

Is Subclinical Thyroid Dysfunction Associated with Coronary Heart Disease?

Elaheh Barghchi^{1*}, Fereidoun Azizi²

¹ Endocrinologist, Internal Medicine, Department of Endocrinology, University of Medical Sciences, Mashhad, Iran

² Endocrinologist, Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

Introduction: Previous cohort studies reported contradictory data on the association between subclinical thyroid dysfunction and coronary heart disease (CHD). Regarding this, the present study was conducted to illuminate this relationship.

Material and Methods: For the purpose of the study, 3,066 participants employed in a study conducted by Azizi et al. aged ≥ 20 years were subjected to thyroid function tests every 3 years over a mean follow-up of 10 years. After the exclusion of the subjects with CHD and those consumed thyroid, anti-thyroid, or corticosteroid preparations, 2,144 subjects remained for analysis and followed up for CHD events in the next 10 years.

Results: At the baseline, 1929, 139, and 76 subjects had euthyroid, subclinical hyperthyroid, and subclinical hypothyroid, respectively. No CHD event occurred in the subclinical hypothyroid group. After the adjustment of all confounders, the subclinical hyperthyroid group had the hazard ratio of 1.01 for CHD with a 95% confidence interval of 0.36-2.85.

Conclusion: The 10 year follow-up of subjects with subclinical thyroid disease revealed no relationship between CHD and subclinical thyroid disorders.

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Introduction

Subclinical thyroid dysfunction is defined as abnormal serum thyroid-stimulating hormone (TSH) with normal FT4 and T3. The prevalence rate of subclinical hypothyroidism ranges within 1-10% and is often up to 15% in females aged over 60 years (1-3). On the other hand, subclinical hyperthyroidism has the prevalence rate of almost 0.7% (4). There is no world consensus on the screening and treatment of subclinical thyroid dysfunction.

Cardiovascular disease is the most prevalent cause of mortality, especially during the sedentary time. According to the World Health Organization annual report 1997, cardio-cerebral accidents are responsible for 30% of total mortality worldwide (5), and coronary

heart disease (CHD) is the major cause of adult mortality, comprising one third of total mortality among the individuals aged over 35 years (6).

Mild disorders in thyroid function are accompanied by changes in serum cholesterol level, heart rhythm, ventricular function, and atherosclerosis (7-11). However, there is a controversy over the association between subclinical thyroid dysfunction and CHD and cardiovascular mortality. Accordingly, the results documented by multiple prospective long cohort studies differ with one another (12-21). In this regard, the largest study reported a rising trend in the risk of cardiovascular mortality in females with one

*Corresponding author: Elaheh Barghchi, Internal Medicine, Department of Endocrinology, University of Medical Sciences, Mashhad, Iran. Tel: +985138543031; Email: barghchie@yahoo.com

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unit rise in TSH (15).

In two studies with similar follow-up durations of about 20 years, CHD events and cardiovascular mortality were reported to increase in the group with subclinical hypothyroidism (17, 20). On the other hand, in another study with a 12.5-year follow-up, the subclinical thyroid dysfunction group showed no increase in the risk of cardiovascular mortality and coronary vascular events, compared with euthyroid individuals (12).

In a study titled, "Tehran Lipid and Glucose Study (TLGS): rationale and design", Azizi et al. followed up a representative population of Tehranian residents for more than a decade to evaluate the association between thyroid status and CHD.

Materials and Methods

Study design

The TLGS study is a prospective research of non-communicable risk factors among the urban population of Tehran. The details of the design of this study have been published previously. For the current study, out of 3,060 TLGS participants aged ≥ 20 years, 916 cases were excluded due to consuming levothyroxin, antithyroid, or corticosteroid preparations and having thyroid disease or ischemic heart disease on the basis of Q wave in the baseline electrocardiography (ECG) or history of CHD. Finally, the data of 2,144 subjects were evaluated for determining the association between subclinical thyroid disorders and cardiovascular outcomes.

