

Association between increased serum thyrotropin concentration and the oldest old: what do we know?

Associação entre aumento da concentração de tirotrópina e longevos: o que sabemos?

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ABSTRACT

To assess studies that evaluate the relation between serum thyrotropin concentration, very old subjects, and their events. We searched the PubMed, SciELO, and LILACS databases for articles published between 2004 and 2012. Our search was restricted to studies involving humans aged 65 years or older, and written in English, Spanish, or Portuguese. Studies that evaluated the association between elevated serum thyrotropin concentration among elderly subjects with subclinical hypothyroidism were chosen since at least in part they included a subpopulation of individuals aged 80 years and above. Thirteen studies were selected. No significant increase in risk of cardiovascular events, coronary heart disease, or total mortality was observed. Elevated thyrotropin concentration was associated with longevity. More randomized controlled trials are required to better define the potential benefits of elevated thyrotropin concentration in this oldest old population, hormone replacement, and longevity.

Keywords: Hypothyroidism; Aged, 80 and over; Longevity

RESUMO

Avaliar os artigos que consideram a relação entre a concentração da tirotrópina sérica, indivíduos muito idosos e seus eventos. Foram selecionados artigos do PubMed, SciELO e LILACS publicados entre 2004 e 2012, que consideraram uma população ≥ 65 anos, escritos em inglês, espanhol ou português. Os estudos que avaliaram a associação entre níveis séricos elevados de tirotrópina sérica e idosos com hipotireoidismo subclínico foram escolhidos, desde que incluíssem uma subpopulação com 80 anos ou mais. Treze estudos foram selecionados. Não houve associação significativa entre maior risco de eventos cardiovasculares, doença coronariana ou mortalidade. A concentração elevada de tirotrópina sérica foi associada à longevidade.

Mais estudos randomizados controlados são necessários para o melhor entendimento do potencial benefício da elevação de concentração da tirotrópina sérica nos longevos, reposição hormonal e longevidade.

Descritores: Hipotireoidismo; Idosos de 80 anos ou mais; Longevidade

INTRODUCTION

Subclinical hypothyroidism is a laboratory diagnosis⁽¹⁾ defined by an abnormally high serum thyrotropin (TSH) level associated with a normal plasma concentration of free thyroxin (fT4).⁽²⁻⁴⁾ It is common among elderly individuals and its prevalence increases with age, affecting 6% of population between 70 and 79 years and 10% of individuals above 80 years of age.^(5,6) The prevalence of subclinical hypothyroidism is lower in blacks compared with whites, in women over the age of 80 years, and in populations with iodine deficiency.⁽¹⁾

Subclinical thyroid dysfunction has been associated with several negative clinical outcomes such as hypercholesterolemia, atherosclerosis,⁽⁷⁾ coronary heart disease events and mortality,^(2,7) cognitive impairment,^(2,8,9) depression,⁽¹⁰⁾ disability,⁽²⁾ lower physical function,⁽¹¹⁾ and risk of progression to overt hypothyroidism.⁽¹²⁾

Serum TSH concentration increases slightly in very old healthy individuals,⁽¹³⁾ regardless of the presence of antithyroid antibodies^(5,14) and along with an age-dependent decline in serum free and total triiodothyronine (T3), suggesting that some very elderly individuals

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may have an altered set point of the hypothalamic-pituitary-thyroid axis.⁽⁴⁾ Despite a likely increase in serum reverse triiodothyronine (rT3) with age,⁽¹¹⁾ free and total serum thyroxin (T4) concentrations remain unchanged, complicating the interpretation of these measurements since concomitant chronic illnesses and use of medications are often present in this population. It is possible that the decrease in thyroid function and metabolic rate⁽¹¹⁾ may be adaptive mechanisms to prevent catabolism and reduce damage to DNA by reactive oxygen species.⁽¹³⁾ Furthermore, reports have demonstrated that centenarians⁽¹⁴⁾ and their offspring have higher serum TSH levels, characterizing a heritable phenotype.⁽¹⁵⁻¹⁷⁾

Despite this evidence, the hypothesis that some degree of physiological decrease in thyroid activity at a tissue level may favor effects in oldest old subjects remains uncertain.

OBJECTIVE

To assess studies that evaluated the relation between elevated serum thyrotropin concentrations in mild hypothyroidism and comorbidities in individuals aged over 80 years.

