	103.8 ± 12.6	**0.008**
DBP (mmHg)	70.1 ± 10.2	64.4 ± 8.6	**0.001**
MBP (mmHg)	82.8 ± 10.6	78.7 ± 9.7	**0.004**
Heart rate (beat/min)	70.1 ± 8.5	73.7 ± 7.5	**0.003**
Circadian Rythm			
SBP (mmHg)	9.0 ± 11.5	8.9 ± 11.3	**0.255**
DBP (mmHg)	9.0 ± 10.9	12.3 ± 9.8	**0.050**
MBP (mmHg)	8.3 ± 10.8	9.5 ± 9.9	**0.333**
Heart rate beat/min)	10.5 ± 10.7	10.5 ± 8.9	**0.112**
Nocturnal Fall			
SBP (%)	7.4 ± 9.6	7.8 ± 10.1	**0.443**
DBP (%)	10.9 ± 13.3	15.6 ± 12.2	**0.050**
MBP (%)	8.5 ± 11.4	10.4 ± 10.8	**0.550**
Heart rate (%)	12.2 ± 13.2	11.9 ± 10.1	**0.221**

fT3: Free triiodothyronin, fT4: Free thyroxin, TSH: Thyroid stimulating hormone, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MBP: Mean blood pressure. Data are presented as mean ± SD.

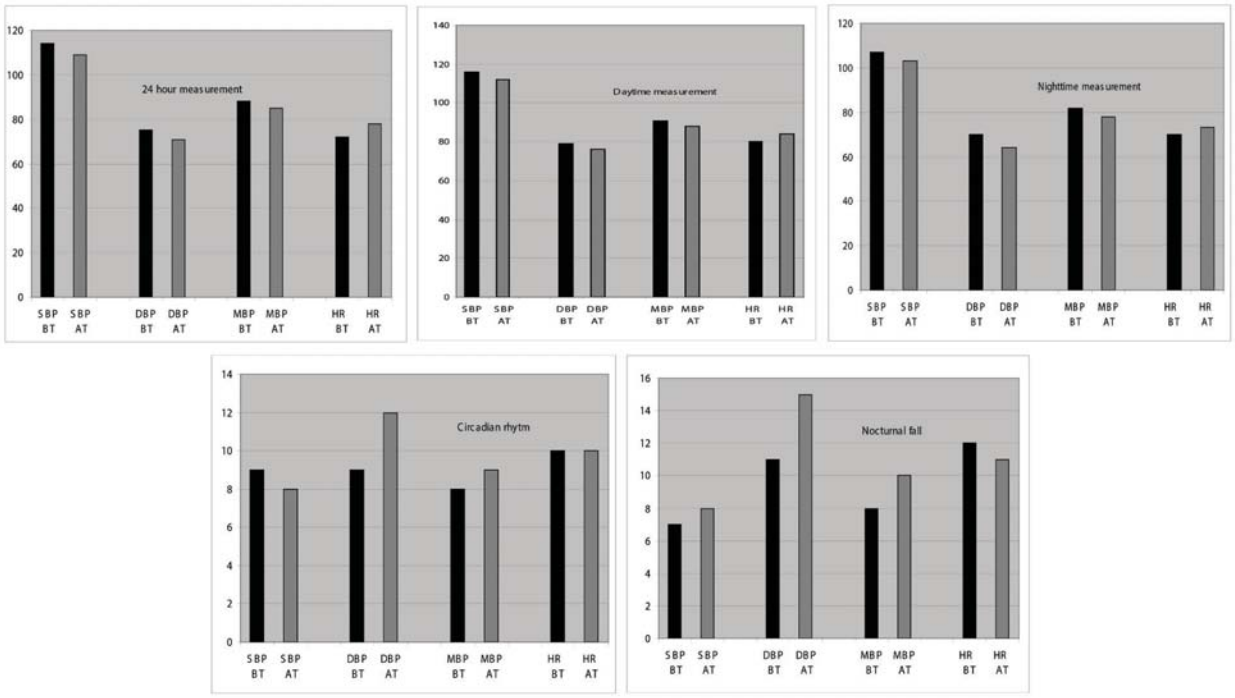

Figure 1. Twenty-four hour, daytime, nighttime measurements, circadian rhythm and nocturnal fall changes of blood pressure values before and after treatment in hypothyroid patients (SBP: Systolic blood pressure, DBP: Diastolic blood pressure; MBP: Mean blood pressure; HR: Heart rate; BT: Before treatment; AT: After treatment).

