

## Cardiovascular Risk and Mild Thyroid Hormone Deficiency: Are there some Differences in the Elderly?

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### Editorial

Subclinical hypothyroidism (sHT) is a clinical condition defined as serum TSH concentration above the upper limit of the reference range in the face of normal free T<sub>4</sub> (FT<sub>4</sub>) and free T<sub>3</sub> (FT<sub>3</sub>) levels. Subclinical hypothyroidism, the prevalence of which increases with age, especially among women, up to almost 20%, encompasses several pathological entities, mainly represented by chronic autoimmune thyroiditis [1,2]. sHT is often associated to symptoms that resembles those of overt hypothyroidism, although to a lesser extent thus, the expression 'mild thyroid impairment' or 'mild thyroid hormone deficiency' would be more appropriate for defining such a condition [1]. Nonetheless, the term sHT is recognized worldwide and will be utilized in the present editorial. Since 90s, a relationship between sHT and increased cardio-vascular (CV) risk (both heart failure and coronary heart disease events) has been reported, although some experiences suggest that the risk may depend on the degree of TSH elevation [1,3-5]. Moreover, several reports from elderly population (>65 years old) showed that this relationship seems no longer evident in such individuals especially in the oldest old (>85 years old) [6-9].

The relationship between thyroid function and ageing has been hypothesized more than almost two decades ago [8]. Several clinical studies confirmed an age-dependent decrease of thyroid function including iodine uptake and thyroid hormone production [9]. However, it should be underlined that direct age-related changes need to be distinguished from the actual alterations induced by thyroid diseases or non-thyroidal illness. In this setting, conflicting results still exist regarding the serum TSH reference range and its modification with ageing between earlier reports (mainly case-control or cross-sectional) and recent large naturalistic studies [3,7-8,10-14]. Given that sHT is essentially recognized as abnormal serum TSH elevation, the definition of a worldwide recognized age-related reference range is clearly warranted.

Thyroid hormones (TH) are implicated in maintaining and integrating metabolic homeostasis at multiple levels, and their deficiency can affect CV system by complex mechanisms involving both myocardium and vasculature, favouring hypertension and diastolic heart alteration. Moreover, sHT is associate to atherogenic conditions such as metabolic alterations, characterized by hypercholesterolemia and glucose intolerance as well as impaired coagulation [9]. These findings may explain the reported association

between thyroid hormone deficiency and increased risk of CV diseases. However, whereas TH deficiency may contribute to atherogenic CV alterations (e.g. increase coronary heart disease (CHD) risk) in young adults (<65 years old) and moderate old patients (<75 years old), data from both humans and animal models showed a negative correlation between serum TH value and longevity [1,10]. In this setting, conflicting data are still existing on the association between sHT and CHD: some studies reporting increased risk [4,11-12], some decreased [13] and some the lack of any association [14-21]. Since inconsistent data were especially obtained in the elderly, the risk of CHD in sHT patients has been suggested to be specific of young adults. However, it is worth to mention that most reports did not accurately explore the possible age-related differences in CHD risk, even in case the elderly represented a large share of the enrolled population.

One of the most recent prospective study by Hyland et al. on 4,863 older people (>65 years), in which thyroid status was updated with subsequent TSH measurements, did not find any association between persistent or transient sHT and incident CHD or CV death. Additional analysis stratified by the degree of serum TSH elevation (4.5-6.9; 7.0-9.9 and 10.0-19.9 mIU/l) confirmed the absence of this association [22]. Accordingly, a cross-sectional study with subgroup analyses by age evidenced an increased CHD risk only in younger sHT participants (<50 years old) [23]. Moreover, a meta-analysis of 5 studies demonstrated that sHT is associated with increased CHD prevalence and events only in young adults (aged <65 years), in which an increased incidence of CHD was present regardless the degree of serum TSH elevation [24]. Interestingly, one of the most interesting study on in the oldest old population (>85 years) suggested that high levels of TSH not only do not exert adverse effects but also may favor a prolonged lifespan [7]. However, in a large prospective study on 1,587 community-dwelling older men, the association between sHT and CV events or total mortality has been obtained independently from TSH elevation (TSH above 10.0 mIU/l was detected only in 8 men) [25]. At partially odds, a very large, recent meta-analysis clearly showed that, in age- and sex-adjusted analyses, the risk of CHD events and mortality increases with rising serum TSH level, reaching the statistical significance only in patients with TSH values above 10 mIU/l regardless of patients' age [26].

Overall the negative effect of sHT on CHD events and mortality appears well established in subjects younger than 65 years but less evident in older people or no present in the oldest old population. However, the inconsistency in results among studies in elderly patients might be due also to the duration of tissue exposure to sHT or of

follow-up, as well as to the presence or not of comorbidity (pre-existing cardiovascular or other chronic diseases).

Another possible explanation of the positive association between sHT and longevity in the oldest old subjects could be that oldest old people is a genetically selected population with a reduced risk of CV diseases. In any case, to shed more light on this aspect large, randomized, prospective studies are warranted to assess whether sHT actually affects CV disease progression and events in older people, analyzing results according to the age groups of participants.

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