METHODS

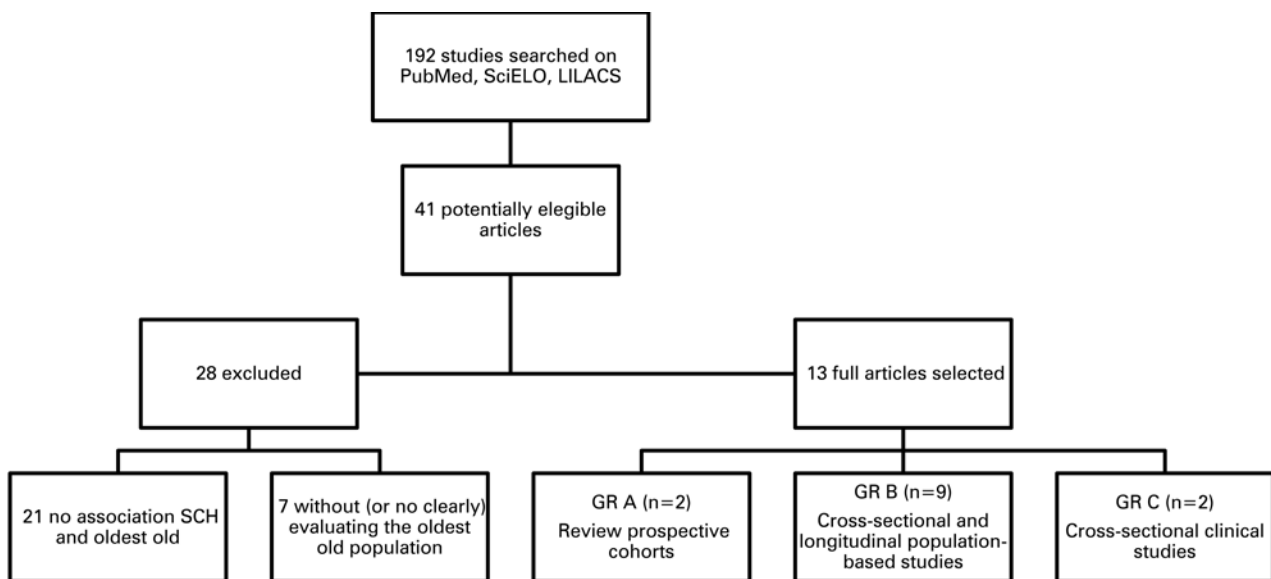
This review was conducted at the Department of Geriatrics and Gerontology, *Universidade Federal de São Paulo*, and approved by the local Research Ethics Committee. We searched the PubMed, Scientific

Electronic Library Online (SciELO), and LILACS databases for articles published between 2004 and 2012, and performed the last survey in April 2013. To conduct the search, we used the following combinations of keywords: “subclinical hypothyroidism” OR “mild hypothyroidism” WITH “oldest old” OR “very old” OR “80 and over” or “centenarians” OR “longevity”. Our search was restricted to studies involving humans aged 65 years or older, and written in English, Spanish, or Portuguese. Studies evaluating the association between elevated serum TSH levels among elderly subjects with subclinical hypothyroidism were included, since at least in part, they included a subpopulation of individuals aged 80 years and more. We excluded studies that lacked this information and studies on non-thyroidal diseases or low-T3 syndrome. Some of these studies did not exclude patients with overt hypothyroidism. We made no restrictions regarding study design or sample size.

RESULTS

Our search identified 192 studies (Figure 1).

Twenty-eight irrelevant studies were excluded for not covering the association between subclinical hypothyroidism and the oldest old (n=21) or not clearly considering the oldest old population (n=9). Thirteen studies were selected and classified according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence.⁽¹⁸⁾ Three studies were conducted in the Netherlands,^(2,11,16) one in the United Kingdom,⁽⁹⁾ one in Italy,⁽¹⁷⁾ four in the United States,^(5,14,15,19) and three in



SCH: subclinical hypothyroidism; GR: level of recommendation.

Figure 1. Criteria applied for selection of the studies

Brazil.⁽²⁰⁻²²⁾ One of the studies included subpopulations from various countries,⁽⁷⁾ (Chart 1). The total number of subjects enrolled in the studies varied from 109⁽²²⁾ to 55,287 individuals.⁽⁷⁾ In studies that have considered the length of follow-up, the average time varied from 2⁽⁹⁾ to 20 years.⁽⁷⁾ Different reference values of TSH were adopted, with the minimum reference ranging from

0.27 to 0.5mIU/L, and the maximum ranging from 4.0 to 5.6mIU/L.