Table 4. Results of thyroid function tests, body mass index and ambulatory blood pressure monitoring in hyperthyroid patients before and after treatment

Variable	Before treatment	After treatment	*P*
fT3 (pmol/L)	9.4 ± 4.7	2.5 ± 0.6	**0.001**
fT4 (pmol/L)	4.4 ± 2.4	1.5 ± 0.2	**0.001**
TSH (mU/L)	0.1 ± 0.1	1.6 ± 0.4	**0.001**
BMI (kg/m2)	25.7 ± 2.6	27.0 ± 3.0	**0.010**
24 h measurement			
SBP (mmHg)	120.0 ± 6.1	113.4 ± 6.9	**0.001**
DBP (mmHg)	72.3 ± 6.1	72.9 ± 6.1	**0.222**
MBP (mmHg)	90.3 ± 8.1	88.4 ± 7.7	**0.001**
Heart rate (beat/min)	85.0 ± 8.4	76.8 ± 6.3	**0.010**
Daytime			
SBP (mmHg)	121.7 ± 9.0	115.6 ± 8.1	**0.001**
DBP (mmHg)	77.2 ± 6.3	77.6 ± 6.6	**NS**
MBP (mmHg)	95.5 ± 7.9	91.8 ± 9.6	**0.001**
Heart rate (beat/min)	90.1 ± 8.1	83.8 ± 8.2	**0.001**
Nighttime			
SBP (mmHg)	109.8 ± 7.4	105.2 ± 6.9	**0.001**
DBP (mmHg)	64.1 ± 5.4	62.4 ± 4.1	**0.004**
MBP (mmHg)	82.2 ± 8.5	79.8 ± 7.5	**0.001**
Heart rate (beat/min)	77.4 ± 8.9	71.1 ± 9.6	**0.001**
Circadian Rythm			
SBP (mmHg)	11.9 ± 5.7	10.4 ± 6.0	**0.050**
DBP (mmHg)	13.1 ± 5.0	15.2 ± 5.0	**0.001**
MBP (mmHg)	13.3 ± 5.9	12.0 ± 7.2	**0.555**
Heart rate (beat/min)	12.7 ± 5.7	12.7 ± 9.2	**0.482**
Nocturnal Fall			
SBP (%)	9.6 ± 4.4	8.8 ± 4.6	**0.050**
DBP (%)	16.8 ± 6.0	19.3 ± 5.3	**0.001**
MBP (%)	13.8 ± 6.2	12.6 ± 8.1	**0.550**
Heart rate (%)	14.0 ± 6.2	14.8 ± 10.8	**0.711**

fT3: Free triiodothyronin, fT4: Free thyroxin, TSH: Thyroid stimulating hormone, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MBP: Mean blood pressure. Data are presented as mean ± SD.

hormone and BMI changes. While there was no statistically significant change in fT3 levels, fT4 levels increased and TSH and BMI decreased after treatment ($P < 0.001$, $P < 0.001$, $P < 0.01$ respectively). As 24 h measurements were concerned, SBP and DBP decreased and heart rate increased after the treatment ($P < 0.001$, $P < 0.01$, $P < 0.01$ respectively). Among day measurements, SBP, DBP, and MBP were found to be decreased and heart rate increased ($P < 0.001$, $P < 0.05$, $P < 0.05$, $P < 0.001$); in night measurements, SBP, DBP and MBP decreased, while heart rate increased ($P < 0.008$, $P < 0.001$, $P < 0.004$, $P < 0.003$ respectively). As we investigated circadian rhythm, we only demonstrated that DBP decreased and as nocturnal fall was concerned, DBP increased (both $P < 0.05$).

Figure 1 illustrates the changes in blood pressure values before and after treatment in hypothyroid patients.

In hyperthyroid patients, we monitored ambulatory blood pressure before and after treatment, as illustrated in Table 4 with thyroid hormone and BMI changes. FT3 and fT4 levels decreased, while TSH, and BMI values increased after the treatment ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.01$ respectively). When we looked at the 24 h measurements, we found that SBP, MBP and HR were decreased ($P < 0.001$, $P < 0.001$, $P < 0.01$ respectively). In daytime measurements, the results were the same. In nighttime measurements, SBP, DBP, MBP and HR were decreased ($P < 0.001$, $P < 0.004$, $P < 0.001$, $P < 0.001$ respectively). When circadian rhythm and nocturnal fall were concerned, there was a significant decrease in SBP and increase in DBP after the treatment ($P < 0.05$ and $P < 0.001$ respectively).

