CLINICAL RESEARCH STUDY

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Subclinical Thyroid Disease and Mortality in the Elderly: A Retrospective Cohort Study

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ABSTRACT

OBJECTIVE: The association between subclinical hypothyroidism and hyperthyroidism and mortality in the elderly is poorly defined. This study was designed to evaluate the association between subclinical hypothyroidism and subclinical hyperthyroidism and mortality in the elderly and to define the thyroid-stimulating hormone values associated with excess mortality in the elderly.

METHODS: We performed a retrospective cohort study with a review of a computerized database of a large health care organization. Patients aged more than 65 years evaluated in the years 2002 to 2012 with documented normal free T4 values were included in the analysis. All cases of known thyroid disease or cases in which thyroid medications were dispensed were excluded. Analysis was performed only on individuals who were not treated for hyperthyroidism or hypothyroidism during the follow-up period. Subjects were divided into 3 groups based on thyroid-stimulating hormone values: normal (normal thyroid-stimulating hormone), subclinical hypothyroidism (thyroid-stimulating hormone >4.2 mIU/L), and subclinical hyperthyroidism (thyroid-stimulating hormone <0.35 mIU/L). All-cause mortality hazard ratio (HR) was compared among the 3 groups, and a subanalysis according to thyroid-stimulating hormone values was performed in those with subclinical hypothyroidism and subclinical hyperthyroidism.

RESULTS: A final analysis was performed on 17,440 individuals with subclinical thyroid disease (538 with subclinical hyperthyroidism [3.1%], 1956 with subclinical hypothyroidism [11.2%], 14,946 normal cases [85.7%], average age of 83 years, 10,289 were women) who were followed up for 10 years. Both subclinical hypothyroidism (HR, 1.75; confidence interval [CI], 1.63-1.88) and subclinical hyperthyroidism (HR, 2.33; CI, 2.08-2.63) were associated with significantly increased mortality, and this association persisted on multivariate analysis (subclinical hypothyroidism HR, 1.68; CI, 1.56-1.8, subclinical hyperthyroidism HR, 1.93; CI, 1.7-2.17). Crude mortality was elevated at 1, 2, and 5 years, but this association seemed to decrease as time from initial analysis increased (most significant association at 1 year). Thyroid-stimulating hormone values greater than 6.38 mIU/L were associated with the highest mortality in those with subclinical hypothyroidism after multivariate adjustment (HR, 1.708; CI, 1.38-2.12), whereas in subclinical hyperthyroidism, no threshold for increased mortality was identified. Mortality was higher.

CONCLUSIONS: Both subclinical hypothyroidism and subclinical hyperthyroidism are associated with increased mortality in the elderly. A threshold thyroid-stimulating hormone value (>6.35 mIU/L) exists for increased mortality in subclinical hypothyroidism, but not in subclinical hyperthyroidism.

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The association between subclinical hypothyroidism and mortality is well established in young individuals.[1,2] Yet, in individuals aged more than 65 years, the association between subclinical hypothyroidism and ischemic heart disease or mortality is far less convincing. Several studies failed to find any association between subclinical hypothyroidism and mortality in this population,[3,4] whereas others found an association at thyroid-stimulating hormone values greater than 10mIU/L.[5,6] In addition, it has been suggested that hypothyroidism may be associated with decreased mortality in those aged more than 85 years irrespective of baseline morbidity,[7] although this has not been substantiated regarding subclinical hypothyroidism.[8] All of the studies evaluating the association between subclinical hypothyroidism and mortality did not evaluate cause-specific mortality, but rather all-cause mortality. Because of the lack of large-scale studies in the elderly, the association between subclinical hypothyroidism and mortality in this population is less clear, and this is particularly true at thyroid-stimulating hormone values less than 10 mIU/L.

The association of subclinical hyperthyroidism and mortality in the elderly is even less clear. Subclinical hyperthyroidism has been reported to be associated with excess mortality in individuals aged less than 65 years, but the evidence for such an association in individuals aged more than 65 years is less robust. Some studies reported increased mortality associated with subclinical hyperthyroidism,[9] whereas others did not find such an association.[10,11] This study evaluated the association between both subclinical hypothyroidism and subclinical hyperthyroidism and mortality in a large cohort of individuals aged more than 65 years.

CLINICAL SIGNIFICANCE

- Subclinical thyroid disease is common, and its prevalence increases with age. As the population ages, the prevalence of subclinical thyroid disease is expected to increase.
- The management of subclinical thyroid disease is questionable, particularly in the elderly. Several studies have reported decreased mortality associated with this condition in the elderly, and others have reported some adverse outcomes associated with subclinical thyroid disease.
- This is a large-scale study performed in a cohort of elderly individuals in whom the association between mortality and subclinical thyroid disease was evaluated.
- The increased mortality associated with both subclinical hypothyroidism and hyperthyroidism and the cutoff of thyroid-stimulating hormone values in which mortality was found to be increased are 2 new findings that we believe supply important information for clinicians and may influence therapeutic decisions in patients in whom the decision to treat is not obvious.

PATIENTS AND METHODS

Patients

This was a retrospective cohort study in which data were collected from the Clalit Health Medical Organization (CHMO) database. The CHMO insures the health care of 3.7 million people in Israel. The CHMO database is a comprehensive state-of-the-art computerized data warehouse that stores demographic and medical data. Data are aggregated by continuous real-time input from physicians and health service providers, and include medical diagnosis, laboratory data, and medications dispensed. The database includes all laboratory tests performed on an individual, both during hospitalization and on an outpatient basis, but for the purpose of this analysis only outpatient laboratory tests were included. Data can be queried to the level of an individual member. For the purpose of this study, we queried demographic data (age, gender), comorbidities, outpatient laboratory data, mortality data, and dispensed medications.

The study population included all individuals aged 65 years or more insured by the CHMO who had at least 1 serum thyroid-stimulating hormone determination in 2002 and for whom follow-up data were available until December 31, 2012. Patients with a thyroid disease that was diagnosed before 2002 or an abnormal serum thyroid-stimulating hormone during 2001, patients treated with lithium or amiodarone during the 10-year interval of the study, and patients with active malignancy or who underwent organ transplantation were excluded from the study. Thyroid disease was defined when a diagnosis of hypothyroidism or hyperthyroidism/thyrotoxicosis was recorded in the medical file, levothyroxine or thionamides were dispensed at least twice per year, or radioactive iodine treatment was given. To eliminate the influence of treatment on outcome, all individuals who were treated for hyperthyroidism (radioiodine, thyroidectomy, or thionamides) or hypothyroidism (levothyroxine) during the follow-up period were not included in the final analysis. The study was approved by the CHMO ethics committee.

Laboratory Analysis and Patient Stratification

Thyroid-stimulating hormone determinations were performed using the Immulite 2000 (Diagnostic Products Corp, Los Angeles, Calif) and Centaur (Bayer HealthCare, Leverkusen, Germany) apparatus for which upper and lower limits are 0.35 to 4.2 mIU/L, as previously described.[12-14] Free T4 determinations were performed as described,[15] for which upper and lower limits are 10 to 20 pmol/L. These cutoffs were used on the basis of the normal values defined by the central laboratory at Clalit Health Services, where the