Laboratory assessments

Thyroid function tests were simultaneously performed on four serum samples obtained from each subject (one at the baseline and others after 3, 6 and 10 years of follow-up). Furthermore, the measurement of free T4 was accomplished using the electro-chemiluminescence assay with a cobas 411 analyzer (Roche Diagnostic USA, Roche, GmbH). The intra- and inter-assay variations were 1.4% and 3.9%, respectively, with a normal range of 12-22 Pmol/L.

The TSH was also measured by immunoelectrochemiluminometric assay, and the inter- and intra-assay variations were 1.1% and 3.6%, respectively, showing a normal range of 0.27-4.2 μ IU/mL. TPO antibody (TPOAb) was evaluated using the enzyme immuno metric assay with Sunrise (Tecan Co, Salzburg, Austria, Monobind, Costa Mesa, CA, USA). The intra- and inter-assay variations were 3.7% and 4.1%, respectively, and values over 40 U/mL were considered positive.

Outcomes

Outcome for any cardiac event was recorded prospectively during the annual follow-up of each subjects. The CHD was defined as myocardial infarction based on definite ECG results and cardiovascular markers. Furthermore, probable myocardial infarction was defined based on positive electrocardiogram with symptoms and signs of coronary disease or positive electrocardiogram with intermediate markers. Additionally, proven coronary heart disease was determined based on angiography.

Definitions

In the TLGS population, the reference range of serum TSH for the study population was defined as 0.4-5.8 μ IU/mL. The following definitions were employed for other medical conditions:

- Euthyroid: $0.4 \leq \text{TSH} \leq 5.8$ μ IU/mL and normal free T4
- Subclinical hyperthyroidism: $\text{TSH} < 0.4$ μ IU/mL and normal free T4
- Subclinical hypothyroidism: $\text{TSH} > 5.8$ μ IU/mL and normal free T4
- Overt hyperthyroidism: $\text{TSH} < 0.4$ μ IU/mL and free T4 > 22 Pmol/L
- Overt hypothyroidism: $\text{TSH} > 5.8$ μ IU/mL and free T4 < 12 Pmol/L.
- Hypertension: systolic blood pressure ≥ 140 , diastolic blood pressure ≥ 90 mm/Hg, or use of antihypertensive drugs
- Diabetes: fasting blood sugar (FBS) ≥ 126 mg/dL, 2 hours post-prandial blood sugar (2hPPBS) ≥ 200 mg/dL, or use of antihyperglycemic agents
- Dyslipidemia: total cholesterol > 200 mg/dL, triglycerides (TG) ≥ 150 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL, or use of drugs for lipids

Statistical analysis

The TG and TSH did not have a normal distribution; therefore, median, range, and first and third quartiles were reported. The categorical variables were documented as number and percentage. We applied Kruskal-Wallis nonparametric analysis for two variables of TSH and TG. There was a significant difference among the three groups in terms of TSH. Nonetheless, no significant difference was observed among the groups regarding TG.

On the basis of the homogeneity test, we compared the sustained variables among the three groups of subclinical hyperthyroid, euthyroid, and subclinical hypothyroid. To this end, the normally and non-normally distributed data were subjected to ANOVA and robustness test, respectively. Therefore, systolic blood

pressure, FBS, 2hPPBS, total cholesterol, low-density lipoprotein cholesterol, HDL-C, and LnTG were analyzed by ANOVA. For HDL, p-value less than 0.005 was considered statistically significant.

Other variables of age, body mass index (BMI), diastolic blood pressure, free T4, and LnTSH were analyzed by the robustness test. P-value of 0.044 was considered statistically significant for age, and regarding free T4 and LnTSH, p-value of < 0.005 was determined as the level of significance. Based on our findings, we applied the post hoc Dunnett test for HDL and age and also for free T4 and LnTSH to facilitate the comparison of both subclinical hyper- and hypo-thyroid groups with euthyroid group. The categorical variables were subjected to Chi-square test, and in case the frequency was > 5, the Fisher's exact test was employed.

