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Thyroid Function and Left Ventricular Structure and Function in the Framingham Heart Study

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Background: Thyroid hormone acts on the heart and peripheral vasculature in multiple ways. Even in patients with subclinical hypo- or hyperthyroidism, subclinical alterations in left ventricular (LV) structure and function may be associated with important clinical effects. Our objective was to determine whether thyroid function is related to echocardiographic indices of LV structure and function.
Methods: Cross-sectional association of serum thyroid-stimulating hormone (TSH) with two-dimensional-guided M-mode echo LV dimensions and function. Participants were 1376 Framingham Heart Study participants (61% women, mean age 69 years) who attended a routine examination 1979–1981. We excluded participants with myocardial infarction or heart failure, renal insufficiency, and missing data, and those using thyroid hormone or antithyroid medications. Serum TSH was measured 1977–1979. The following echocardiographic measurements were analyzed both as continuous variables and dichotomized at the top quintile: LV end-diastolic dimensions, LV wall thickness, LV mass, LV fractional shortening (an indicator of systolic function), and left atrial diameter. Sex-specific multiple regression models were adjusted for age, height, weight, blood pressure, heart rate, total to high-density lipoprotein cholesterol ratio, and the presence of diabetes, hypertension treatment, and valve disease.
Results: In multivariable linear models, log-TSH was not related to LV mass, LV wall thickness, or left atrial size in either sex, or to LV systolic function in men. Log-TSH had a borderline inverse association with fractional shortening ($p = 0.06$) in women. In multivariable logistic models, women with TSH <0.5 mU/L ($n = 81$) had a greater odds of being in the highest quintile of fractional shortening compared to euthyroid subjects (odds ratio 2.2, 95% confidence interval 1.3–3.8, $p = 0.01$).
Conclusions: In our moderate-sized community-based sample, TSH concentration was not associated with LV structure in either sex, but was inversely related to LV contractility, consistent with the known inotropic effects of thyroid hormone.

Introduction

Thyroid dysfunction is relatively common, and its prevalence increases with advancing age. Hyperthyroidism is present in 1.3% of the U.S. population (overt in 0.5% and subclinical in 0.7%), and hypothyroidism in 4.6% (overt in 0.3% and subclinical in 4.3%) (1). Data from the Framingham Heart Study have shown that some degree of hypothyroidism, as evidenced by elevated serum thyroid-stimulating hormone (TSH) levels (>5 mU/L), is present in 10.3% of unselected individuals over age 60 years, with a higher prevalence in women (13.6%) than in men (5.7%) (2).

Thyroid hormone acts on the heart and peripheral vasculature in multiple ways. Triiodothyronine, the bioactive hormone, is known to affect tissue oxygen consumption, vascular resistance, blood volume, cardiac contractility, and heart rate (3). In overt hyperthyroidism, increased cardiac contractility and altered left ventricular (LV) loading result in a hyperdynamic state, with high cardiac output at rest and a suboptimal response to exertion (4,5). In addition, heart rate increases. Patients with underlying cardiac disease may be unable to compensate for increased metabolic demands (6). The cardiac effects of subclinical hyperthyroidism have primarily been studied cross sectionally in patients on TSH-suppressive

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L-thyroxine (T4) doses, and results have been inconsistent (7,8). It remains unclear whether subclinical hyperthyroidism has cardiac effects similar to those seen in overt hyperthyroidism (9). It has been shown clearly, however, that patients with both overt and subclinical hyperthyroidism are at increased risk for atrial fibrillation (10).

Patients with overt hypothyroidism have bradycardia, decreased ventricular filling, and decreased cardiac contractility, which lead to decreased cardiac output (11). The decrease in myocardial oxygen consumption is less than the decrease in cardiac work, making the heart less efficient (12). Subclinical hypothyroidism may have similar but more subtle effects on cardiac function (13–16). Some studies have demonstrated mild systolic and diastolic dysfunction in patients with subclinical hypothyroidism that is reversible with L-T4 treatment (17–19), but this has not been a universal finding (20–22).

Even in asymptomatic patients with subclinical hypo- or hyperthyroidism, subclinical alterations in LV structure and function may be associated with important clinical effects. Accordingly, the objective of the present study was to examine the association of thyroid function with echocardiographic LV and left atrial structure and LV function cross sectionally in the Framingham Heart Study cohort.

