

RELATION OF THYROID FUNCTIONS WITH PULSE RATE, BLOOD PRESSURE, AND PULSE PRESSURE IN MILD SCH AND EUTHYROID SUBJECTS



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ABSTRACT

Background

Overt hypothyroidism affects the cardiovascular system and blood pressure regulation. There is controversy on the relation of subclinical hypothyroidism (SCH) with the cardiovascular system, and this relation is not assessed yet in mild SCH (SCH with TSH < 10 mIU/L).

Objectives

To find differences in systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure, and pulse rate between mild SCH and Euthyroidism, furthermore to evaluate the relationship of these cardiovascular characteristics.

Methods

This prospective case-control study involved 186 participants; 43 mild SCH and 142 Euthyroid. The studied subjects were further subdivided into two groups according to age. Pulse rate and blood pressure (SDP and DBP) were measured, and mean and pulse pressure were calculated. The following biochemical parameters were measured; fasting plasma glucose (FPG) and thyroid function test (TFT; TSH, FT4, FT3, and anti-TPO antibody). The parameters were compared between SCH and Euthyroid groups using Student T-test and the correlation between variables was assessed using Pearson's correlation, with a P-value \leq of 0.05 is regarded as significant.

Results

The mean TSH level in the mild SCH group is 5.47 (0.89) mIU/L. Mild SCH has higher DBP compared to Euthyroid subjects (81.93 vs 77.64 mmHg), and in the age group of <35 years, each of the DBP, SBP, and mean pressure were higher in SCH compared to control individual, in this group, there is a significant inverse correlation between FT4 and DBP. And in subjects with >35 years significant inverse correlation exists between FT4 and mean pressure, $P < 0.05$. No significant association is present between TSH level and pulse rate, blood pressure, and pulse pressure.

Conclusion

Data of the present study revealed that even mild SCH, is associated with higher DBP compared to Euthyroid subjects and the FT4 level in the SCH has a negative correlation with DBP, while there was no significant correlation between pulse pressure, pulse rate with thyroid function test in subject with mild SCH. Follow-up of mild SCH subjects is recommended for blood pressure assessment.

Keywords: *Systolic blood pressure, Diastolic blood pressure, TSH, FT4, Mild SCH, Euthyroid.*

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INTRODUCTION

Thyroid hormone has a relation with the function of the cardiovascular system (CVS)^(1, 2). Effects of free triiodothyronine (FT3) on the blood vessel are relaxation of arteriole and dilation, with a resultant decrease in peripheral vascular resistance⁽²⁾. Thyroid hormone (TH) and in particular FT3 affect the rate and force of ventricular contraction and increased cardiac output⁽³⁻⁵⁾. When TH level decreased substantially as studied in overt hypothyroidism, all these machines will be reversed⁽⁵⁾. The clinical feature of overt hypothyroidism is vague but some clinical manifestations that related to CVS might appear; heart rate decreased, vascular resistance and diastolic blood pressure increased, and cardiac output decreased, with resultant narrowing in pulse pressure⁽⁵⁻⁷⁾.

Although in overt hypothyroidism mild degree of hypertension might occur because of the aforementioned mechanisms, there are controversy in Subclinical hypothyroid (SCH) subjects who have elevated thyroid-stimulating hormone with normal free TH level^(6, 8, 9). In some studies, the same associations were found, and SCH were found to have related to impaired endothelial function⁽¹⁰⁾, hyperlipidemia⁽¹⁾, hypertension, and increased risk of coronary heart disease and congestive heart failure particularly in SCH subjects with TSH level above 7 mIU/L⁽¹¹⁾, while other studies are failed to find any association between thyroid functions and hypertension in SCH⁽⁹⁾.

SCH subjects might have different characteristics according to the degree of TSH level elevation. Moreover, researchers graded these subjects into mild subclinical hypothyroidism; including persons with TSH < 10 mIU/L and SCH with prominent TSH elevation; TSH > 10 mIU/L⁽¹²⁾.