In order to compare the hyperthyroid group with the euthyroid group, the Cox hazards regression model was utilized to adjust all the confounder's covariates. In the final analysis, three models were used. In the first model, age and gender were adjusted. The second model was adjusted for age, gender, history of cerebrovascular accident, BMI, premature cardiovascular disease in family members, and smoking. The third model included all the covariates of the first and second models, along with FBS, 2hPPBS, systolic and diastolic blood pressure, and dyslipidemia. The TPOAb positivity was not adjusted due to the lack of events, and

the outcome for subclinical hypothyroidism was not analyzed. Data analysis was performed in SPSS (version 15) and STATA, and p-value less than 0.05 was considered significant.

Results

The baseline characteristics of the study groups with different thyroid functions are presented in Table 1. Out of 2,144 participants, 1929, 139, and 76 subjects had euthyroid, subclinical hyperthyroid, and subclinical hypothyroid, respectively. The mean age of the subjects was comparable in the three groups. The percentages of women and TPOAb positivity were statistically higher in the subclinical hypothyroid as compared to those in the other two groups. Furthermore, serum HDL-C was higher in the subclinical hypothyroid group and lower in the subclinical hyperthyroid group, compared to that in the euthyroid group.

The 10-year follow-up revealed no cardiovascular mortality; furthermore, no CHD event was observed in the subclinical hypothyroid group. On the other hand, euthyroid and subclinical hyperthyroid groups had 73 and 5 CHD events, respectively. According to the Cox hazards regression analysis, in model 1 after adjusting for age and gender, the hazard ratio (HR) was 0.96 with a 95% CI of 0.39-2.37 for CHD in the subclinical hyperthyroid group, compared to the euthyroid group. In model 2, the HR was 0.96 with a 95% CI of 0.38-2.39, and in model 3, it was 1.01 with 95% CI of 0.36-2.85. In none of the

Table 1. Baseline characteristics of 3 groups at beginning of the study

variables	Subclinical hyperthyroid(n=139)	Euthyroid (n=1929)	Subclinical hypothyroid (n=76)	P value
Age (yrs)*	42.7±11.9	40.7±13.8	38.26±13.23	
Female (%)‡	78(56.1%)	1194 (61.9%)	64(84.2%)	p<0.05
TSH (µIU/ml) †	0.22(0.00-0.40)	1.57(0.40-5.80)	7.37(5.84-32.58)	p<0.05
Free T4 (Pmol/L) *	16.75±2.32	15.59±2.02	14.43±1.97	p<0.05
BMI (Kg/m ²)*	26.69±3.96	26.74±4.41	26.39±5.33	
SBP (mmHg)*	118±16	117±17	115±16	
DBP (mmHg)*	77±12	77±10	76±10	
FBS (mg/dl)*	100±33	95±30	94±36	
2h PPBS (mg/dl)*	118±55	113±51	112±71	
Cholesterol (mg/dl)*	201±42	207±43	212±47	
LDL (mg/dl)*	127±36	132±36	135±38	
HDL (mg/dl)*	39.47±8.98	42.37±10.97	46.84±12.94	p<0.05
Triglycerides (mg/dl) †	150(40-570)	139.50(30-1752)	111(45.00-494.00)	
TPO Ab+ (%)‡	10(7.2%)	198(10.3%)	40(52.6%)	p<0.05
Hypertension (%)‡	25(18.4%)	344(18.3%)	13(17.3%)	
Hypertension drugs (%)‡	11(8%)	119(6.3%)	4(5.3%)	
History of CVA (%)‡	0(0%)	14(0.7%)	0(0%)	
Diabetes (%)‡	20(14.7%)	191(10.6%)	6(8.6%)	
Lipid lowering drugs (%)‡	1(0.7%)	64(3.4%)	3(4%)	
Dyslipidemia (%)‡	112(81.2%)	1534(79.9%)	48(63.2%)	p<0.05
Premature CHD in family (%)‡	27(19.7%)	277(14.6%)	16(21.3%)	
Never (%)‡	109(80.1%)	1586(83.9%)	67(89.3%)	
Smoking Current (%)‡	19(14.0%)	189(10.0%)	2(2.7%)	
Past (%)‡	8(5.9%)	116(6.1%)	2(8%)	