Materials and Methods

Subjects

Participants for this investigation were drawn from the original cohort of the Framingham Heart Study. Beginning in 1948, 5209 men and women aged 28–62 years were enrolled in the Framingham Heart Study as previously described (23). Cohort members have subsequently been followed biennially. The study protocol was approved by the Boston University Medical Center Institutional Review Board, and informed consent was obtained from all participants.

The study sample for the present investigation consisted of Framingham Heart Study participants who attended routine biennial examinations 15 (1977–1979) and 16 (1979–1981). Two thousand and sixteen individuals had undergone echocardiography at examination cycle 16. We excluded 157 participants with prevalent myocardial infarction, 57 with heart failure, 8 with serum creatinine >2 mg/dL, and 413 participants missing serum TSH values. We also excluded 104 individuals using thyroid hormone. Some participants only had left atrial diameter measurements performed, but not other echocardiographic measurements. For analyses of left atrial diameter, the final sample included 1376 participants (60% women), whereas the final sample for all other analyses included 1001 participants (62% women, mean age 69 years).

Measurements

Serum TSH measurements were obtained at examination cycle 15 using a chemiluminescence assay (London Diagnostics, Eden Prairie, MN; this assay is now made by Nichols Institute Diagnostics, San Juan Capistrano, CA). The sensitivity was 0.005 mU/L, with an interassay coefficient of variation (CV) of 5% at 1 mU/L and 11% at 0.04 mU/L.

Two-dimensional-guided M-mode echocardiograms were obtained at examination cycle 16. M-mode measurements of LV internal dimension in diastole (LVDD) and systole (LVDS), and end-diastolic posterior wall (PW) and interventricular septum (IVS) thicknesses, and aortic root diameter, and end-systolic left atrium were obtained using a "leading edge" technique, averaging measurements in three cardiac cycles according to the American Society of Echocardiography guidelines (24). LV mass was calculated by using the formula $0.8\,[1.04\,(\mathrm{LVDD}+\mathrm{IVS}+\mathrm{PW})^3-(\mathrm{LVDD})^3]+0.6$. LV wall thickness was defined as the sum of the end-diastolic thicknesses of the PW and IVS. LV fractional shortening, a measure of the percent change in LV dimensions with systole, was calculated as $(\mathrm{LVDD}-\mathrm{LVDS})/\mathrm{LVDD}$.

Diabetes was defined as a fasting blood glucose greater than 126 mg/dL and/or the use of oral hypoglycemic medications or insulin. Valve disease was defined clinically as a systolic murmur of grade 3/6 or more, or any diastolic murmur on auscultation by a Heart Study physician. The echocardiographic examination antedated Doppler technology presently used to determine valvular heart disease.

Statistical methods

TSH was analyzed both as a continuous variable (natural log-transformed to normalize a skewed distribution) and using clinical categories (TSH <0.5, 0.5–2.5, 2.5–5, and >5.0 mU/L). It was decided *a priori* to analyze the following echocardiographic measurements both as continuous variables and dichotomized at the top quintile (increased [Q5] vs. nonincreased [Q1–4]): LV mass, LV wall thickness, LV end-diastolic dimensions, fractional shortening, and left atrial diameter. Separate analyses were performed for each echocardiographic measure.

We used sex-specific analyses of covariance to examine for a trend for any differences in echocardiographic measurements across TSH categories, and sex-specific multiple linear regression models to relate log-TSH to continuous echocardiographic LV measures. Sex-specific multivariable logistic regression models were used to evaluate the association of TSH categories and log-TSH values with the odds of having echocardiographic measurements in the top quintile. For all analyses, several models were considered in hierarchical fashion: (1) models adjusting for age, height, and weight; (2) models adjusting for age, height, weight, systolic blood pressure, the use of antihypertensive medications, diabetes, heart rate, and the presence of valve disease; (3) additional models adjusted for covariates defined above and lipid measures—total cholesterol/high-density lipoprotein cholesterol given recent evidence that lipid measures may influence LV remodeling (25) and in view of the effects of thyroid hormone status on lipid status (26).

Results

Table 1 shows the baseline clinical and echocardiographic characteristics of our study sample. The sample was 61% women with a mean age 69 years. In men, serum TSH values ranged from 0.3 to 51.9 mIU/L (median 1.4, 95% of values 0.3–5.7). In women, serum TSH values ranged from 0.2 to 183 (median 1.7, 95% of values 0.3–12.6).

