

THYROID STIMULATING HORMONE AS RISK FACTOR FOR CORONARY HEART DISEASE

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ABSTRACT

Background: Subclinical hypothyroidism has been associated with hypercholesterolemia and atherosclerosis, so screening and treatment have been advocated to prevent cardiovascular disease. **Objectives:** clarification of cardiovascular risk of subclinical hypothyroidism.

Patients and Methods: 300 patients were admitted with coronary heart disease and data collected for demographic characteristics, baseline TSH and T₄ levels., baseline cardiovascular risk factors such as diabetes, blood pressure, smoking, LDL and HDL-cholesterol serum levels, baseline used drug therapy. The 300 patients were divided into two groups; Gr.(1): 160 patients with coronary heart disease and subclinical hypothyroidism. Gr. (2) 140 patients with coronary heart disease and euthyroidism. Statistical correlation between coronary heart disease events and different TSH-serum levels was followed.

Results: As regards to age, sex and FT₄ serum levels, there were no statistical differences. Actually, we noticed that patients whatever with unstable angina (50%), revascularization (21.25%), or presented with acute myocardial infarction (15%), had TSH serum level 4.5 or greater and less than 20 mIU/L with normal serum levels of L-thyroxine, which undergo what is known as underactive thyroid or subclinical hypothyroidism.

Conclusion: subclinical hypothyroidism is associated with an increased risk of coronary heart disease especially in those with higher TSH levels and significantly elevated in adults with TSH levels of 10 mIU/L or greater. The results of our present study may help in refining a TSH threshold at which larger clinical benefits of thyroxine replacement would be expected.

KEYWORD:TSH-CHD-Atherosclerosis-Dyslipidemia-Controversy of TSH level.

INTRODUCTION

Thyroid hormones have profound effects on the heart and peripheral vasculature¹. Subclinical hypothyroidism has been associated with hypercholesterolemia² and atherosclerosis³, so screening and treatment have been advocated to prevent cardiovascular disease⁴. Controversy persists on the indications for screening and threshold levels of thyroid-stimulating hormone (TSH) for treatment of subclinical hypothyroidism⁵, defined as elevated serum TSH levels with normal thyroxine (T₄) concentrations. However data on the associations with coronary heart disease (CHD) attacks and mortality are conflicting among several large prospective cohorts^{6,7}. Three recent study-level meta-analyses⁸⁻¹⁰ found modestly increased risks for CHD and mortality, but with heterogeneity among individual studies that used different TSH cutoffs, different confounding factors for adjustment and varying CHD definitions⁸. One cohort study suggested particularly high risk in participants with subclinical hypothyroidism and preexisting cardiovascular disease⁶. Part of heterogeneity might also be

related to differences in participants' age, sex, or severity of subclinical hypothyroidism (as measured by TSH level)². Aim of the work was clarification of cardiovascular risk of subclinical hypothyroidism.

PATIENTS AND METHODS

INCLUSION CRITERIA: (1) measured thyroid function including TSH and thyroxine (T₄) levels at baseline in adults. (2) assessed coronary heart disease (CHD) events and outcome.(3) comparative group of euthyroidism. **EXCLUSION CRITERIA:** (1) taking antithyroid medications. (2) thyroxine replacement. (3) amiodarone therapy. (4) overt hypothyroidism including low T₄ and elevated TSH levels. (5) abnormal T₄ values, suggestive of nonthyroidal illness whatever low TSH and FT₄ or low TSH (<0.5mIU/L). (6) missing T₄ level. The present study was carried out retrospectively and involved 300 patients were admitted with coronary heart disease to HGH, from August, 2011 to May, 2012 and data collected for demographic characteristics, baseline TSH and T₄ levels., baseline cardiovascular risk factors such as diabetes, blood pressure, smoking, LDL and HDL-cholesterol serum levels, baseline used drug therapy. The 300 patients were divided into two groups; Gr.(1): 160 patients with coronary heart disease and subclinical hypothyroidism. Gr. (2) 140 patients with coronary heart disease and euthyroidism. For clarification of defined subclinical hypothyroidism, serum level of TSH (4.5mIU/L to less than 20mIU/L, and normal T₄ level. While euthyroidism was defined as serum TSH level (0.5mIU/L to less than 4.5mIU/L)¹¹. CHD was defined as nonfatal acute myocardial infarction, hospitalization for angina or coronary angioplasty or CABG (coronary revascularization)¹². **STATISTICS:** clinical data and coronary heart disease events were analyzed in relation to different TSH serum levels and the later were represented as percentages where applicable.