Figure 2 illustrates the changes in blood pressure values before and after treatment in hyperthyroid patients.

In summary, in hypothyroid group 24 hour MBP and DBP and HR daytime DBP, nighttime all pressures were higher and as circadian rhythm was concerned, MBP was lower than the control group and as nocturnal fall was concerned, DBP and MBP were lower than the control. After treatment, 24 hour SBP, DBP fell, daytime and nighttime pressures fell, and HR rose in all measurements. As circadian rhythm and nocturnall fall were concerned, DBP was found to be higher after treatment. In the hyperthyroid group, 24 hour and daytime SBP, MBP and HR were higher, all nighttime blood pressure values, as well as HR were higher than the control group. As nocturnal fall was concerned, DBP, MBP fell less than the control group. After treatment, 24 hour, daytime SBP, MBP and HR values fell, nighttime pressures fell, and HR decreased in all measurements. As circadian rhythm and nocturnall fall were concerned, SBP was found to be lower and DBP was found to be higher after the treatment.

If the nocturnal fall of the parameter was $\geq 10\%$, it was classified as dipper, and $\leq 10\%$ was classified as non-dipper. Regarding before treatment values being dipper, percentages from the largest to smallest pertained to control, hyperthyroid and hypothyroid. In both hypothyroids and hyperthyroids, non-dipper percentages were higher than controls. In the hypothyroid group, there were 46.7% dipper patients before and 53.3% patients after the treatment. There was no statistical difference. In the hyperthyroid group, there were 66.7% dipper patients before and 76.7% patients after the treatment. The difference was statistically significant ($P < 0.05$) (Table 5).

