

## CLINICAL STUDY

## Invited Commentary: Cardiovascular mortality in subclinical hyperthyroidism: an ongoing dilemma

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### Abstract

The association of endogenous subclinical hyperthyroidism (SHyper) with cardiovascular mortality is controversial. This may reflect the different causes of endogenous SHyper in the population studied due to differences in iodine intake, and different selection criteria, e.g. sex, age, and race, the cutoff for serum TSH level, the duration of follow-up, and the presence of co-morbidities. A small sample size of SHyper patients could have caused a low statistical power in some of these studies. In other studies, the results were not adjusted for relevant confounders. Importantly, various meta-analyses have also given conflicting results. This issue of the *European Journal of Endocrinology* contains two articles that address the association between endogenous SHyper and cardiovascular and total mortality: one study was conducted in a north-eastern German population and the other in a Japanese–Brazilian population. After adjusting for relevant confounders, there was no association between decreased serum TSH levels and all-cause and cardiovascular mortality in the Pomerania study; on the contrary, all-cause mortality and cardiovascular mortality were significantly higher for individuals with SHyper in the Japanese–Brazilian population. Interestingly, both studies had similar characteristics in terms of selection criteria and duration of follow-up. It remains controversial whether or not to treat middle-aged patients with low serum TSH levels. Large prospective randomized controlled double-blind studies of young and middle-aged patients with SHyper and without underlying cardiac disease are required to assess the potential benefits of treating endogenous SHyper in these age groups.

*European Journal of Endocrinology* 162 587–589

Subclinical thyroid dysfunction (STD) has been associated with important cardiovascular risk factors. However, it remains controversial whether this disease is associated with an increased cardiovascular mortality in middle-aged and older adults (1). Importantly, various meta-analyses have also given conflicting results (2). In particular, persistent subclinical hyperthyroidism (SHyper) has been associated with repeated subnormal (0.1–0.4 mIU/l) or undetectable serum thyrotropin (TSH) levels (<0.1 mIU/l) and normal free thyroid hormone levels (1). It may be related to exogenous conditions during TSH suppression induced by L-thyroxine (T<sub>4</sub>) therapy, or endogenous conditions due to thyroid autonomy (1). The prevalence of endogenous SHyper is between 0.7 and 7% or higher, and it is inversely correlated with the population's iodine intake (1). Its prevalence is also related to the degree of TSH suppression, with the age of the population studied being higher in subjects above the age of 60–70 years with low serum TSH levels (1). It is well recognized that the risk of adverse effects of SHyper is higher in elderly subjects because this disease could increase the risk of

atrial fibrillation in the presence of subnormal (3) and undetectable serum TSH levels (3, 4).

Studies on the relationship between cardiovascular morbidity and mortality in exogenous SHyper (5–8) induced by long-term treatment with L-T<sub>4</sub> have yielded conflicting results (9). In the very recent large population-based study by Flynn *et al.* (6), among 17 684 patients affected by exogenous SHyper (mean age 61.6 years), those with undetectable serum TSH levels ( $\leq 0.03$  mU/l) were at increased risk for cardiovascular morbidity and mortality, dysrhythmias, and fractures: hazard ratio (HR) 1.37 (1.17–1.60), 1.6 (1.10–2.33), and 2.02 (1.55–2.62) respectively, after adjusting for age, sex, history of a thyroid condition, history of cardiovascular disease, and the presence of diabetes, during a median follow-up of 4.5 years. In the same population, patients with subnormal serum TSH levels did not have an increased risk of any of these outcomes. This is in line with a previous study in which low serum TSH levels ( $\leq 0.5$  mU/l) were not significantly linked to excess mortality among older women using thyroid hormone (5). On the contrary, there

are two reports that subnormal serum TSH levels ( $<0.3$  mU/l) (7) and high free  $T_4$  ( $FT_4$ ) values had adverse prognostic effects in very elderly subjects (7, 8).

Thus far, only a few studies have examined the risk of cardiovascular mortality in patients with endogenous SHyper (3, 10, 11); these were performed in middle-aged (11) and elderly subjects (3, 10). Three studies have been performed in patients with co-morbidity associated with SHyper (12–14). Similar to exogenous disease, the association of endogenous SHyper with cardiovascular mortality is controversial (2). This may reflect the different causes of endogenous SHyper in the population studied due to differences in iodine intake, and different selection criteria, e.g. sex, age, and race, the cutoff for serum TSH level, the duration of follow-up, and the presence of co-morbidities. A small sample size of SHyper patients could have caused a low statistical power in some of these studies. In other studies, the results were not adjusted for relevant confounders.

A recent meta-analysis concluded that evidence of an association between heart disease events and mortality in SHyper was weak (15). However, another recent meta-analysis concluded that untreated endogenous SHyper is more harmful in patients with co-morbidities such as cardiac disease and diabetes mellitus, and in patients recovering from stroke (16).