RESULTS

Demographic features and characteristics of coronary heart disease patients with subclinical hypothyroidism of the group 1 and those patients with euthyroidism of the group 2, were represented in the table 1. As regards to age, sex and FT₄ serum levels, there were no statistical differences. Actually, we noticed that patients whatever with unstable angina (50%), revascularization by coronary angioplasty or coronary artery bypass graft (21.25%), or presented with

acute myocardial infarction (15%), had TSH serum level 4.5 or greater and less than 20 mIU/L with normal serum levels of L-thyroxine, which undergo what is known as under active thyroid or subclinical hypothyroidism. While patients with euthyroidism mostly had stable angina (75%), and unstable angina (25%), but no cases found to presented with AMI or revascularization,(tab.1). Mortality outcome was 8 patients out of 160 of the group 1(5%), while that of patients of group 2, was (0%), reflecting that there was certain correlation of high TSH serum levels and the risk for

mortality of patients suffered from CHD. Therefore, we classified CHD patients of group 1 in correlation to different serum TSH levels and that represented in the table 2. CHD patients with TSH (4.5 to less than 7), 19 out of 154(12.34%) , those with TSH (7 to less than 10), 33 out 154(21.43%) and those with TSH (10 to less than 20), 102 out 154(66.23%). These obtaining data indicated that high TSH is strong risk factor for CHD, especially TSH of 10 mIU/L or greater.

Table 1. Characteristics of CHD-Patients With Subclinical Hypothyroidism(gr.1) and Euthyroidism (gr.2).

Character	Gr.1 No=160	Gr.2 No=140
M/F	120/40	105/35
Age-median(range)	52 (39-66)	56 (46-76)
CHD°--- Stable angina	16(10%)	105(75%)*
-----AMI-----	24(15%)	00(0%)*
Unstable angina----	80(50%)	35(25%)*
Revascularization----	34(21.25%)	00(0%)*
TSH level-----0.5-<4.5-----	0(0%)	140(100%)*
4.5-<7.0-----	17(10.62%)	0(0%)*
7.0-<10.0-----	43(26.88%)	0(0%)*
10.0-<20.0-----	94(58.75%)	0(0%)*
	6(3.75%)#	
FT ₄ level---median(range)	14(12-22)	15(12-22)
Mortality outcome	8(5%)	0(0%)*

CHD= Coronary heart disease

TSH=Thyroid stimulating hormone(mIU/L).

*=P value< 0.005

#=missed results.

Table 2. TSH In Correlation to Presentation of Coronary Heart Disease of Group 1.

CHD Presentation No=154	TSH (4.5-<7) No=19	TSH (7-<10) No=33	TSH (10-<20) No=102
Stable angina no(%)	2(1.29)	3(1.95)	11(7.14)
Unstable angina no(%)	9(5.84)	16(10.39)	55(35.71)
AMI----- no(%)	3(1.95)	6(3.90)	15(9.75)
Revascularization no(%)	5(3.25)	8(5.19)	21(13.65)

TSH=thyroid stimulating hormone (mIU/L). AMI=acute myocardial infarction.

DISCUSSION

Experts estimate that as many as 17% of the general population suffer from a mild form of underactive thyroid known as subclinical hypothyroidism. Typically, doctors have not treated subclinical hypothyroidism, claiming that there is no demonstrable benefit from that to the patients. It is a controversial topic however, some studies have shown that failing to treat subclinical hypothyroidism can have negative consequences. In particular the relationship between untreated hypothyroidism and the risk of developing heart disease and metabolic syndrome has been a topic of controversy. The researchers concluded that treating subclinical hypothyroidism can improve a number of heart disease risk factors as well as certain quality of life

measurements¹³. Several CHD risk factors including age, male gender, systolic blood pressure, triglycerides, and fibrinogen were more common in hypothyroid patients. Prevalence of CHD was more common in hypothyroid and moderate subclinical hypothyroidism patients¹. In the two studies, thousands of patients in the U.S and Australia agreed to be followed for a period of years, in an effort to evaluate the ability of various risk factors to predict subsequent disease. One of the laboratory tests measured at the beginning of these studies was the TSH level. Investigators of the U.S study, the Health, Aging and Body Composition Study, found that patients with elevated TSH levels (at least 4.5 mIU/L) had a significantly higher risk of developing heart failure over the next 4 years than patients with normal TSH levels. In the Australian study, the

Brusselton Health Study, patients with elevated TSH levels had an increased risk of hospitalization or death from coronary artery disease. In both studies, the higher the TSH level, the higher the risk. The highest risk was seen in patients with TSH levels of 10 mIU/L or greater¹⁴. In our present study, we found that number of CHD patients was increasing directly with increasing the TSH serum level (tab.2). That reflecting the same data of the previous mentioned two studies¹⁴, and that clarify the strong correlation between TSH and CHD. Even mild TSH elevation (4.5-<7), also was noticed in 19 out 154 (12.34%), and that leading us to controversy about the TSH range at which we consider our patients with subclinical hypothyroidism are under proper treatment and less liable for risk factors which progress the atherosclerosis and its complications in form of coronary artery disease or what is called coronary heart disease (CHD). Serum lipid profiles may be influenced by thyroid function, but the detailed mechanism remains unclear. Increasing evidence suggests that thyrotrophin hormone (TSH) may exerts an extra-thyroidal effects¹⁵. In recent years, more and more evidence has demonstrated that hypothyroidism is associated with the increased prevalence of CHD¹⁶.