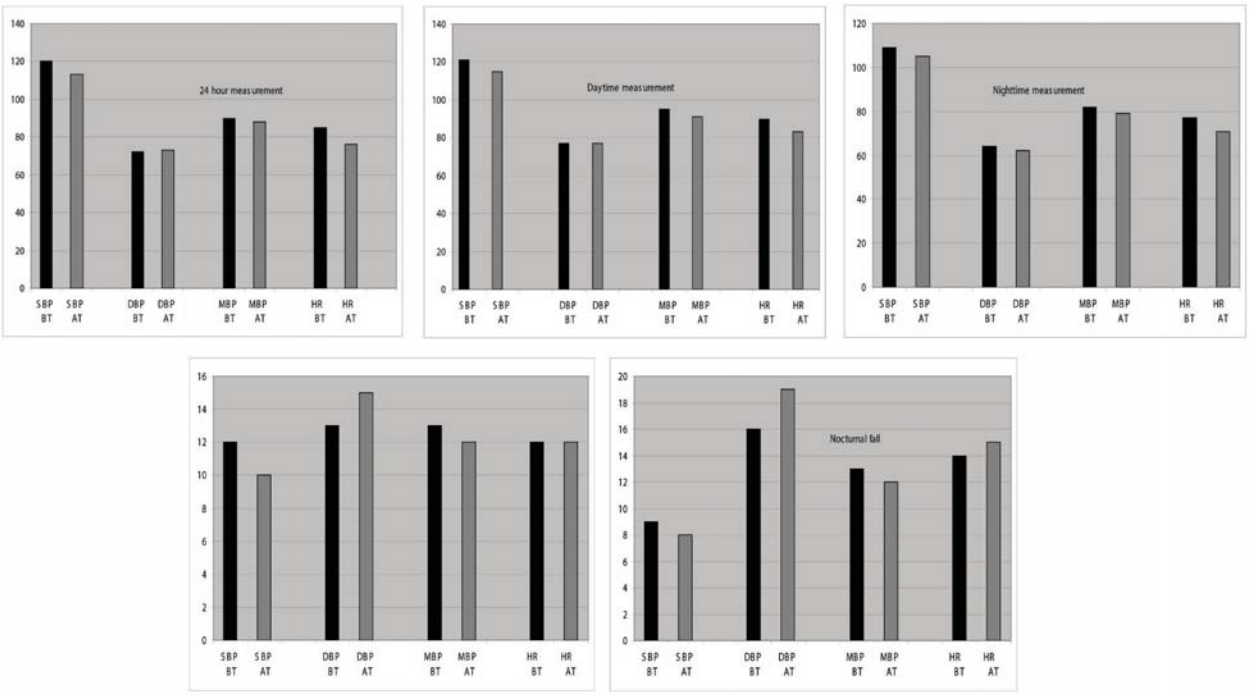

Figure 2. Twenty-four hour, daytime, nighttime measurements, circadian rhythm and nocturnal fall changes of blood pressure values before and after treatment in hyperthyroid patients (SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MBP: Mean blood pressure; HR: Heart rate; BT: Before treatment; AT: After treatment).

Table 5. Dipper and non-dipper number and percentages of control group, hypothyroid and hyperthyroid group either before and after treatment

Variable	Control	Hypothyroid		Hyperthyroid	
		Before t.	After t.	Before t.	After t.
Dipper	38 (86.0%)	14 (46.7%)	16 (53.3%)	20 (66.7%)	23 (76.7%)
Non-dipper	8 (17.4%)	16(53.3%)	14 (46.7%)	10 (33.3%)	7 (23.3%)
P	- - -	**0.077**		**0.038**	
t: treatment					

Discussion

Although the effects of thyroid hormone on the cardiovascular system and blood pressure regulation are well recognized, there have been few studies investigating the long-term and circadian effects of thyroid hormone metabolism on blood pressure and heart rate. Nowadays, ABPM is used extensively in blood pressure monitoring, but there is not much data about its use in hypo- and hyperthyroidism. In our study, we investigated the effects of hypo- and hyperthyroidism on blood pressure and heart rate control using ABPM and also examined the effects of treatment of these diseases on the above mentioned measurements.

In our study in hypothyroid patients, most of the blood pressure values, especially DBP, were higher and HR was lower than the control group in 24-hour, daytime and nighttime measurements. As circadian rhythm was concerned, because nocturnal fall in DBP was less than the controls, the difference was not statistically significant. After thyroid hormone replacement therapy, blood pressure values diminished and HR increased. DBP circadian rhythm values were found to be significantly high after thyroid hormone replacement therapy. It was obvious that this result was caused by the sharp fall in diastolic blood pressure values in the night period. This result suggested that DPB was mostly affected by low thyroid hormone levels and mostly corrected by treatment.

Most of the recent studies have shown the relationship between hypothyroidism and hypertension especially diastolic hypertension.[1,5,18,31,32] We also demonstrated the same relationship. We also found high SBP values in our hypothyroid patients, especially nighttime. Those values fell after treatment as in the study by Kotsis.[20] The cause of increase in blood pressure of hypothyroid patients was supposed to be increased peripheric vascular resistance,[1,2,33,34] increased arterial stiffness[35,36] or sympathetic and adrenal activation[18] or all together.

Although in subclinical hypothyroidism, the risk of atherosclerosis was found to be higher than normal subjects,[31,37–39] blood pressure values were not found to be different.[39,40] We believe that a limitation of our study was that we did not include patients with subclinical hypothyroidism, whichc needs to be addressed in future studies.

HR values of our hypothyroid individuals were lower than the controls, although not all of them were statistically significant. The values increased after treatment as expected.

It was demonstrated that hypertension in hyperthyroidism was mainly caused by systolic hypertension.[25,41–43] In our study, SBP values were also higher in hyperthyroid patients than the controls and decreased after treatment like recent studies.[25,44] The effects of hyperthyroidism on blood pressure regulation include increased cardiac inotropy and chronotropy, decreased systemic vascular resistance, increase in the number of cardiac β adrenergic receptor and activation of renin-angiotensin-aldosterone.[31,38,45] As we searched the literature, we found a few studies about hyperthyroidism and circadian regulation of blood pressure. In Minami's study a nocturnal fall in blood pressure was measured in patients with essential hypertension and mild to moderate hyperthyroidism, as well as normal subjects, but not those with severe hyperthyroidism.[24] In two studies, Middeke showed that in hyperthyroidism related hypertensive patients nighttime blood pressure fall was less than normal individuals.[26,46] In another study which compared hypertensive hyperthyroids with normotensives and primary hypertensives, circadian rhythm was found to be lower.[47] In Kohno's study on mild hyperthyroidic patients, no difference was found in these measurements.[48] Iglesias, et al. also showed no difference in circadian rhythm in 20 normotensive hyperthyroid patients.[25]