The recommendation for treating SCH includes subjects with a TSH level of ≥ 10 mIU/L and old individuals (over the seventies), while a decision to treat subjects without these two criteria is arguable and requires clinical, investigational, and risk factor assessments for each subject⁽¹³⁾.

In recent years arguments were raised upon the upper limit of normal for TSH level, and some regarded the TSH of more than 3 or even 2.5 as abnormal, which will change the definition and the number of subjects diagnosed with SCH and their treatment⁽¹⁴⁻¹⁶⁾ and more recently a higher clinical score and anti-thyroid peroxidase antibody (TPO-AB) was found in subjects with mild SCH⁽¹⁷⁾.

For the sake of the researcher it is not clear whether TSH level in subjects with mild SCH affects cardiovascular and blood pressure or not.

This study aims to compare some cardiovascular measures like; pulse rate, systolic and diastolic blood pressure, mean pressure, and pulse pressure between subjects with mild SCH and Euthyroid subjects and to reveal whether there is any correlation between thyroid function and blood pressure values among mild SCH group.

SUBJECTS AND METHODS

This prospective case-control study is conducted between the period of July 2018 to Dec. 2019 at Shar Hospital, Sulaymaniyah city, Iraq. It includes; healthy adults the age of ≥ 18 years who visited Shar hospital Consulting Department for usual health check-ups, it also includes the hospital staff and friends who volunteered to participate in the study. Among 218 subjects who participated in the study, 33 subjects were excluded because of the presence of one of the exclusion criteria.

Exclusion criteria include subjects; with any chronic systemic disease like Diabetes Mellitus and Cardiovascular disease (e.g. Hypertension), who were on treatment within two weeks from the hospital visit, and previous thyroid disease, treatment, or surgery.

Patient preparation and ethical consideration

All the participant gave their informed consent and the study is approved by the Ethical Committee of the College of Medicine, University of Sulaimani, and Shar Hospital Administration, Internal Medicine and Laboratory Departments approval were taken.

The subjects were assessed from 9:00 to 11:00 am and asked to overnight fast. Detailed questionnaires were filled for each participant, information obtained includes sociodemographic data, the drug history, and past medical and surgical history. The anthropometric data were assessed for all participants, waist circumferences were measured, and with the use of the same scale and balance the height and weight were measured and recorded.

Pulse rate and Blood pressure measurements: blood pressure and pulse rate were assessed while the subjects are relaxed and comfortable for 20 minutes, the pulse rate was assessed, and for blood pressure measurement the arm was supported and blood pressure was evaluated two times on two separate days

on the left arm with the use of Sphygmomanometer; Rossmax Swiss GmbH. The cuff was wrapped around the arm above the cubital fossa with the stethoscope on the brachial artery. The systolic and diastolic blood pressures were measured, the average of the two blood pressure measurements with the mean pressure and pulse pressure were calculated and the data were recorded.

Laboratory Investigations

Two mL of venous blood were taken from each subject after estimation of FBS via Contour Blood Glucose meter, Switzerland the blood was left for about 15 minutes then centrifuged and the serum was separated and brought to analysis.

The tests were analyzed with the use of electrochemiluminescence immunoassay, a recent immunoassay technique. The same kit type was used for all tests from Roche Diagnostics GmbH, Germany, with the use of the same device; Cobas e 411 analyzers (Hitachi High-Technologies Corporation, Germany). The quality control was performed during running the test.

Laboratory reference ranges for the kits that are used;

TSH: 0.27–4.2 mIU/L, FT4: 0.93–1.70 ng/dl, FT3: 2.0–4.4 pg/ml, Anti-TPO up to 34 IU/ml, and FPG of 70–120 mg/dL.

Group definition

The participants were grouped into two groups according to their thyroid status into Euthyroid subject; in whom the thyroid function is normal with TSH value below 4.2 mIU/L and SCH subjects; includes those with TSH value ≥ 4.2 with normal FT4 and FT3. The studied participants were further subdivided according to their age into the age group of less than 35 and the age group of ≥ 35 years.

