SUBCLINICAL THYROID DYSFUNCTION

There is a strong relationship between subclinical hyperthyroidism and all-cause and cardiovascular mortality in Japanese–Brazilians, but not with subclinical hypothyroidism


SUMMARY

BACKGROUND
The influence of subclinical thyroid disease (SCTD) on morbidity and mortality remains uncertain. The object of this prospective study was to investigate the relationships between SCTD and the cardiometabolic profile and cardiovascular disease, and all-cause and cardiovascular mortality.

METHODS
The study was conducted by survey of a uniform population of Japanese–Brazilian individuals living in Bauru, a Brazilian city in the midwestern region of São Paulo, with the aim of estimating the prevalence of diabetes mellitus and associated diseases in this population, a description of which was published previously. The age of the original cohort of 1751 individuals was ≥30 years. Among this group, 1330 (76%) agreed to participate in the study. Excluded from the study were those who self-reported thyroid disease; were taking amiodarone, lithium, or corticosteroids; or had missing data on electrocardiograms (ECGs) and ankle-brachial pressure indexes. The cross-sectional phase of the study was conducted from 1999 through 2000, during which the prevalence of thyroid dysfunction and the association of SCTD with cardiovascular disease were assessed. A total of 1110 individuals thus comprise the study cohort. Follow-up of this group was performed from 1999 through 2007 to investigate the influence of SCTD on all-cause and cardiovascular mortality.

RESULTS

Patient Demographics (Figure 1)
There were no significant differences in the demographics of patients excluded (n = 220) as compared with those included (1110) in the study. The study cohort comprised 591 women (53%) with a mean (±SD) age of 56.9±12.5 years. The demographics and thyroid status of the study group are shown in Figure 1.

Cross-Sectional Analysis (Figures 1 to 4)
The prevalence rates for each thyroid status category, including hyperthyroidism, hypothyroidism, and subclinical hypothyroidism, were compared with the prevalence rates for each category of thyroid function shown in Figures 1 and 2. The median urinary iodine concentration was 210 µg/L, with no statistical difference among the thyroid status categories.
age are shown in Figure 1. Euthyroidism, overt hyperthyroidism, and SChyper were found in 82.3, 1.8, and 6.2%, of the participants, respectively, (Figure 2), with no difference in sex distribution (Figure 3). However, unsuspected overt hypothyroidism and SChypo were identified in 0.8% and 8.9% of the participants, respectively, and both were significantly more common in women (P = 0.04) (Figure 3). The mean age was similar among the groups, except for the SChyper group, which had a significantly higher age as compared with the euthyroid group (Figure 4). Among the groups, there were no statistically significant differences in body-mass index, smoking status, systolic and diastolic blood pressure, fasting blood glucose, homeostasis model assessment for insulin resistance insulin (HOMA-IR), high-density lipoprotein cholesterol, or triglyceride levels. However, mean total cholesterol (P = 0.03) and LDL cholesterol (P = 0.02) were both significantly increased in subjects with overt hypothyroidism as compared with euthyroid subjects, but not in those with SChypo (Figures 3 and 4). There were significantly more subjects with overt hypothyroidism and with SChypo taking statins as compared with the euthyroid group. For the use of statin, the odds ratio (OR), adjusted for age and sex, was significantly higher in the SChypo subjects.
(OR, 3.4; 95% confidence interval, 1.2 to 9.8), as compared with euthyroid individuals (Figure 4).

**Longitudinal Analysis during 7.5 Years of Follow-up (Figure 5)**

During the 7.5 years of follow-up, there were 83 deaths (7.5%), 4 of which were by unnatural causes (suicide or trauma) and 3 by unknown causes. Deaths mainly were the result of cardiovascular events, (51.3%), cancer (22.3%), or infectious disease (14.5%). Among the dead, 50 (65.8%) were characterized as euthyroid, 14 (17.7%) as SChyper, and 13 (16.5%) as SChypo. No patients with overt thyroid disease were reported to have died. However, baseline serum FT4 levels were significantly higher (P = 0.018) (Figure 4) among individuals who had died as compared with those who were alive at the end of follow-up, but there was no difference in TSH among the two groups. Figure 4 shows the relationship between SCTD and mortality. All-cause mortality was significantly higher in SChyper (20.3%) and SChypo (13%) as compared with euthyroid individuals (5.7%) (P<0.0001).

**COMMENTARY**

The main finding in this study was a strong relationship between SChyper all-cause and cardiovascular mortality, but not with SChypo, in Japanese–Brazilians.

The relationship of subclinical thyroid dysfunction with cardiovascular morbidity and mortality is controversial. Especially controversial is the treatment of cardiovascular disease. A comprehensive review of subclinical hypothyroidism by Biondi and Cooper (1) found four double-blind, randomized, controlled trials that concluded that replacement therapy may have had a beneficial effect on the lipid profile but does not appear to affect on lipoprotein (a), homocysteine, or C-reactive protein. The relatively high prevalence rates of subclinical thyroid dysfunction reported by Sgarbi et al. is consistent with that in several studies (2,3). Haentjens et al. (2) found that individuals with subclinical hyperthyroidism demonstrate a 41% increase in relative mortality as compared with control subjects, and for SChypo, the relative risk of all-cause mortality is increased only in patients with comorbid conditions. Likewise, Ochs et al. (3) concluded that SChypo and SChyper may be associated with a modest increased risk for congestive heart disease and mortality. On the other hand, Rodondi et al. (4) concluded that as compared with euthyroid older adults, those with a serum TSH concentration ≥10.0 mIU/L have a moderately increased risk of heart failure and alterations in cardiac function, which was not found in older adults with a serum TSH <10.0 mIU/L.

LONGITUDINAL ANALYSIS DURING 7.5 YEARS OF FOLLOW-UP

Kaplan–Meier analysis demonstrated that overall mortality for both SChyper (P<0.0001) and SChypo (P = 0.0035) as compared with the euthyroid group (Figure 5). Cardiovascular mortality was significantly associated with SChyper (P<0.0001). Cox regression analysis demonstrated that the associations of SChyper and SChypo remained as independent features, even after adjusting for age, sex, and multiple potential confounders (Figure 6).

**CONCLUSION**

This study shows that subclinical hypothyroidism is an independent risk factor for all-cause cardiovascular mortality, whereas subclinical hyperthyroidism is associated with all-cause mortality among Japanese–Brazilians.

This study shows a strong relationship between SChyper and all-cause and cardiovascular mortality, whereas SChypo was significantly associated with all-cause mortality, which was apparent after 4 years of follow-up.

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**References**