In our hyperthyroid patients, most of the blood pressure values especially SBP were higher than the control group in 24 hour daytime and nighttime measurements. As circadian rhythm was concerned, all blood pressure values were not different compared to the controls, but nocturnal fall were less than the controls, some of them non-statistically significant. Like some other studies, in our study with normotensive hyperthyroid patients, circadian rhythm was not different from normal subjects. It is not known whether inclusion of patients with hyperthyroidism and hypertension or patients with severe hyperthyroidism would have yielded different result.

After antithyroid treatment, blood pressure values diminished. These changes were minimal in DBP values. After therapy, circadian SBP values decreased, but DBP values increased, nocturnal fall in SBP was less than the values before treatment, but it was inverse for DBP. Like some other studies after antithyroid therapy, circadian SBP values decreased. We may explain this result by the smaller fall of nighttime SBP values than the fall of those values in daytime. This result may indicate the dynamic effects of thyroid hormone on SBP in daytime when the sympathetic system is more active. Another finding supporting this notion is the increased circadian rhythm values of DBP after treatment.

An important finding of our study was the higher SBP values in hyperthyroid patients than control subjects in both daytime and nighttime measurements. According to the control group, this difference was more important in daytime period, but in nighttime, the SBP increase was minimal. Our study is one of the few studies in which SBP decreased after normalization of thyroid hormone levels in hyperthyroidic patients. Besides the positive change in before and after treatment values of SBP values, we also demonstrated beneficial changes in DBP and MBP measurements;

only no difference was obtained in daytime DBP values. We may state that there is a reversible blood pressure increase pattern in awake and sleep periods in normotensive hyperthyroid patients.

As suggested by much data, measurement of nighttime BP yields additional prognostic data in terms of all-cause mortality and cardiovascular events.[49–52]

Failure of the blood pressure to fall by at least 10% during sleep is called nondipping. Independent of the degree of hypertension, nondipping is thought to be an important risk factor for heart failure and other cardiovascular complications,[53,54] diabetic nephropathy[55] decline in glomerular filtration rate,[56] and sleep apnea.[57] Whether reversal of nondipping is possible or beneficial is uncertain. Among our groups, the non-dipper blood pressure pattern was more common in hypothyroids and hyperthyroids compared to the controls. In both hypothyroids and hyperthyroids after treatment, the number of patients with non-dipper pattern diminished, which was statistically significant only in hyperthyroids. After our search in the literature, we found only two studies demonstrating the effect of elevated TSH,[23] and decreased fT3,[21] levels on the risk of nondipping. Despite the fact that the effect of thyroid hormone on non-dipper blood pressure profile has not been completely understood, we believe that thyroid hormon dysfunctions may increase the risk of non-dipping, but further studies are warranted.

There are a few limitations in this study. One is the moderate sample size. Second, we do not know how much time is needed for the adaptation of blood pressure, passing through thyroid hormone dysfuction to euthyroidism. The exact time of the measurements, that is when we must measure blood pressure values after reaching normal thyroid hormone levels, is not decided. Third, we did not include subclinic thyroid dysfunctions in our study. Finally, the findings are limited to our groups, which included only adults from our district, so our results may not be applicable to all our country or other nationalities.

In conclusion, we demonstrated that thyroid hormones beyond their effects in almost all tissues may cause changes in blood pressure measurements, most of them reversible by treatment of either hypothyroidism or hyperthyroidism. Early diagnosis and appropriate treatment of these disorders may reverse unfavorable changes in cardiovascular system and end-organs.