SBP: systolic blood pressure, DBP: diastolic blood pressure, FBS: fasting blood glucose
Data are shown as mean±SD*, median, and range (†), number and percent (‡).
p<0.05 for comparison with the euthyroid group.

three models, the difference between the subclinical hyperthyroid and euthyroid groups was statistically significant in terms of CHD incidence (Table 2).

Figure 1a and 1b illustrate the Kaplan-meier curve of cumulative hazard and survival of CHD for patients with subclinical hyperthyroidism versus subjects with euthyroidism. The Kaplan-meier curve revealed no difference between the subclinical hyperthyroidism and euthyroid groups in terms of cumulative hazard and survival of CHD.

Table 2. Hazard ratio with 95% CI for coronary heart disease in subclinical hyperthyroid group.

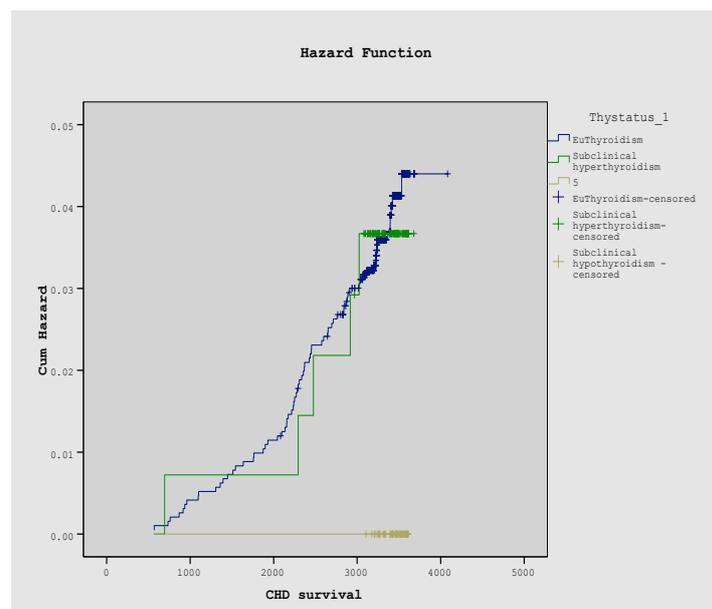
Model 1	0.96(0.39-2.37)
Model 2	0.96(0.38-2.39)
Model 3	1.01(0.36-2.85)

Applying Cox proportional hazard regression analysis with confounders adjustment in 3 models

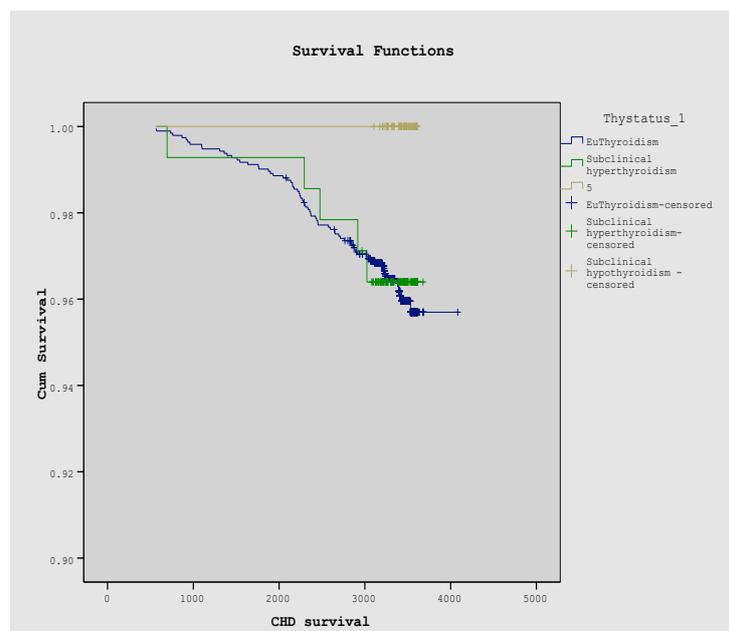
Model 1- adjustment for age and sex

Model2-adjustments of cofounders of model 1 and also history of CVA, BMI, history of premature heart disease in family and Smoking.

