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ORIGINAL ARTICLE

Are Serum Thyrotropin level and Subclinical Hypothyroidism Predisposing Factors for Coronary Artery Disease?

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Overt hypothyroidism has been found to be associated with cardiovascular diseases. Whether or not subclinical hypothyroidism is also a risk factor for cardiovascular disease is controversial. The aim of this study was to investigate serum thyrotropin levels and subclinical hypothyroidism in relation to presence and extent of coronary artery disease (CAD).

Materials and Methods: In a sample of 390 persons (239 men and 151 women) with mean age of 55.12±10.52 years who had referred for coronary angiography, data on general health, thyroid status, medications and previous myocardial infarction were obtained at baseline. They were screened for impaired thyroid function using a sensitive immunoradiometric assay for thyrotropin. Subclinical hypothyroidism was defined as an elevated serum thyrotropin level (≥ 4. 0mU/L) and a normal serum free thyroxine level. A single-, two- or triple vessel disease or normal vessels was documented by coronary angiography.

Results: Subclinical hypothyroidism was present in 6.4% of persons and was not associated with a higher frequency (P=0.51) or greater severity (x2=2.172; P=0.70) of CAD. The mean serum thyrotropin level was significantly higher in women (P<0.001). There was neither correlation between serum thyrotropin level and the presence of CAD (P=0.37) in either sex (men: P=0.67 /women: P=0.97) nor with the extent of CAD (P=0.30) in either of the two groups (men: P=0.70 /women: P=0.34). Also, serum thyrotropin level was not higher significantly in patients who had has previous myocardial infarction (P=0.95).

Conclusions: There was no correlation between thyrotropin levels or subclinical hypothyroidism and presence or severity of CAD in a cohort of patients who referred for coronary angiography.

Key Words: Thyrotropin, Subclinical hypothyroidism, Hypothyroidism, Coronary disease, Coronary angiography

Introduction

Overt hypothyroidism, with its accompanying hypercholesterolemia and hypertension, has been found to be associated with cardiovascular disease.[1,2] Subclinical hypothyroidism, defined as elevated serum concentration of thyrotropin and normal serum concentration of free thyroxine,[3] is highly prevalent in the elderly especially in women.[4-6] Whether or not subclinical hypothyroidism is a risk factor for cardiovascular disease is controversial.[7-10]

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In the late 1960s and early 1970s, autopsy studies[11,12] and studies in hospital inpatients [11,13] suggested that autoimmune thyroiditis was an important risk factor for coronary artery disease (CAD). These findings, however, were not confirmed by other studies.[14-17] The Rotterdam study was the first to describe an association between subclinical hypothyroidism in elderly women and atherosclerosis as assessed by a noninvasive measurement in a general population sample.[18] Another study suggested that a raised serum thyroid stimulating hormone may be one of the risk factors for the development of peripheral arterial disease in women, possibly by increasing cholesterol levels.[19] To our knowledge there is no published study to compare the serum thyrotropin (thyroid stimulating hormone-TSH) level with the severity of angiographically documented CAD.

In this study we examined whether the serum thyrotropin level and subclinical hypothyroidism are correlated with the presence and extent (severity) of CAD in patients referred for coronary angiography.

Materials and Methods

This is a cross-sectional study, done over a two-year period (November 2001 to November 2003). Four hundred persons that referred to the Namazi Hospital for coronary angiography were entered into the study consecutively. The sample size was calculated according to the previous studies [4,5,20] on prevalence of subclinical hypothyroidism with a power of 80 percent. The study was approved by the institutional review board. After obtaining informed consent, data on age, sex, general health, thyroid status, medications, previous myocardial infarction and coronary risk factors (e. g. , smoking, diabetes, hypertension and hyperlipidemia) were obtained at baseline. Persons with any chronic debilitating illnesses like renal failure, Addison's disease and those receiving medications that interfere with thyroid function, like thyroid hormones, antithyroid drugs or amiodarone, were excluded. Previous myocardial infarction was assessed by self-report, hospital records and by analysis of the standard 12-lead electrocardiograms, by a cardiologist who was unaware of the person's thyroid status. Blood samples in a fasting state were obtained before coronary angiography. The persons were screened for impaired thyroid function using a sensitive immunoradiometric assay (IRMA) for thyrotropin (normal range 0.3-3.9mU/L). Then free thyroxine levels were checked in the samples with serum thyrotropin levels equal or greater than 4.0mU/L. Subclinical hypothyroidism was defined as an elevated serum thyrotropin level ($\geq$ 4.0mU/L) and a normal serum free thyroxine level (11.1 to 21.6pmol/L). Coronary angiography was performed by the percutaneous transfemoral technique (Judkin's method) and recorded on 35 mm cine film with the aid of cesiumiodide-activated image intensifiers. Cine films were processed in the conventional manner and viewed with a Tagarno projector. Evaluations were performed in a blinded manner. A single-, two- or triple vessel disease scoring system was applied on major coronary vessels (Left anterior descending, Left circumflex and Right coronary arteries) as follows: 0 (Normal), normal lumen appearing perfectly smooth or with stenotic lesions reducing the lumen <50%; 1(Single vessel disease), lumen diameter reduced >50% in a single major coronary vessel; 2 (Two vessel disease), lumen diameter reduced >50% in two of major coronary vessels; 3 (Three vessel disease), lumen diameter reduced >50% in all of three major coronary vessels; 4 (Left main disease), lumen diameter reduced >50% in the left main coronary artery. Finally, the serum thyrotropin levels were compared with the score of coronary stenosis, and patients with subclinical hypothyroidism were evaluated for the presence and extent of CAD.