Two selected studies were multicenter trials. One was a longitudinal epidemiological study⁽⁹⁾ involving six centers in England and Wales evaluating the association between cognitive decline, assessed by the Mini-Mental State Examination (MMSE), and high TSH levels in

Chart 1. Studies evaluating the association between subclinical hypothyroidism and the oldest old

Author	Year	Study design	n	Age	TSH (upper limit) (mIU/L)	Follow-up	Endpoints	Exclusion criteria	Outcomes/results
Gusseklou et al. ⁽²⁾	2004	Prospective cohort	704	80-84	4.8	4 years	Thyroid status, disability, cognition, survival	N/A	Abnormally high levels of TSH may prolong life span
Surks et al. ⁽⁶⁾	2007	SR of cohort	16,533	12-80+	4.5	N/A	Prevalence of SCH	Report of thyroid disease, goiter, or use of thyroid-related medications	SCH is overestimated, unless an age-specific range for TSH is used
Rodondi et al. ⁽⁷⁾	2010	SR of prospective cohort	55,287	18-100	4.5	Variable	CHD and CHD mortality	Mainly symptomatic individuals and/or overt hypothyroidism	SCH associated with risk of CHD and CHD mortality in individuals with TSH > 10 mIU/L
Hogervorst et al. ⁽⁹⁾	2008	Prospective cohort	1,047	64-94	4.8	2 years	Cognition	Physical frailty or severe cognitive impairment	High log TSH levels associated with lower MMSE scores
Van den Beld et al. ⁽¹¹⁾	2005	Cross-sectional	403	73-94	4.3	4 years	Thyroid hormones, physical function, mortality	Females, individuals who did not live independently, severe mobility problems, severe systemic disease, physical or mental incapacity to visit study center	Low serum fT4 associated with better 4-year survival, reflecting an adaptive mechanism to prevent excessive catabolism
Atzmon et al. ⁽¹⁴⁾	2009	Case-control	232	97+	4.0	NA	Longevity and TSH	NA	TSH higher in centenarians and may contribute to longevity
Atzmon et al. ⁽¹⁵⁾	2009	Case-control	598	69-85+	4.0	NA	Genetic of high TSH and longevity	NA	SNPs in the TSHR contribute to decreased thyroid function and longevity
Rozing et al. ⁽¹⁶⁾	2010	Cross-sectional	859	89+	4.8	N/A	Longevity and thyroid function	N/A	Low thyroid activity constitutes a heritable phenotype and contributes to familial longevity
Corsonello et al. ⁽¹⁷⁾	2010	Cross-sectional	604	60-85+	4.2	N/A	Longevity and thyroid function	N/A	Decreased thyroid function related to longevity
Spencer et al. ⁽¹⁹⁾	2008	SR of cohort	16,088	12-80+	4.5	NA	TSH and aTPO	Report of thyroid disease or use of thyroid-related medications	Upper limits of TSH may be skewed by aTPO-negative individuals with occult autoimmune thyroid dysfunction
Duarte et al. ⁽²⁰⁾	2009	Case-control	399	60-92	4.0	NA	Prevalence of thyroid dysfunction in the elderly	Report of thyroid or liver disease, thyroid surgery, radioactive iodine therapy, radiologic tests with contrast media or use of thyroid-related medications	The elderly have higher prevalence of hypothyroidism and thyroid nodules; one-third have elevated urinary iodine excretion and autoimmune thyroiditis
Benseñor et al. ⁽²¹⁾	2011	Cross-sectional	1,373	65-80+	5.0	N/A	Prevalence of thyroid dysfunction in the elderly	N/A	Prevalence of thyroid disease in men, and undiagnosed hypothyroidism is higher
Tonial et al. ⁽²²⁾	2007	Cross-sectional	109	60-80	5.6	N/A	Prevalence of hypothyroidism in the elderly	N/A	High prevalence of hypothyroidism

TSH: thyroid stimulating hormone; N/A: not applicable; SR: systematic review; SCH: subclinical hypothyroidism; CHD: coronary heart disease; MMSE: Mini-Mental State Examination; fT4: free thyroxin; TSHR: thyroid-stimulating hormone receptor; aTPO: antithyroperoxidase antibody; SNPs: single nucleotide polymorphisms.

elderly individuals. The other included 11 prospective cohorts from different countries (United States, Australia, Europe, Brazil and Japan) and showed an increased risk of coronary heart disease and coronary heart disease mortality in individuals with TSH concentrations of 10mIU/L or above.⁽⁷⁾ However, when the analysis included only individuals aged 80 years and more, no significant increase in risk of cardiovascular events, coronary heart disease, or total mortality was observed.⁽⁷⁾