Model 3-adjustments of cofounders of model 1 and 2 and also fasting blood sugar ,2 hours pp,systolic blood pressure,diastolic blood pressure, dyslipidemia.



(panel a)



(Panel b)

Figure 1. (panel a): Kaplan Meier of cumulative hazard of CHD for subjects with subclinical hyperthyroidism versus subjects with euthyroidism, in subclinical hypothyroidism we had no events (Panel b): Kaplan- Meier cumulative survival of CHD for patients with subclinical hyperthyroidism versus subjects with euthyroidism, in subclinical Hypothyroidism we had no CHD events

Discussion

The results of the present prospective study of subclinical thyroid subjects in Tehran with a 10-year follow up demonstrated no CHD event in the subclinical hypo- and hyper-thyroid groups. In addition, the euthyroid subjects showed no significant difference with the subclinical hypo- and hyper-thyroid groups in terms of CHD HR.

Previous studies about the association of subclinical thyroid disorders with CHD and cardiovascular mortality have documented controversial results. For instance, in a study conducted by Asvold et al. (15) on a sample size of 25,313 and with a follow-up of about 8.3 years, it was demonstrated that the risk of mortality due to CHD in women increased for each rise of TSH in the reference range with an HR of 1.3 and 95% CI of 1.06-1.60. However, in another study performed by Boekholdt et al. on 12,000 participants and a follow-up duration of 10.6 years, the risk of CHD and mortality in the subclinical thyroid disorder group did not increase when compared to those in the euthyroid group (14).

In addition, in a study with a mean follow-up duration of 12.5 years, the subclinical thyroid disorder group showed no increased risk of cardiovascular mortality and CHD events, compared to the euthyroid group (12). Using a follow-up of 10 years, Imaizumi reported that only the risk of total mortality increased in men with subclinical hypothyroidism with an HR of 1.9 and 95% CI of 1.1- 3.2 (21). Nonetheless, Iervasi et al., adopting only a 32-month follow-up, showed that the risk of cardiovascular mortality did not increase in subjects with subclinical thyroid disorders, compared to that in the euthyroid group (16).

In two studies carried out by Vanderpump et al. with 20 years of follow-up, the risk of ischemic heart events and cardiac mortality increased in the subclinical hypothyroid group, compared to that in the euthyroid group with the HRs of 1.76 (95% CI: 1.15-2.71) and 1.79 (95% CI: 1.02-3.76) for ischemic heart event and cardiovascular mortality, respectively (18, 19). In another study with a 20-year follow-up (20), the risk of CHD events increased in only subclinical hypothyroid group showing an HR of 1.8 with a 95% CI of 1.2-2.7.

Regarding the limitations and strengths of this study, the lack of observing any association between subclinical thyroid dysfunction and CHD may be due to the young study population (mean age 40.7±13.8 years). Another limitation was the exclusion of CHD at the beginning of the study on the basis of ECG rather than angiography.

The main strength of the current study is the employment of a well-controlled cohort design

with 10 years of follow-up. Moreover, four records of data were collected for each subject, namely one baseline data and three follow-up data (every three years). Additionally, all subjects with intervening variables were excluded at the beginning of the study.

Conclusion

As the findings of the present indicated, the incidence of CHD and cardiovascular mortality was very low among the Tehranians during the 10-year follow-up. Furthermore, subclinical thyroid disorders showed no relationship with CHD and cardiovascular mortality. This study was performed in the Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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None.

Conflict of Interest

The authors declare no conflict of interest.

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