The Prevalence and Prognostic Effects of Subclinical Thyroid Dysfunction in Dilated Cardiomyopathy Patients: A Single-Center Cohort Study

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ABSTRACT

Background: Subclinical thyroid dysfunction may be a risk factor for mortality in patients with heart failure and may be associated with dilated cardiomyopathy (DCM). This was a cohort study to examine the possible association between subclinical thyroid dysfunction and all-cause mortality in DCM patients, because the current evidence on this association remains elusive.

Methods and Results: A total of 963 DCM patients were evaluated for thyroid function. Of these patients, 7.1% (n = 68) had subclinical hyperthyroidism (defined as serum thyroid-stimulating hormone [TSH] <0.35 μIU/mL), 84.7% (n = 816) had euthyroidism (TSH 0.35-5.5 μIU/mL), and 8.2% (n = 79) had subclinical hypothyroidism (TSH >5.5 μIU/mL). There was a significant difference in all-cause mortality rates between patients with euthyroidism and patients with subclinical hyper- and hypothyroidism (21%, 38.2%, and 26.6%, respectively; log-rank $\chi^2 = 13.104$; $P = .001$) with mean follow-up of 3.5 years. After adjustment for other confounding factors at baseline, QRS duration, N-terminal pro−B-type natriuretic peptide, New York Heart Association functional class, left atrial diameter, and subclinical hyperthyroidism (hazard ratio 1.793, 95% CI 1.010−3.183; $P = .046$) emerged as significant predictors of all-cause mortality.

Conclusion: DCM patients with subclinical hyper- and hypothyroidism had higher all-cause mortality rates. However, only subclinical hyperthyroidism, not subclinical hypothyroidism, was an independent predictor for increased risk of all-cause mortality. (*J Cardiac Fail 2014;20:506−512*)

Key Words: Subclinical thyroid dysfunction, dilated cardiomyopathy, survival.

Dilated cardiomyopathy (DCM), the most common form of cardiomyopathy, is a disease of the heart muscles that is characterized by ventricular dilation and impaired systolic function.[1] DCM is a leading cause of heart failure (HF) and has a poor prognosis. However, the prediction of death remains a challenge for clinicians.[2]

Thyroid hormone plays an essential role in the maintenance of cardiovascular homeostasis under physiologic and pathologic conditions, and it is involved in the modulation of cardiac contractility, heart rate, diastolic function, and systemic vascular resistance. A typical pattern of subclinical thyroid dysfunction, including subclinical hyper- and hypothyroidism, is characterized by abnormal serum thyroid-stimulating hormone (TSH) levels in the presence of free thyroxine (FT_4) and total or free triiodothyronine (FT_3) within their reference ranges and is accompanied by abnormal cardiovascular hemodynamics.[3−7] Subclinical hypothyroidism is associated with left ventricular (LV) diastolic dysfunction evidenced by delayed relaxation, impaired systolic function on effort that results in poor exercise capacity, decreased cardiac preload, and increased

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See page 511 for disclosure information.

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afterload with a consequent reduction in stroke volume.[5,6] In contrast, subclinical hyperthyroidism produces a marked decrease in systemic vascular resistances.[7] In cardiomyopathic hamsters, a nonhuman animal model of subclinical hypothyroidism, thyroid hormone treatment prevented the decline in heart rate and LV function, prevented the loss of myocytes, and improved the LV ejection fraction (LVEF).[8] Several clinical studies have investigated the prognostic impact of subclinical thyroid dysfunction in heart disease, but the data are inconclusive and conflicting.[9−24] One of the major limitations in comparing the existing studies is that the selection of populations and the definitions of subclinical thyroid dysfunction according to the TSH level were heterogeneous.[25−28] Therefore, whether subclinical thyroid dysfunction is a clinically and prognostically relevant entity in HF remains unclear.

However, 2 clinical case reports indicated a potential association between subclinical hyperthyroidism and DCM and that treatment for thyrotoxicosis caused a reversal of dilated cardiomyopathy.[29,30] These results indicate that subclinical thyroid dysfunction was associated with DCM. There were a few studies on the prognostic effects of subclinical thyroid dysfunction in HF,[31,32] but, to our knowledge, there are no data on the association between subclinical thyroid dysfunction and survival in DCM. Therefore, we collected a large clinical cohort to investigate whether subclinical thyroid dysfunction had an impact on all-cause mortality in DCM patients.