In men, serum TSH concentration (analyzed as a continuous variable and as clinical categories) was not related to LV end-diastolic dimensions, LV wall thickness, LV mass, fractional shortening, or left atrial size, whether the echocardiographic measurements were modeled as continuous or as dichotomous variables (Table 2).

Table 1. Characteristics of Study Sample

Characteristic	*Men* (n = *543*)	*Women* (n = *833*)
Clinical variables		
Age, years	68.7 ± 6.5	70.0 ± 6.9
Weight, kg	79 ± 12	64 ± 12
Systolic blood pressure, mm Hg	139 ± 19	140 ± 20
Hypertension treatment, %	30	39
Diabetes, %	6	7
Heart rate, beats/min	71 ± 13	73 ± 12
Valve disease, %	5	4
Biochemical characteristics		
HDL cholesterol, mg/dL[a]	44.7 ± 13.6	55.0 ± 15.3
Total cholesterol, mg/dL[a]	218 ± 37.3	240 ± 39
TSH, mU/L[a]	2.0 ± 3.1	2.7 ± 4.4
Echocardiographic characteristics		
Left ventricular internal diameter in diastole, cm[b]	5.0 ± 0.5	4.5 ± 0.4
Left ventricular internal diameter in systole, cm[b]	3.2 ± 0.5	2.7 ± 0.4
Left ventricular wall thickness, cm[b]	2.1 ± 0.4	1.9 ± 0.3
Left ventricular mass, g[b]	200 ± 61	149 ± 42
Fractional shortening[b]	0.37 ± 0.05	0.40 ± 0.05
Left atrial diameter, cm	4.2 ± 0.6	3.8 ± 0.5

[a]Examination 15.
[b]Data for 380 men and 621 women.
HDL, high-density lipoprotein; TSH, thyroid-stimulating hormone.

In women, log-TSH was not related to LV end-diastolic dimensions, LV wall thickness, LV mass, or left atrial size. Log-TSH had a borderline inverse association with fractional shortening ($p = 0.06$) in multivariable-adjusted models. TSH categories were also not associated with continuous echocardiographic measurements (all p-values exceeded 0.05). In multivariable-adjusted logistic regressions, TSH (modeled as a continuous variable or as clinical categories) was not associated with LV end-diastolic dimensions, LV wall thickness, LV mass, or left atrial size. However, women with TSH <0.5 mU/L had a greater odds of being in the highest quintile of fractional shortening compared to euthyroid (TSH 0.5–2.5 mIU/L) women (odds ratio 2.2, 95% confidence interval 1.3–3.9, $p = 0.01$) (Table 3). Log-TSH was inversely associated with odds of having a fractional shortening in the top quintile ($p = 0.02$).

Given the lack of association of TSH with echocardiographic measures in men, and with most LV measures in women (except for fractional shortening), we estimated our statistical power to detect associations: at an α of 0.05, we had 71–87% power to detect an increment in R^2 as small as 1.5% attributable to TSH, assuming that the R^2 value for all other clinical correlates ranged from 0.1 to 0.4 (consistent with prior Heart Study observations).

Discussion

We observed that in women, but not in men, low serum TSH concentrations (<0.5 mIU/L) were associated with increased LV contractility at rest, as assessed by echocardiographic LV fractional shortening. There were no significant associations between TSH concentrations and left atrial size or LV mass, internal dimensions, or wall thickness in women or men.

Hypothyroidism and LV structure/function

Overt hypothyroidism has been associated with decreased cardiac contractility and ejection fraction (3,12,27). Monzani *et al.* noted significantly higher values for LV mass and LV wall thickness in 20 patients with subclinical hypothyroidism as compared to controls (18). However, most other groups have reported no significant associations between subclinical hypothyroidism and LV mass (17,19,22,28–30) or LV wall thickness (19,28,30), similar to the findings of the present study.

Consistent with the present study, most investigators have reported no association between subclinical hypothyroidism and fractional shortening (17–19,22,31). Overall, although the effects of subclinical hypothyroidism on LV systolic function at rest remain unclear (15,29), previous studies suggest that exertional LV systolic function (not evaluated in the present study) may be impaired (14,22). In addition, previous studies have consistently shown alterations in resting LV diastolic dysfunction in individuals with subclinical hypothyroidism, as evidenced by standard echocardiographic measurements (17,18,22), pulsed tissue Doppler (19,28,30), and radionuclide ventriculography (32). LV diastolic function and LV systolic function during exercise were not assessed in the present study.