Statistical analysis

All data were entered and analyzed using the SPSS-22 software program. The normality test was assessed for all variables. The normally distributed variables were compared using the Student t-test, and their values are expressed as mean [\pm SD]. Chi-square was used to compare frequencies and they were expressed as numbers and percentages. The non-parametric variables including; Age, Thyroid functions, FPG, and pulse pressure are presented as Median and

range and compared using Mann–Whitney test. Correlation between variables was performed using Pearson's correlation; the non-parametric data were log-transformed before correlation analysis, to correct skewness. The significant level was set at 0.05.

RESULTS

After the exclusion of 33 subjects, 185 participants were included in the current study; 142 Euthyroid and 43 SCH. The mean age of studied participants was 31 years (18-70 years). The general characteristics of the studied participants were shown in Table 1-a.

Mean diastolic blood pressure is significantly higher in SCH compared to the Euthyroid group in studied participants, as shown in Figure 1 and Table 1-b. Median TSH and anti-TPO are significantly higher while FT4 is significantly lower in SCH compared to the Euthyroid group, with the mean TSH of 5.47 (0.89) mIU/L and median 5.25 (4.28-7.28) mIU/L in the SCH group. The non-descriptive data are presented as %, and chi-square is used to find significance. The parameters not normally distributed are expressed as median [range], and the groups are compared using the Mann–Whitney test. The parameters not normally distributed are expressed as median [range], and the groups are compared using the Mann–Whitney test. In the age group of <35 y; DBP, SBP, and mean pressure were significantly higher in SCH compared to Euthyroid subjects, $P \leq 0.05$; Table 2. There is no significant difference in the pulse rate and pulse pressure between the SCH and Euthyroid groups. Similarly, FPG is not different between the two groups, 87 [41] vs 93 [43] mg/dL, in euthyroid vs SCH, respectively in subjects with the age of < 35 , $P = 0.125$.

a The parameters not normally distributed are expressed as median [range], and the groups are compared using the Mann–Whitney test

A significant inverse correlation was found between mean FT4 and mean DBP in Euthyroid subjects with age <35 y as revealed in Figure 2; ($r = -0.219$, $P = 0.038$).

Figure 3, demonstrate significant negative correlation between mean FT4 and mean pressure in subjects with age ≥ 35 y, ($r = -0.242$, $P = 0.042$).

No significant correlations were found between mean TSH (log transformed TSH) level and each of the following; pulse rate ($r = -0.032$, $P = 0.666$), SBP ($r = -0.027$, $P = 0.720$), DBP ($r = 0.048$, $P = 0.515$), Pulse pressure -log transformed ($r = -0.070$, $P = 0.342$); while, with grading TSH level, the higher TSH level

show significantly higher SBP and DBP significantly, with the exception of subjects with TSH level of < 1.5 mIU/L. The mean of Systolic and Diastolic BP according to different TSH levels was shown in Figure 4.

Table 1-a. General characteristics of studied participants.

Variables	Euthyroidism N = 142 Mean (SD)	SCH N = 43 Mean (SD)	P-value
Gender			
male	29 (20.3%)	5 (11.6%)	0.262
female	114 (79.7%)	38 (88.4%)	
Age (y)	31 [53]	32 [52]	0.886
BMI (Kg/m²)	27.01 (4.98)	28.17 (3.97)	0.120
Waist (cm)	83.73 (11.36)	85.53 (9.61)	0.363

Table 1-b. Cardiovascular and biochemical parameters of the studied participants.