This association is partly due to decreased levels of thyroid hormones, which lead to an atherogenic lipid profile characterized by increased levels of total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C)¹⁷. Traditionally, the main function of TSH is to stimulate the synthesis and release of thyroid hormones in the thyroid gland via the specific cell membrane receptor-TSHR. It is now recognized that TSHR is expressed widely in a variety of extra-thyroidal organs including kidney, bone marrow and adipose tissue¹⁸, and act as a physiological regulator in the growth and development of adipocytes¹⁹. A late study²⁰, revealed that TSH promoted the expression of hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) resulting in increased TC levels in CHD patients. Also, study of Xing W. et.al.¹⁵, reported that TSH in the upper limit of normal might exert adverse effects on the lipid profile and thus might represent a risk factor for hypercholesterolemia and triglyceridemia in CHD patients.

The increased risk of CHD events associated with higher TSH levels in the present study might be related to the known effects of thyroid hormone on the heart and metabolism, consistent with the concept that subclinical hypothyroidism is a milder form of overt hypothyroidism²¹⁻²². Increased systemic vascular resistance, arterial stiffness, altered endothelial function, increased atherosclerosis, and altered coagulability have been reported to be associated with subclinical hypothyroidism and may accelerate development of CHD^{2&23}. Other potential mechanisms include elevated cholesterol level^{2&22}. Adults with higher TSH levels also are more likely to develop overt hypothyroidism and it is possible that this progression explains the association with subclinical hypothyroidism.

In the guidelines of the National Academy of Clinical Biochemistry (NACB), reported that the current TSH reference range which usually runs from approximately 0.5-4.5 may be too wide and actually may include people with thyroid disease²⁴. When more sensitive screening was done, which excluded people with thyroid disease, 95 percent of population tested actually had a TSH level

between 0.4-2.5. As a result NACB recommended reducing the reference range to that. Meaning anything below or above that could be a sign of thyroid disease²⁵. The NACB guidelines led to a recommendation in 2003 by the American Association of Clinical Endocrinologists (AACE), calling for doctors to “consider treatment for patients who test outside boundaries of a narrower margin based on a target TSH level of 0.3-3.0.”

The statement also said “AACE believes the narrow range will result in proper diagnosis for millions of Americans who suffer from a mild thyroid disorder, but have gone untreated until now”²⁶. More recently, researchers have looked at an important question: if the normal TSH range were narrowed, as has been recommended by AACE and The National Academy of Clinical Biochemistry, what are the implications?. One study found that using a TSH upper normal range of 5.0, approximately 5% of the population is hypothyroidism. However, if the upper portion of the normal range was lowered to 3.0, approximately 20% of the population would be hypothyroidism¹⁵. Among the limitations of the present study, the number of the involved patients may not be enough to represent accurate percentage of CHD patients with different events in correlation to the different levels of serum TSH.

In addition to that, thyroid function tests were done only at baseline and there was no follow up to detect how many patients progressed from euthyroidism to subclinical hypothyroidism and also from subclinical to overt hypothyroidism. There are many much-needed revisions that need to be made in the process of diagnosing and treating thyroid disease, and we can only hope that it doesn't take decades for AACE to catch up with patients and the more innovative practitioners who are making breakthroughs in the understanding, treating, living with and even overcoming thyroid disease.

In summary, subclinical hypothyroidism is associated with an increased risk of coronary heart disease especially in those with higher TSH levels and significantly elevated in adults with TSH levels of 10 mIU/L or greater. The results of our present study may help in refining a TSH threshold at which larger clinical benefits of thyroxine replacement would be expected. Moderate, but not mild, subclinical hypothyroidism is associated with increased CHD prevalence and all-cause mortality¹. These data suggest patients with moderate, but not mild, SCH and patients at high risk for CHD should be treated with thyroid replacement therapy. In the treatment of CHD and dyslipidemia, thyroid function (especially the serum TSH level) should be monitored and maintained in the relatively low-normal range. Large-scale studies with longer follow-up periods will be needed to estimate the real impact of TSH on CHD.

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