Statistical analysis: Conventional methods were used for calculations of means and standard deviations. Differences in continuous variables between groups were tested by Student's unpaired two-tailed t test. The chi-

square and Fisher's exact tests were applied for frequency comparison. Relations between serum thyrotropin levels and coronary stenosis scores were analyzed by computation of Spearman rank correlation coefficients. A P value of less than 0.05 was considered statistically significant.

Results

Four hundred subjects were entered into the initial study. Ten were excluded due to inadequate data about their medications or a history of previous coronary artery bypass graft. Thus, at the end of the study, 390 persons remained (239 men and 151 women). The mean age of the individuals was 55.12±10.52 years (maximum=85 years and minimum=20 years). The mean serum thyrotropin level was 2.20±5.34mU/L (maximum=60.60mU/L and minimum=0.01mU/L). The mean serum thyrotropin level in women was 3.32±7.72mU/L and in men 1.50±2.78mU/L (t=-3.331; P<0.001). Thirty-one persons (7.9%) had serum thyrotropin level ≥ 4.0mU/L, of which 25 patients (6.4%) had subclinical hypothyroidism and six patients (1.5%) had overt hypothyroidism (Free thyroxine <11.1pmol/L).

There were 119 persons (52 men and 67 women) with normal coronary angiograms and 271 persons (187 men and 84 women) with stenotic coronary arteries. The difference between mean serum thyrotropin levels of both groups was statistically insignificant (P=0.37). Also, there was no correlation between serum thyrotropin level and extent of CAD (P=0.30). (Table 1)

There was no statistical difference between mean serum thyrotropin levels in persons with and without CAD in each sex group (men: P=0.67 / women: P=0.97). Also, there was no correlation between serum thyrotropin level and extent of CAD in either sex (men: r=-0.028; P=0.70, women: r=-0.106; P=0.34) (Table 2).

Nine out of 119 persons with normal coronary arteries had subclinical hypothyroidism as compared to 16 out of 271 persons with CAD (P=0.51) (Table 3). Furthermore, the CAD was not more severe in patients with subclinical hypothyroidism (x2=2.172; P=0.70).

Data on previous myocardial infarction was available in 380 persons. The difference between mean serum thyrotropin level in patients with previous myocardial infarction (2. 02±5. 00mU/L) as compared with those without myocardial infarction (2. 05±4.36mU/L) was statistically nonsignificant (t=0.064; P=0.95).

Table 1. Distribution of persons and mean serum thyrotropin level in relation to coronary stenosis score

Group*	Coronary stenosis score	n	%	Thyrotropin (mU/L)†	P value
I	0	119	30.5	2.58±5.8	0.30
II	1	78	20	3. 00±8.5	
	2	77	19.7	2.21±4.0	
	3	107	27.4	1.28±1.2	
	4	9	2.3	1.54±1.2	

* I: denotes normal coronary angiogram, II: denotes coronary artery disease; † Mean±SD

Table 2. Sex distribution and mean serum thyrotropin level in relation to coronary stenosis score

		Without coronary stenosis		With coronary stenosis
Men	n	52		187
	Thyrotropin (mU/L)†	1.65±4.11		1.46±2.30
	P value		P=0.67	
Women	n	67		84
	Thyrotropin (mU/L)†	3.30±6.72		3.34±8.48
	P value		P=0.97	

