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

Sgarbi JA, Matsumura LK, Kasamatsu TS, Ferreira SR, Maciel RM. Subclinical thyroid dysfunctions are independent risk factors for mortality in a 7.5-year follow-up: the Japanese-Brazilian thyroid study. Eur J Endocrinol 2010;162:569-77.

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.

Definitions Subclinical hyperthyroidism (SChyper) was defined as a serum thyrotropin (TSH) <0.45 mIU/L with elevated free thyroxine (FT_4). Subclinical hypothyroidism (SChypo) was defined as a TSH >4.5 mIU/L with a normal FT_4, and overt hypothyroidism was a TSH >4.5 mIU/L with low FT_4, or a TSH >20 mIU/L. Hypertension was defined as a blood pressure ≥140/90 mm Hg or as the use of antihypertensive drugs. Diabetes mellitus was defined according to the American Diabetes Association criteria, and dyslipidemia was defined as total cholesterol ≥200 mg/dl or triglycerides ≥150 mg/dl or low-density lipoprotein (LDL) cholesterol >130 mg/dl. At baseline, cardiovascular disease was defined as a history of myocardial infarction (MI) as recorded by a physician or as shown by major electrocardiographic (ECG) abnormalities of an old MI (Q waves) or a history of angioplasty or revascularization or stroke. Peripheral arterial disease was defined as any ankle-brachial pressure index <0.9.

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

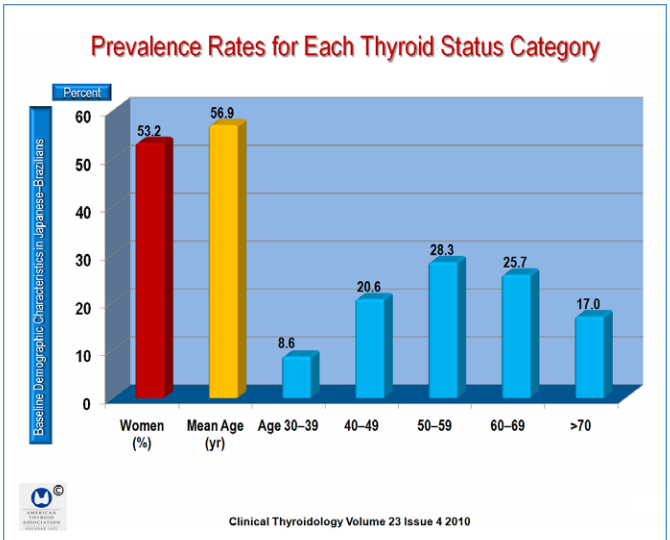

Figure 1. This figure shows the prevalence rates for each category of thyroid function shown in Figures 1 and 2. The median urinary iodine concentration was 210 µg/L, with no statistical difference among the thyroid status categories

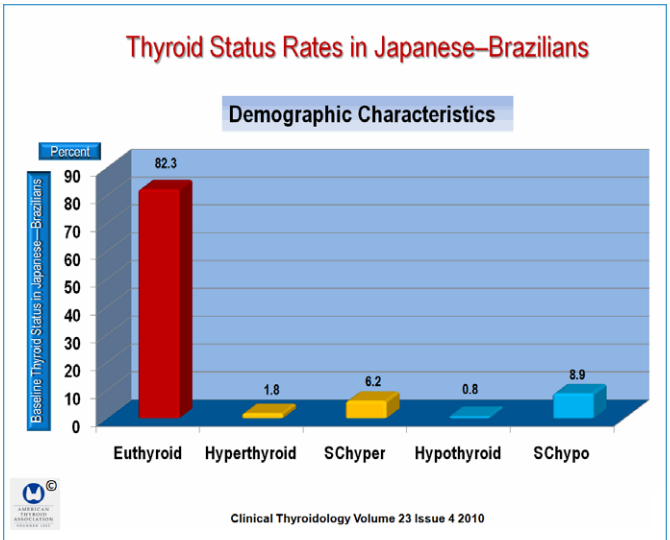

Figure 2. This figure shows the prevalence rates of euthyroidism (n = 913 patients), overt hyperthyroidism (n = 20), and subclinical hyperthyroidism (n = 69). SChyper = subclinical hyperthyroidism; SChypo = subclinical hypothyroidism.