Variables	Euthyroidism N = 142 Mean (SD)	SCH N = 43 Mean (SD)	P value
FPG (mg/dL)	88 [52]	93 [43]	0.478
TSH (mIU/L)	1.95 [3.8]	5.25 [3.0]	< 0.001
FT4 (ng/dL)	1.23 [1.22]	1.12 [0.66]	0.003
FT3 (pg/mL)	2.33 [2.75]	2.03 [2.95]	0.895
Anti-TPO (IU/ml)	6.75 [332.9]	13.54 [389.4]	0.004
Pulse rate (beats/min)	80.41 (10.45)	81.05 (9.49)	0.711
Systolic BP (mmHg)	117.35 (14.33)	120.93 (11.97)	0.108
Diastolic BP (mmHg)	77.64 (10.24)	81.93 (10.97)	0.026
Mean pressure (mmHg)	90.87 (10.73)	92.38 (17.45)	0.594
Pulse pressure (mmHg)	40 [55]	41 [19]	0.931

Table 2. Comparison of cardiovascular parameters in Euthyroid and SCH subjects with the age group of less than 35 y.

Variables	Euthyroidism N = 90	SCH N = 23	P value
Pulse rate (beats/min)	80.85 (11.14)	81.36 (10.81)	0.845
Systolic BP (mmHg)	114.06 (11.89)	118.57 (7.47)	0.028
Diastolic BP (mmHg)	75.50 (9.27)	79.57 (8.76)	0.058
Mean pressure (mmHg)	88.35 (9.09)	92.57 (6.84)	0.018
Pulse pressure (mmHg)	39 [55]	43 [44]	0.567

Relation of Thyroid Functions with Pulse Rate, Blood Pressure ...

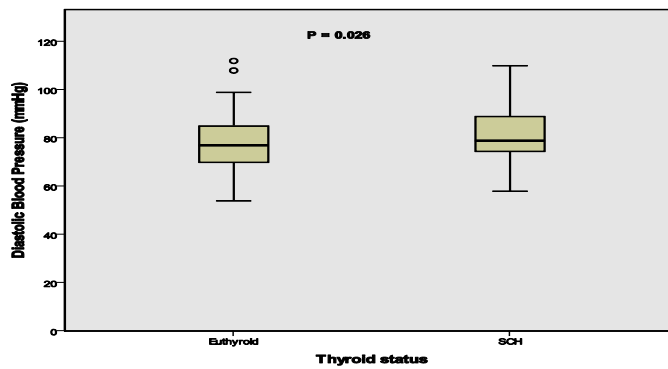


Figure 1. Comparison of mean diastolic blood pressure (Diastolic BP by mmHg) between Euthyroid and SCH subjects in studied participants.

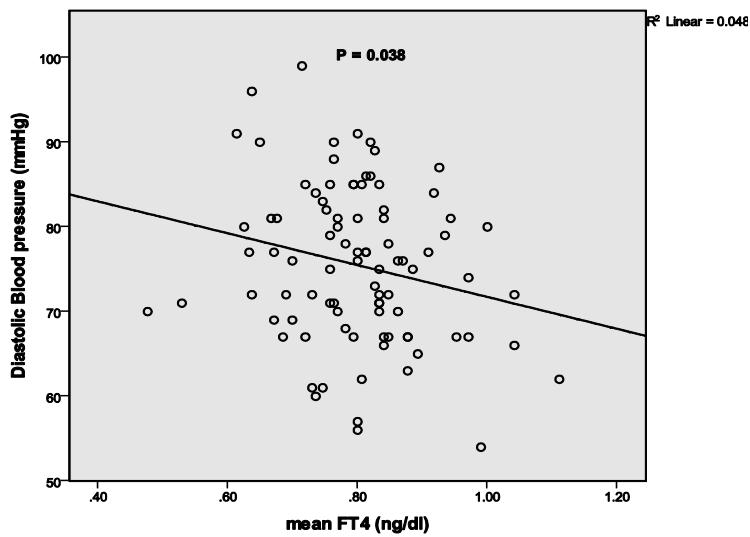


Figure 2. A negative correlation between FT4 and DBP in Euthyroid with the age group of less than 35 y.