Hyperthyroidism and LV structure/function

An increased prevalence of LV hypertrophy (33) and increased LV contractility and LV ejection fractions (3) have been reported in patients with overt hyperthyroidism. Enhanced resting diastolic function has also been reported in

Table 2. Adjusted Odds Ratio for Being in the Highest Quintile for Each Echocardiographic Measurement Compared to Euthyroid Subjects in Men

	Odds ratio compared to TSH 2.5–5.0 mU/L group (95% CI)		
Echocardiographic measurement	*TSH <0.5 mU/L*	*TSH 2.5–5 mU/L*	*TSH >5.0 mU/L*
Left ventricular internal diameter in diastole	0.6 (0.2–1.6)	0.7 (0.3–2.2)	1.0 (0.3–3.7)
Left ventricular internal diameter in systole	0.9 (0.4–2.3)	0.7 (0.2–2.1)	0.7 (0.2–3.1)
Left ventricular wall thickness	1.2 (0.6–2.6)	1.6 (0.7–3.7)	1.9 (0.8–4.5)
Left ventricular mass	0.7 (0.3–1.5)	1.3 (0.5–3.5)	0.7 (0.2–2.7)
Fractional shortening	2.1 (1.0–4.5)	1.9 (0.9–3.9)	1.3 (0.5–3.4)
Left atrial diameter	1.1 (0.6–2.3)	1.1 (0.5–2.1)	1.6 (0.7–4.0)

CI, confidence interval.

Table 3. Adjusted Odds Ratio for Being in the Highest Quintile for Each Echocardiographic Measurement Compared to Euthyroid Subjects in Women

	Odds ratio compared to TSH 2.5–5.0 mU/L group (95% CI)		
Echocardiographic measurement	*TSH <0.5 mU/L*	*TSH 2.5–5 mU/L*	*TSH >5.0 mU/L*
Left ventricular internal diameter in diastole	0.7 (0.4–1.5)	0.6 (0.3–1.2)	1.0 (0.5–2.0)
Left ventricular internal diameter in systole	0.6 (0.3–1.3)	0.7 (0.4–1.4)	1.5 (0.8–2.8)
Left ventricular wall thickness	0.8 (0.4–1.5)	1.5 (0.8–2.5)	0.5 (0.2–1.0)
Left ventricular mass	0.5 (0.2–1.2)	1.0 (0.5–1.9)	0.6 (0.2–1.4)
Fractional shortening	2.2 (1.3–3.9)	0.7 (0.4–1.3)	0.8 (0.4–1.6)
Left atrial diameter	0.8 (0.4–1.4)	1.0 (0.6–1.7)	0.9 (0.4–1.7)

association with overt hyperthyroidism (34). Previous studies have shown that patients with exogenous (excessive L-T4 therapy) and endogenous subclinical hyperthyroidism have significantly increased LV mass (7,8,35–38) and LV wall thickness (34,35,36,37). Although not a universal finding (8,36), most previous studies have demonstrated increased fractional shortening in individuals with exogenous and endogenous subclinical hyperthyroidism (7,35,37).

Strengths and limitations

A strength of the present investigation was its use of a large community-based, single-site sample. We used rigorous and standardized criteria for the collection and analysis of laboratory specimens and for the ascertainment of information about covariates. Unlike some previous studies, we adjusted adequately for confounders such as heart rate and body size. One limitation of our investigation was that the TSH measurements and echocardiograms were performed approximately 2 years apart in some individuals. Another limitation is the lack of data regarding other thyroid hormone measurements (such as free T4). Although we were able to categorize subjects based on their serum TSH concentrations, the lack of peripheral thyroid hormone levels made it impossible to assign definitive thyroid diagnoses. The large number of statistical tests performed could have led to spurious positive results. Finally, the Framingham study population is almost exclusively white, and our results may not be generalizable to other ethnic groups.

In conclusion, in women, but not in men, low serum TSH concentrations (<0.5 mIU/L) were associated with increased LV contractility, consistent with the known inotropic effects of thyroid hormone. We observed no associations between higher or lower serum TSH concentrations and other echocardiographic measurements. Additional studies are warranted to replicate our findings and to elucidate mechanisms underlying the sex-related differences observed.

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Disclosure Statement

The authors declare that no competing financial interests exist.

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