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

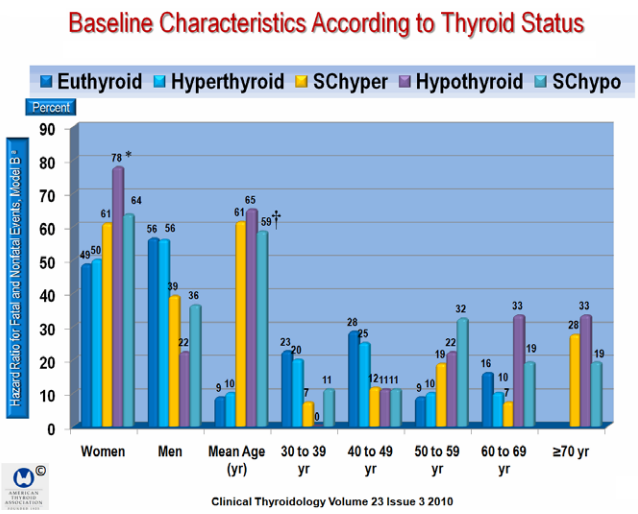

Figure 3. This figure shows the baseline characteristics according to thyroid status. Data are mean percentages (±SD [not shown]) SChyper = subclinical hyperthyroidism; SChypo = subclinical hypothyroidism. *P<0.05. †P<0.01. ‡P< 0.001. §P <0.0001. Values were log-transformed for statistical analysis. Data for this figure were obtained from Tables 1 to 4 in Sgarbi et al.

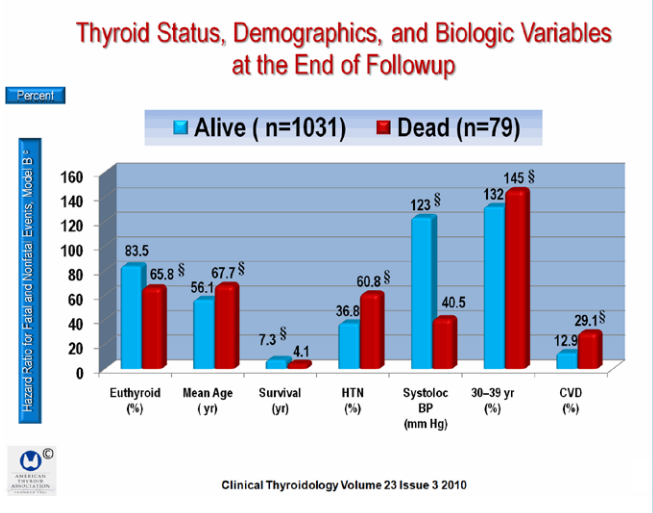

Figure 5. This figure shows the status and demographics and biologic variables at the end of follow-up. BP = blood pressure; CVD = cardiovascular disease; HTN = hypertension These data were derived from Table 3 of Sgarbi et al. *P<0.05. †P<0.01. ‡P< 0.001. §P <0.0001.