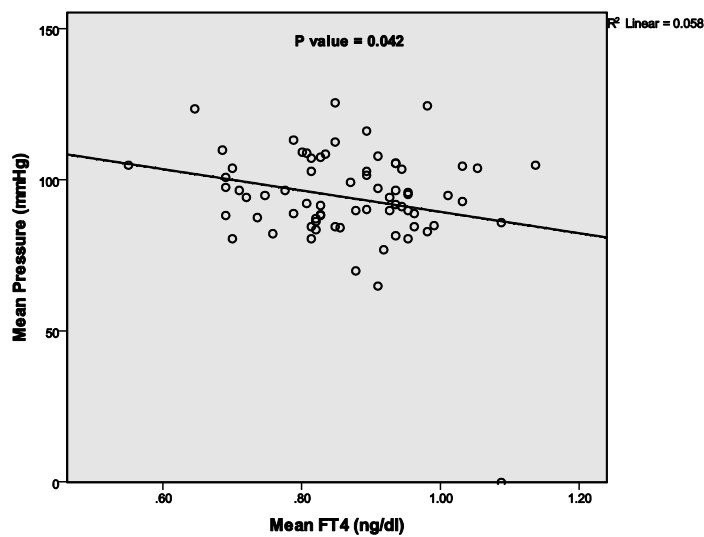


Figure 3. A negative correlation between mean FT4 and mean arterial pressure in the age group more than 35 y.

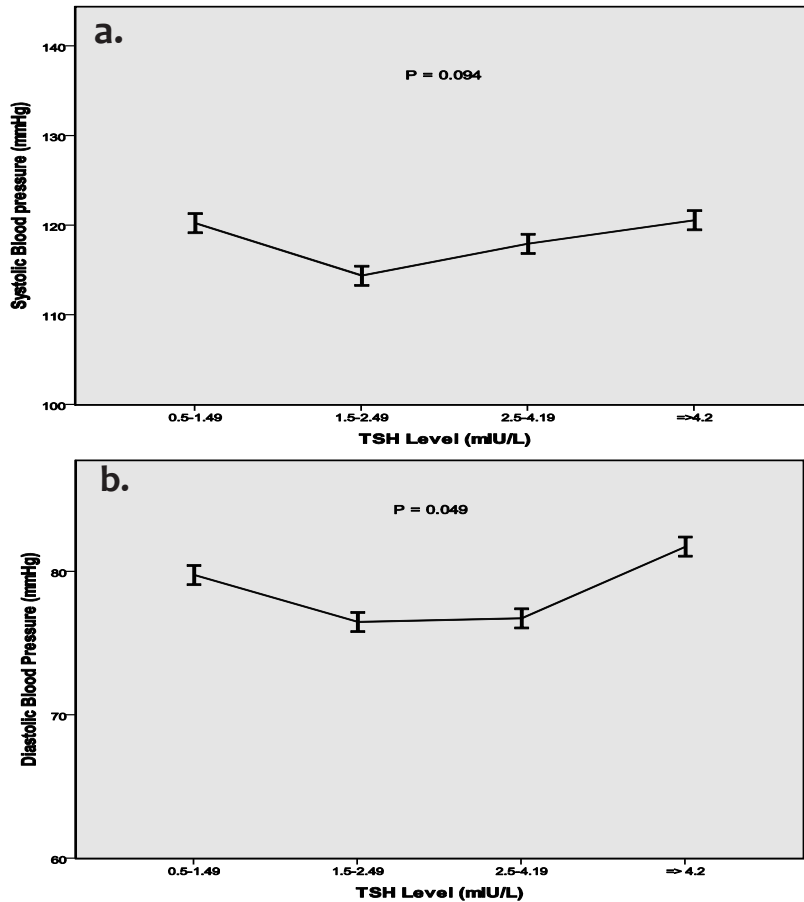


Figure 4. Mean systolic (a.), and mean Diastolic (b.) blood pressure in participants according to different TSH levels.

DISCUSSION

The current study revealed that DBP was significantly higher in SCH compared to the Euthyroid group with no significant difference in SBP, mean pressure, pulse rate, and pulse pressure in studied participants regardless of age group. The increase in peripheral vascular resistance could be responsible for higher DBP in the SCH group, as explained in previous studies (2,5-7). Meanwhile, significantly higher DBP, SBP and mean pressure were observed in SCH compared to the Euthyroid group in subjects below 35 years, which might suggest that, the effect of decreased TH on salt sensitivity, sodium metabolism, and blood pressure regulation were more profound in the younger age group^(18, 19).