Subjects and Methods

Patients and Follow-up

An observational cohort study of 1,317 DCM patients was performed from 2003 to 2011. The patients were admitted owing to decompensation symptoms, and physical signs of HF and DCM were defined as systolic dysfunction (LVEF <50%) with LV dilation in the absence of an apparent secondary cause of cardiomyopathy.[33] Of the 1,317 enrolled patients, 179 patients with missed thyroid function test results and 175 patients who had various secondary cardiomyopathies were excluded from the study: 80 patients with ischemic heart disease by coronary angiography or coronary CT scan, 26 with overt hyper- and hypothyroidism, 24 with alcohol-induced cardiomyopathy, 16 with congenital heart disease, 16 with LV noncompaction, 7 with chronic anemia (hemoglobin <60 g/L), 2 with peripartum cardiomyopathy, and 4 with rheumatic heart disease and systemic immune disease. Thus, the final cohort comprised 963 DCM patients; 42.3% of the patients were newly diagnosed, and 57.7% were established DCM patients. The end point of the study was all-cause mortality, which was assessed in all patients based on their medical records and medical follow-up telephone calls. The follow-up rate was 86.6%, and the mean follow-up period was 3.5 ± 2.3 years. Mortality data were obtained from all study patients from hospitalization until death. Institutional Review Board approval was obtained, and patient consent for participation in the retrospective data analysis was obtained.

Thyroid Hormone Sampling and Measurement

Fasting baseline thyroid function was assessed at hospital admission. Serum FT_3, FT_4, T_3, T_4, and TSH levels were measured with the use of an Advia Centaur CP immunoassay system (Siemens Healthcare Diagnostics, Walpole, Massachusetts, USA). The following reference intervals for our laboratory test results were used: FT_3, 1.79−4.09 pg/mL; FT_4, 0.80−1.88 ng/dL; T_3, 0.65−1.91 ng/mL; T_4, 4.29−12.47 μg/mL; and TSH, 0.35−5.5 μIU/mL. The assay received regulatory approval based on an analytical sensitivity of 0.2 pg/mL for FT_3, 0.1 ng/dL for FT_4, 0.1 ng/mL for T_3, 0.3 μg/mL for T_4, and 0.008 μIU/mL for TSH. The intra- and interassay coefficients of variation were ≤10.0% in all of the assays. Euthyroidism was defined as a TSH level of 0.35−5.5 μIU/mL, subclinical hyperthyroidism was defined as TSH <0.35 IU/mL, and subclinical hypothyroidism was defined as TSH >5.5 IU/mL, with the last 2 entities having normal FT_4 levels.

Statistical Analysis

Continuous variables are expressed as the mean ± SD or as median and interquartile range. Comparisons of categoric variables between groups were performed with the use of chi-square tests. Analysis of variance was used for the comparison of means between multiple groups. Univariate and multivariate logistic analyses tested the associations between baseline variables and subclinical thyroid dysfunction. Multivariate analysis was performed with the variables found to be significant in the univariate analysis, age, sex, and conventional cardiac risk factors. Kaplan-Meier survival curves were compared with the use of the log-rank test. The Cox proportional hazards model was used to examine the associations between independent factors and survival after adjustment for potential confounders. Analysis was performed with the SPSS statistical software (version 16.0; SPSS, Chicago, Illinois, USA). All tests were 2 sided, and P values of <.05 were considered to be statistically significant.

Results

Characteristics of the Study Population

The cohort consisted of 963 DCM patients. Of these 963 patients, 7.1% (n = 68) had subclinical hyperthyroidism (serum TSH <0.35 μIU/mL), 84.7% (n = 816) had euthyroidism (TSH 0.35−5.5 μIU/mL), and 8.2% (n = 79) had subclinical hypothyroidism (TSH >5.5 μIU/mL). Compared with the patients with euthyroidism, subclinical hyperthyroidism was more common in smokers and in patients with New York Heart Association (NYHA) functional class III or IV, and it was associated with higher heart rate, higher circulating creatinine and blood urea nitrogen levels, higher FT_3 and T_3 levels, and low LVEF values; subclinical hypothyroidism was associated with longer disease duration, higher diastolic blood pressure (DBP), lower serum T_3 and FT_3 levels, longer QRS duration, and larger LV and left atrial (LA) diameters (Table 1).

Association of Baseline Variables With Subclinical Thyroid Dysfunction

Univariate logistic analysis in the cohort of 963 patients revealed that subclinical hypothyroidism was associated with serum FT_4 and T_4 levels, smoking status, and disease duration. Subclinical hyperthyroidism was associated with age, NYHA functional class, smoking status, and serum