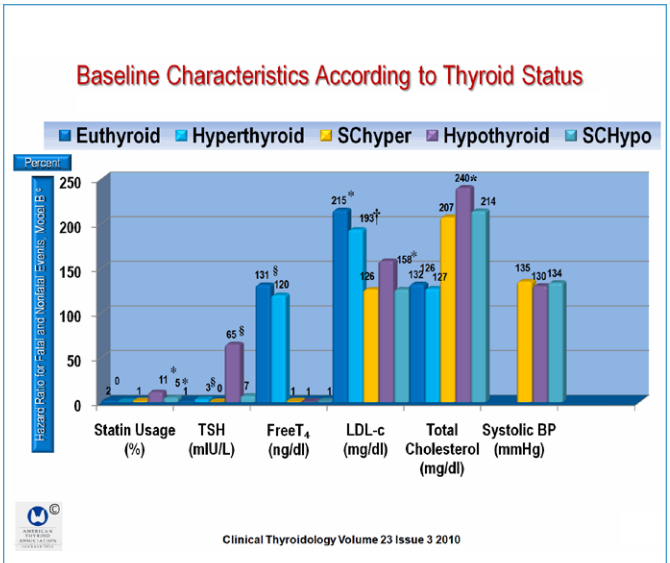

Figure 4. This figure shows the baseline characteristics according to thyroid status. Data are presented as the percent of mean (±SD), unless otherwise noted. BP = blood pressure (in mm Hg); LDL-c = low-density lipoprotein cholesterol;T_4 = thyroxine; TSH= thyrotropin

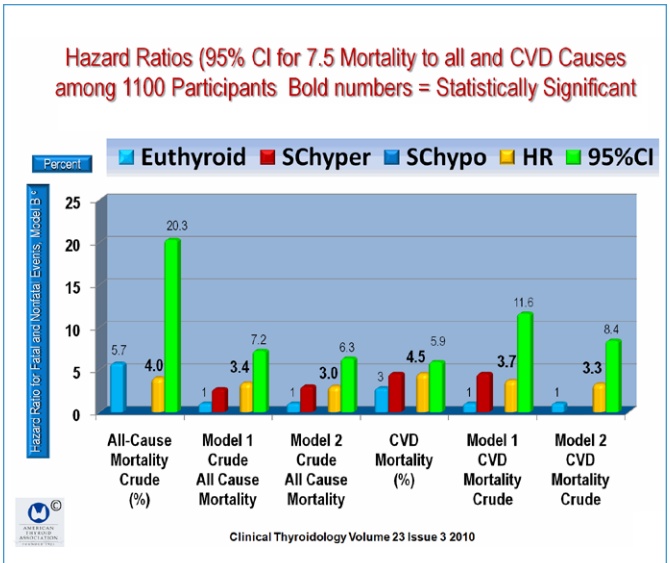

Figure 6. This figure shows the hazard ratios (HR) and the 95% confidence intervals (CIs) for 7.5-year mortality due to all cardiovascular causes among 1110 Japanese –Brazilians. CVD = cardiovascular disease. These data were derived from Table 4 of Sgarbi et al.

(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 FT_4 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). 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 SChyo 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 hypothyroidism 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.

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. A relatively recent review by Völzke et al. (5) concluded that the currently available evidence for a causal association of both hyperthyroidism and hypothyroidism with mortality is weak and should not be used to decide whether patients with subclinical thyroid conditions should be treated.

The Sgarbi study found that subclinical hypothyroidism was significantly associated with death by all causes, but not with cardiovascular mortality. They point out that the small number of cardiovascular deaths (five events) probably limited their ability to detect an association between subclinical hypothyroidism and cardiovascular mortality and that the hazard ratios might have been statistically significant with a larger number of outcomes. Also, the data in this study are based on a baseline set of thyroid tests, with which the authors acknowledge they cannot exclude the possibility of an undetected influence of progression from subclinical to overt thyroid dysfunction. Another limitation that the authors mention is the lack of analysis stratified according to age, sex, and TSH levels due to the small number of events. In addition, they were unable to exclude the possibility of overt thyrotoxicosis in some of the subjects with SC hyperthyroidism and SChypo .

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References

1. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev 2008;29:76-131.

2. Haentjens P, Van Meerhaeghe A, Poppe K, Velkeniers B. Subclinical thyroid dysfunction and mortality: an estimate of relative and absolute excess all-cause mortality based on time-to-event data from cohort studies. Eur J Endocrinol 2008;159:329-41.

3. Ochs N, Auer R, Bauer DC, et al. Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. Ann Intern Med 2008;148:832-45.

4. Rodondi N, Bauer DC, Cappola AR, et al. Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure. The Cardiovascular Health study. J Am Coll Cardiol 2008;52:1152-9.

5. Völzke H, Schwahn C, Wallaschofski H, et al. Review: The association of thyroid dysfunction with all-cause and circulatory mortality: is there a causal relationship? J Clin Endocrinol Metab 2007;92:2421-9.