Some of the cross-sectional and longitudinal population-based studies recognized that the upper limits of serum TSH levels could have been skewed by individuals with occult autoimmune thyroid dysfunction and negative serum thyroperoxidase antibody (aTPO),⁽¹⁴⁾ whereas others considered the results to overestimate thyroid hypofunction since no age-specific range for TSH was adopted, with the possibility of identifying healthy individuals as having subclinical thyroid disease.⁽⁵⁾ Despite these facts, most studies confirmed that serum TSH is elevated in this population, increases gradually with age,⁽²¹⁾ and that this finding is very common in the population over 80 years of age.⁽¹⁴⁾ Elevated TSH was associated with longevity, especially in the oldest old,^(2,14,19) extended to family members,^(16,17) and could be correlated with better survival.⁽⁸⁾ Results from cross-sectional clinical studies have reported higher prevalence of both subclinical and overt hypothyroidism in oldest old subjects.⁽²¹⁻²³⁾

DISCUSSION

Different studies have suggested that the thyroid gland undergoes anatomical and physiological changes with time, providing evidence that its function declines with age.

A meta-analysis demonstrated that cardiovascular events and mortality in patients with subclinical hypothyroidism were restricted to those younger than 65 years of age.^(24,25) In contrast, it showed no association between a higher risk of coronary events or mortality and elevated TSH for individuals aged 80 years or more.⁽⁷⁾ A possible explanation for this discrepancy may be that participants with subclinical hypothyroidism included in these studies already had preexisting comorbidity factors (such as dyslipidemia and endothelial dysfunction), or even cardiovascular disease, and by becoming exposing to more serious or fatal outcomes before the age of 80 years, increased their risks for cardiovascular events.⁽²⁶⁾ Thus, those who survived would have a higher chance of getting old. It is unclear why inadequately high TSH would be associated with lower mortality⁽²⁾ and longevity. It is possible that a lower metabolic rate

and fluctuating concentration of serum TSH may be represented by early signs of thyroid hypoechogenicity on ultrasound,^(27,28) decreased fT4, increased rT3, and altered pituitary set point,^(14,23) as has been documented in centenarians, and could possibly denote adaptive metabolic processes to prevent excessive catabolism.^(11,23) Indeed, relatives of the oldest old tended to repeat this laboratorial finding^(16,17) showing down-regulation of thyroid hormones due to genetic predisposition⁽¹⁵⁾ and benefiting from a longer life span.^(2,11,15,17)

Elderly patients with subclinical thyroid disease had worse overall results in the MMSE. The association between overt hypothyroidism and cognitive impairment is well established, and there are cases described of secondary dementia due to thyroid dysfunction.⁽⁹⁾ In contrast, some controversial studies have reported an inverse association between high TSH and memory function⁽⁹⁾ or even no association at all when considering the elderly aged over 85 years.⁽²⁾ A similar observation has been made with depression. While some studies report worsening of mood with subclinical hypothyroidism,⁽¹⁰⁾ others have not confirmed this association.^(29,30)

The studies selected showed no evidence that reduced thyroid function had a positive association with disability⁽²⁾ or lower physical function.⁽¹¹⁾

The literature lacks information on the risks of mildly elevated TSH levels on health both in the general population and in the oldest old individuals. Abnormal concentrations of TSH are often found in these elderly individuals and are associated with a prolonged life span, although the exact mechanism for that remains unclear.

Maybe the use of age-specific reference values could offer a more reliable TSH distribution, more representative of the elderly population. This could be an opportunity to redefine the upper limit of normal for serum TSH, at least for the very elderly population.⁽³¹⁾

Targets for TSH level during levothyroxine replacement therapy tend to be individualized and should be adjusted to around 6mIU/L in individuals older than 70 years.⁽⁶⁾ Although it seems that levothyroxine replacement is unlikely to benefit and may even be harmful,^(12,13) treatment should be administered to patients considered at high risk for cardiovascular disease (*diabetes mellitus*, diastolic dysfunction or hypertension, atherosclerosis, smokers) with TSH greater than 10mIU/L and to those with antithyroid antibodies and/or positive ultrasound findings who may progress to overt hypothyroidism.^(6,12,32)

CONCLUSION

Current clinical implications and treatment recommendations for oldest old individuals with subclinical hypothyroidism are still unclear. With the gradual expansion of the

age group of very old individuals, more randomized controlled trials are required to better define the potential benefits of thyroid hormone replacement for this population.

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