Authors' Contributions

Design: *Mutlu Demirel, Mehmet Yıldız;* ***Analysis and interpretation of the data:*** *Mutlu Demirel, Gül Gürsoy, Mehmet Yıldız;* ***Final approval of the article:*** *Mutlu Demirel, Gül Gürsoy, Mehmet Yıldız;* ***Statistical expertise:*** *Mutlu Demirel;* ***Collection of data:*** *Mutlu Demirel.*

Conflict of Interests: *Authors have no conflict of interests.*

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References

1. Klein I, Ojamaa K. Thyroid hormone and cardiovascular system. *The New England J of Medicine*. 2001; 344: 501 – 509.
2. Biondi B, Kein I. Hypothyroidism as a risk factor for cardiovascular disease. *Endocrine*. 2004; 24: 1 – 14.
3. Tang YD, Kuzman JA, Said S, Anderson BE, Wang X, gerdes AM. Low thyroid function leads to cardiac atrophy with chamber dilatation, impaired myocardial blood flow, loss of arterioles and severe systolic dysfunction. *Circulation*. 2005; 112: 3122 – 3130.
4. Kisso B, Patel A, Redetzke R, Gerdes AM. Effect of low thyroid function on cardiac structure and function in spontaneously hypertensive heart failure rats. *J Card Fail*. 2008; 14: 167 – 171.
5. Danzi S, Klein I. Thyroid hormone and blood pressure regulation. *Current Hypertension Reports*. 2003; 5: 513 – 520.
6. Pickering TG, Miller NH, Ogedegbe G, Krakoff LR, Artinlan NT, Goff D, et al. Call to action on use and reimbursement for home blood pressure monitoring: Executive summary: A joint scientific statement from the American Heart Association, American Society Of Hypertension, and Preventive Cardiovascular Nurses Association. *Hypertension*. 2008; 52: 1 – 9.
7. Head GA, Mihailidou AS, Duggan KA, Beilin LJ, Berry N, Brown MA, et al. Definition of ambulatory blood pressure targets for diagnosis and treatment of hypertension in relation to clinic blood pressure: prospective cohort study. *BMJ*. 2010; 340: c1104.
8. Mancia G, Sega R, Bravi C, Valaqussa F, Cesana G, Zanchetti A. Ambulatory blood pressure normality: results from the PAMELA study. *J Hypertens*. 1995; 13: 1337 – 1390.
9. Fan HQ, Li Y, Thijs L, Hansen TW, Boqqia J, Kikuya M et al. Prognostic value of isolated nocturnal hypertension on ambulatory measurement in 8711 individuals from 10 populations. *J Hypertens*. 2010; 28: 2036 – 2039.
10. Salles GF, Leite NC, Pereira BB, Nascimento EM, Cardoso CR. Prognostic impact of clinic and ambulatory blood pressure components in high – risk type 2 diabetic patients: The Rio de Janeiro Type 2 Diabetes Cohort Study. *J Hypertens*. 2013; 31: 2176 – 2186.
11. Piper MA, Evans CV, Burda BU, Margolis K, O'Connor E, Whitlock EP. Diagnostic and predictive accuracy of blood pressure screening methods with consideration of rescreening intervals: A systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2015; 162: 192 – 199.
12. Fagard RH, Celis H. Prognostic significance of various characteristics of out of the office blood pressure. *J Hypertens*. 2004; 22: 1663 – 1666.
13. Hansen TVV, Jeppesen J, Rasmussen S, Ibsen H, Torp–Pedersen C. Ambulatory blood pressure and mortality: a population based study. *Hypertens*. 2005; 45: 499 – 504.
14. Fagard RH, Staessen JA, Thijs L. Prediction of cardiac structure and function by repeated clinic and ambulatory blood pressure. *Hypertens*. 1997; 29: 22 – 29.
15. Mancia G, Verdecchia P. Clinical Value of ambulatory blood pressure. *Circ Res*. 2015; 116: 1034 – 1045.
16. Eguchi K, Hoshide S, Ishikawa S, Shimada K, Kario K. Aggressive blood pressure–lowering therapy guided by home blood pressure monitoring improves target organ. damage in hypertensive patients with type 2 diabetes/prediabetes. *J Clin Hypertens*. 2012; 14: 422 – 428.
17. Ferreira MM, Teixeira Pde F, Mansur VA, Reuters VS, Almeida CP, Vaisman M. Ambulatory blood pressure monitoring in normotensive patients with subclinic hypothyroidism. *Arq Bras Cardiol*. 2010; 94: 806 – 812.
18. Fommei E, Iervasi G. The role of thyroid hormone in blood pressure homeostasis: Evidence from short–term hypothyroidism. *J Clin Endocrinol Metab*. 2002; 87: 1996 – 2000.
19. Botella–CarreteroJl, Gomez–Bueno M, Barrios V, Caballerro C, Garci–Robles R, Sancho J, et al. Chronic thyrotropin suppresive therapy with levothyroxine and short term hypothyroidism after thyroxine withdrawal are associated with undesirable cardiovascular effects in patients with differentiated thyroid carcinoma. *Endocr Relat Cancer*. 2004; 11: 345 – 356.
20. Kotsis V, Alevizaki M, Stabouli S, Pitiriga V, Rizos Z, Sion M et al.Hypertension and hypothyroidism: results from an ambulatory blood pressure monitoring study. *J Hypertens*. 2007; 25: 993 – 999.
21. Kanbay M, Turgut F, Karakurt F, Işık B, Alkan R, Akçay A, et al. Relation between serum thyroid hormone and non–dipper circadian blood pressure variability. *Kidney Blood Pres Res*. 2007; 30: 416 – 420.
22. Volkov VS, Makusheva MV, Kleinikov DV. Twentyfour hour profile of arterial pressure in patients with hypothyroidism. *Klin Med*. 2007; 85: 37 – 39.
23. Inal S, Karakoc MA, Kan E, EbinÇ FA, Törüner FE, Arslan M. The