Previous studies found the same results with significantly higher mean DBP in adults with SCH compared to the control group, with no significant difference in SBP (20-22). The age group of the Iranian study⁽²¹⁾ is comparable to our study, while the studies by Canbolat et al and Nagasaki et al^(20,22), do not clear

whether the younger age group has the sole difference in DBP or not, because the mean age of SCH in these studies was higher, and age groups were not separated. In a meta-analysis examining the relationship of SCH with blood pressure, higher SBP, and a slightly higher DBP were found in SCH compared to the control group⁽⁷⁾. The same results were also found in another study⁽²³⁾.

No significant differences were observed in the mean PR and pulse pressure between the two groups in this study which is comparable to Nagasaki et al study from Japan⁽²²⁾. No significant associations between thyroid function and each of the PR and pulse pressure were also found in the SCH and Euthyroid group. Similarly, in agreement with the present study, no significant differences were found in PR between SCH and normal individuals in another study⁽²⁴⁾.

Fasting plasma glucose failed to show a significant difference between SCH and control group, this is in opposition to the cross-sectional study performed in Japan⁽²⁴⁾, which documented higher FPG and HBA1c

% in the SCH group compared to Euthyroid subjects. This inconsistency might be related to the difference in the age group between the studies; the present study assessed the younger age group (mean of 31 years) compared to the Japanese study, in which the mean age in the SCH group of their study was 69 (\pm 10) years⁽²⁴⁾ and the older age group associated with higher FPG even in non-Diabetic subjects⁽²⁵⁾.

The current study demonstrated a significant negative correlation between FT4 and mean pressure in the age group of more than 35 y, and FT4 and DBP, in Euthyroid subjects with the age group of less than 35 y, which suggest that even with a normal FT4 level of euthyroid or SCH state, the mean blood pressure and in particular DBP has increased with a slight degree of decrease in the FT4, this finding is consistent with the previous study in which significant association of FT4 with systolic and diastolic BP were found⁽²⁴⁾.

In this study, TSH level has no significant correlation with blood pressure in SCH and Euthyroid subjects an observation goes in line with Takashima et al study⁽²⁴⁾, while other researchers demonstrate a significant association of TSH with Systolic and Diastolic BP in Euthyroid subjects^(26, 27), the difference in age group, ethnicity might be responsible for this discrepancy throughout the studies.

In the present study when we graded the mean TSH level of the Euthyroid subjects into different grades, the higher the TSH value associated with a higher SBP and DBP, although both are within the reference range. Except for subjects with TSH levels of less than 1.5 mIU/L who showed higher SBP and DBP compared to the TSH value above 1.5 mIU/L.

This suggests that in the TSH level of less than 1.5 mIU/L, the thyroid hormone has the same effect on increasing BP as subjects with TSH of $>$ 4.19 mIU/L.

Thus thyroid hormone and TSH within the 1.5-2.5 might be related to more ideal blood pressure levels.

In conclusion, these findings conclude that even mild SCH has been associated with a higher level of diastolic blood pressure compared to Euthyroid, while no differences in pulse rate, pulse pressure existed in this SCH stage. It also concludes that FT4 inversely correlated with DBP in the TSH range of the Euthyroid status. This finding is of importance during diagnosing subjects with SCH, which require follow-up and assessment of blood pressure on each visit, even in the

TSH range of $<$ 10 mIU/L.

The limitation of this study is a small number of SCH subjects due to exclusion of subjects with previous thyroid disease or surgery/radiation, any systemic disease or anti-thyroid or other medication treatments, and the participants were not assessed for other physiological cardiovascular parameters. Further studies are recommended to include a greater number of participants with SCH and comparing them with overt hypothyroidism patients.

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