This issue of the *European Journal of Endocrinology* contains two articles that address the timely issue of the association between endogenous SHyper and cardiovascular and total mortality: one study was conducted in a north-eastern German population (17) and the other in a Japanese–Brazilian population (18). In the former study, Itterman *et al.* analyzed the data of 3651 individuals (aged 20–79 years) living in Pomerania, without known thyroid disorder or thyroid treatment, and found that 270 individuals had decreased serum TSH levels (7.4%). A total of 299 individuals (6.9%) died during the follow-up. More individuals with decreased serum TSH levels (15.98 deaths per 1000 person years) died than individuals with serum TSH levels within the reference range (9.45 deaths per 1000 person years; relative risk 1.67; 95% confidence interval (CI) 1.19, 2.33). The cause of death was not available for 41 individuals. Survival time was also shorter in subjects with decreased serum TSH levels than in the euthyroid individuals (log-rank test;  $P=0.003$ ). However, after adjusting for age and sex, there was no association between decreased serum TSH levels and all-cause mortality (HR 0.95; 95% CI 0.67, 1.36). Furthermore, Cox regression analysis revealed no significant association between decreased serum TSH levels and cardiovascular (HR 1.08; 95% CI 0.61, 1.91;  $P=0.846$ ) and cancer mortality (HR 1.05; 95% CI 0.57, 1.93;  $P=0.890$ ). The results did not change after applying a different cutoff for decreased serum TSH levels, and no association was found for all-cause, cancer, and cardiovascular mortality in patients with subclinical and overt hyperthyroidism (17).

In the second prospective observational study, Sgarbi *et al.* observed the entire population ( $n=1751$ ) living in Bauru (São Paulo, Brazil), aged  $\geq 30$  years, to assess the relationship between STD with all-cause and cardiovascular mortality during a 7.5-year follow-up (18). A total of 1330 (76%) individuals agreed to participate in the study; of these, 69 were affected by SHyper. Interestingly, at baseline, no association was found between STD and cardiovascular disease. However, all-cause mortality was significantly higher for individuals with SHyper (20.3%) and for those with subclinical hypothyroidism (SHypo) (13.1%) than for individuals with euthyroidism (5.7%;  $P<0.0001$ ). The Kaplan–Meier analysis revealed higher overall mortality in SHyper ( $P<0.0001$ ) and SHypo ( $P=0.0035$ ) individuals than in the euthyroid group. Cardiovascular mortality was significantly associated with SHyper ( $P<0.0001$ ); this finding emerged after 4 years of follow-up. The Cox regression analysis revealed that these significant associations persisted even after adjusting for age, sex, and multiple potential confounders (18).

How can we explain the different results of these two studies?

Interestingly, both studies had similar characteristics in terms of selection criteria and duration of follow-up. In fact, both studies were conducted in areas of previous iodine deficiency in which iodine supplementation was implemented in recent years; the prevalence of SHyper was similar (6.2% in the Japanese–Brazilian study and 7.4% in the West Pomerania study); both studies were performed on the entire population, including women and men with a wide age range (mean age 60 years); the length of the follow-up was similar (7.5 years in the Japanese–Brazilian study and 8.5 years in the West Pomerania study); and lastly, both studies excluded subjects who self-reported thyroid disease or who were taking thyroid medications (although in the Japanese–Brazilian cohort, subjects using drugs interfering with thyroid function were excluded).

Serum TSH, free triiodothyronine ( $FT_3$ ), and  $FT_4$  levels were determined in the north-eastern German population study (17). Decreased TSH was defined as serum TSH levels below 0.25 mIU/l, according to the reference range recently established for this region (0.25–2.12 mIU/l). In the Japanese–Brazilian study, the TSH cutoff for SHyper was below 0.45 mIU/l with normal  $FT_4$  levels;  $FT_3$  levels were not determined in this study (18).

There were some limitations in both these studies. First, only baseline thyroid function test results are reported, so we do not know whether the disease was stable, progressive, or reversible after diagnosis. However, this is a limit shared by many epidemiological studies of patients with SHyper. Secondly, neither study provides information about the treatment of participants after baseline diagnosis.

In the study by Ittermann *et al.* patients were informed about their thyroid dysfunction during the 5-year follow-up (17). The knowledge of their thyroid

dysfunction could have induced the patients and doctors to pay more attention to their clinical condition. Treatment of their thyroid dysfunction or treatment of cardiac adverse effects related to SHyper may have influenced the survival rate in this study.

Interestingly, similar to the results reported by Sgarbi *et al.* obtained in middle-aged and elderly individuals (18), an increased circulatory mortality in patients with mild SHyper was observed by Parle *et al.* (10) during the first 5 years of follow-up in elderly subjects with mild SHyper. On the contrary, Parle *et al.* did not find an association between SHyper and either all-cause or circulatory mortality over a complete follow-up period of 10 years; the authors attributed these results to the fact that many patients died before the census date (10).

In their studies, Sgarbi *et al.* (18) and Itterman *et al.* (17) focused on mortality and did not evaluate the risk of atrial fibrillation, cerebrovascular disease, or fracture, which are well-recognized consequences of SHyper (1, 2). In fact, in the West Pomerania study, participants with decreased serum TSH levels more frequently reported a history of stroke, were more often hypertensive, and had higher fibrinogen levels than euthyroid subjects (17). These data support the argument in favor of treating elderly patients with SHyper rather than simply monitoring them, although there are no data showing the benefit of treating elderly patients affected by SHyper. Treatment is safe and less expensive than some serious potential complications related to SHyper in elderly subjects.

It remains controversial whether or not to treat middle-aged patients with low serum TSH levels (2). Large prospective randomized controlled double-blind studies of young and middle-aged patients with SHyper and without important cardiovascular risk factors and underlying cardiac disease are required to assess the potential benefits of treating endogenous SHyper in these age groups.

## Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

## Funding

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

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Received 5 January 2010

Accepted 5 January 2010