effect of overt and subclinical hypothyroidism on the development of non – dipper blood pressure. *Endokrynol Pol*. 2012; 63: 97 – 103.
24. Minami N, Imai Y, Abe K, Munakata M, Sakurada T, Yamamoto M, et al. The circadian variation of blood pressure and heart rate patients with hyperthyroidism. *Tohoku J Experimental Medicine*. 1989; 159: 185 – 193.
25. Iglesias P, Acosta M, Sanchez R, Fernandez–Reyes MJ, Mon C, Diez JJ. Ambulatory blood pressure monitoring in patients with hyperthyroidism before and after control of thyroid function. *Clinical Endocrinology(Oxford)*. 2005; 63: 66 – 72.
26. Klüglich M, Middeke M. Circadian blood pressure rhythm in hyperthyroidism and primary hyperparathyroidism. *Z Cardiol*. 1992; 81: 33 – 36.
27. Imai Y, Abe K, Munakata M, Sakuma H, Hashimoto J, Imai K, et al. Circadian blood pressure variations under different pathophysiological conditions. *J Hypertens Suppl*. 1990; 8: s125 – s132.
28. Ivanovic B, Paunovic I, Nikcevic D, Cvijanovic D, Kalezic N, Simic D. Ambulatory arterial blood pressure monitoring in patients before and after thyroidectomy. *Vojnosanit Pregl*. 2008, 65: 135 – 139.
29. Safa–Tiseront V, Ponchon P, Laude D, Elghozi JL. Contribution of the autonomic nervous system to blood pressure and heart rate variability changes in early experimental hyperthyroidism. *Eur J Pharmacol*. 1998; 352: 247 – 255.
30. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. Management of arterial hypertension of the European Society of Hypertension, European Society of Cardiology, 2007 guidelines for the management of arterial hypertension. *J Hypertens*. 2007; 251: 1105 – 1107.
31. Fazio S, Palmieri EA, Lombardi G, Biondi B. Effects of thyroid hormone on the cardiovascular system. *Recent Prog Horm Res*. 2004; 59: 31 – 50.
32. Ladenson PW, Singer PA, Ain KB, Bagchi N, Bigos ST, Levv EG, et al. Thyroid association guideliness for detection of thyroid dysfunction. *Archives of Internal Medicine*. 2000; 160: 1573 – 1575.
33. Dernellis J, Panaretou M. Effects of thyroid replacement therapy on arterial blood pressure in patients with hypertension and hypothyroidism. *Am Heart J*. 2002; 143: 718 – 724.
34. Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. *J Clin Endocrinol Metab*. 2003; 88: 2433 – 2444.
35. Dagre AG, Lekakis JP, Papaionnou TG. Arterial stiffness is increased in subjects with hypothyroidism. *Int J Cardiol*. 2005; 103: 1 – 6.
36. Hamano K, Inoue M. Increased risk for atherosclerosis estimated by pulse wave velocity in hypothyroidism and its reversal with appropriate thyroxine treatment. *Endocrine Journal*. 2005; 52: 95 – 101.
37. Biondi B, Palmieri EA, Lombardi G. Effects of subclinic thyroid dysfunction on the heart. *Ann Int Med*. 2002; 137: 904 – 911.
38. Kahaly GJ. Cardiovascular and atherogenic aspects of subclinic hypothyroidism. *Thyroid*. 2000; 10: 665 – 679.
39. Hak AE, Pols HA, Visser TJ, Dexhage HA, Hoffmnan A, Witteman JC. Subclinic hypothyroidism is an independent risk factor for atherosclerosis and myocardila infarction in elderly women: The Rotterdam Study. *Ann Int Med*. 2000; 132: 270 – 278.
40. Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, et al. Subclinic thyroid dysfunction and blood pressure: a community based study. *Clin Endocrinol*. 2006; 26: 486 – 491.
41. Saito I, Saruta T. Hypertension in thyrpid disorders. *Endocr Metab Clin North Ame*. 1994; 23: 379 – 386.
42. Klein I, Ojama K. Thyrotoxicosis and the heart. *Endocr Metab Clin North Ame*. 1998; 27: 51 – 62.
43. Saito I, Ito K, Saruta T. The effect of age on blood pressure in hypertension. *J Ame Geriatr Soc*. 1985; 33: 19 – 22.
44. Marcisz C, Jonderko G, Kuarrz E. Changes of arterial pressure in patients with hyperthyroidism during therapy. *Med Sci Monit*. 2002; 8: 502 – 507.
45. Marchant C, Brown L, Sernia C. Renin–angiotensin system in thyroid dysfunction in rats. *J Cardiovasc Pramacol*. 1993; 22: 449 – 455.
46. Middeke M, Kluglich M, Holzgreve H. Circadian Blood pressure rhytm in primary and secondary hypertension. *Chrono–Biology Int*. 1991; 8: 451 – 459.
47. Spieker C, Barenbrock M, Rahn KH, Zidek W. Circadian Blood pressure variations in endocrine disorders. *Blood Pres*. 1993; 2: 35 – 39.
48. Kohno I, Iwasaki H, Okutani M, Mochizuki Y, Sano S, Satoh Y, et al. Circadian Blood pressure and heart rate profiles in normotensive patients with mild hyperthyroidism. *Chrono–Biology Int*. 1998; 15: 337 – 347.
49. Dörr M, Wolff B, Robinson DM, John U, Lüdemann J, Menq V, et al. The association of thyrpid function with cardiac mass and left ventricular hypertrophy. *J Clin Endocrinol Metab*. 2005; 90: 673 – 677.
50. Petretta M, Bonaduce D, Spinelli L, Vicario ML, Nuzzo V, Marciano F, et al. Cardiovascular haemodynamics and cardiac autonomic control in patients with subclinical and overt hyperthyroidism. *Eur J Endocrinol*. 2001; 145: 691 – 696.
51. Boggia J, Li Y; Thijs Boggia J, Hansen TW, Kikuya M, Björklund–Bodegard K, et al. International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO) investigators. Prognostic accuracy of day versus night ambulatory blood pressure: A cohort study. *Lancet*. 2007; 370: 1219 – 1229.
52. Ben – Dov IZ, Kark JD, Ben – Ishay D, Mekler J, Ben-Arie L, Burszlyn M. Predictors of all–cause mortality in clinical ambulatory monitoring: Unique aspects of blood pressure during sleep. *Hypertension*. 2007; 49: 1235 – 1241.
53. Ingelsson E, Björklund–Bodegård K, Lind L, Arnlöv J, Sundström J. Diurnal blood pressure pattern and risk of congestive heart failure. *JAMA*. 2006; 295: 2859 – 2866.
54. Metoki H, Ohkubo T, Kikuya M, Asayama K, Obara T, Hashimoto J, et al. Prognostic significance for stroke of a morning pressor surge and a nocturnal blood pressure decline: The Ohasama study. *Hypertension*. 2006; 47: 149 – 154.
55. Lurbe E, Redon J, Kesani A, Pascual JM, Tajons J, Alvarez V, et al. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. *N Engl J Med*. 2002; 347: 797 – 805.
56. Davidson MB, Hix JK, Vidt DG, Brotman DJ. Association of impaired diurnal blood pressure variation with a subsequent decline in glomerular filtration rate. *Arch Intern Med*. 2006; 166: 846 – 852.
57. Narkiewicz K, Kato M, Phillips BG, Pesek CA, Davison DE, Somers VK. Nocturnal continuous positive airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea. *Circulation*. 1999; 100: 2332 – 2335.