*Coronary artery disease; † Mean±SD

Table 3. Distribution of coronary stenosis score according to thyroid function

Coronary stenosis score	No thyroid Dysfunction	Subclinical Hypothyroidism	Overt Hypothyroidism†	Total	P value
0	107	9	3	119	
(1+2+3+4)*	252	16	3	271	P=0.51‡
T o t a l	359	25	6	390	

*Coronary artery disease; † Small sample size for statistical analysis; ‡ Nonsignificant for patients with subclinical hypothyroidism

Discussion

Our results show that subclinical hypothyroidism is highly prevalent among elderly individuals but is not associated with a greater frequency of CAD. Approximately 8 percent of persons in our sample had a thyrotropin level equal to or greater than 4. 0mU/L. This prevalence in a hospital referred population closely resembles that reported in the community based Whickham survey,[4] the Framingham study,[5] and a study in community-dwelling elderly persons.[20] Among all persons in our sample for analysis, six (1.5%) had unrecognized overt hypothyroidism, which is in agreement with reports of prevalence found during screening.[3] These data suggest that our sample is representative of the general population.

Data on relations between atherosclerosis and serum thyrotropin level or subclinical hypothyroidism are scarce. A case-control study in elderly women suggested an association between subclinical hypothyroidism and peripheral arterial disease; the arterial disease in the aortotibial segment was documented by an abnormal brachial/ankle pressure index.[19] Another study showed an association between borderline low thyroid function and autoimmunity and CAD which was not mediated through a raised serum cholesterol; CAD was indicated by evaluation of electrocardiograms.[21,22] The Rotterdam study showed a greater frequency of aortic atherosclerosis and myocardial infarction among elderly women with subclinical hypothyroidism; aortic atherosclerosis was assessed on a lateral radiographic film of the lumbar spine by detecting calcified deposits in the abdominal aorta.[18] Although radiographic assessment was shown to be highly specific and

in most cases visible, calcification represented advanced intima atherosclerosis,[23] the interpretation of coronary angiogram is a better method for meticulous evaluation of atherosclerosis and CAD. Quantitative assessment of coronary artery lesions was initially suggested by Brown et al[24] and is currently in use for lesion morphology assessment and for interventional work.[25] In this study, after evaluation of the coronary angiograms, there was no correlation between serum thyrotropin level and subclinical hypothyroidism with presence/extent of CAD; the number of patients with overt hypothyroidism was small for statistical analysis. The studies with positive findings on an association between subclinical hypothyroidism and CAD were in the elderly female populations.[18,19] At first, we thought that the lack of association in our results and other previous researches was probably due to the studies being conducted in a male-dominated sample. But, after separation of the sample according to sex, our study revealed no correlation between level of thyrotropin and CAD in either sex group, albeit a significantly higher serum thyrotropin level in women than men. The number of patients with subclinical hypothyroidism was small in either sex group for statistical analysis.

There are some limitations in our study. One limitation is the cross-sectional nature of the design, which necessitates careful interpretation of the results. It is possible that patients in studies with positive findings on an association between subclinical hypothyroidism and CAD had a longer duration of disease. But, in this study we did not consider the duration of the subclinical hypothyroidism. So, we must follow the patients in a prospective study for development of CAD. Furthermore, the number of patients with subclinical hypothyroidism was small in each group of coronary stenosis score for powerful statistical analysis of the severity of CAD in subclinical hypothyroidism. Also, we must consider the fact that elevated serum thyrotropin levels may be caused by a nonthyroidal illness.[26,27] Although all of our cases that referred for coronary angiography were on an outpatient basis with normal routine laboratory work up, we also excluded those with chronic debilitating illnesses or those receiving medications that interfere with thyroid function. Therefore, it is unlikely that nonthyroidal illnesses affected the validity of our results. Another limitation of our study is the simple scoring system for coronary angiograms as single-, two- or triple-vessel disease categorization. It was more apt to apply quantitative scoring of each lesion by computer, by the method advocated by Gensini[28] (standardized scoring system). The resulting score, which allowed the disease to be expressed as a continuous variable, was effectively used to see the correlations between the severity of CAD and individual risk factors.[29]

This cross sectional study in our selected sample suggests that level of thyrotropin and subclinical hypothyroidism are not predisposing factors for development of CAD. Additional research should be done to determine whether the association can be confirmed in a prospective study.

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