

REVIEW

Association between serum TSH concentration within the normal range and adiposity

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Abstract

Background: Overt hypothyroidism is clearly related to body weight gain and greater adiposity, but the range of hormonal change in serum TSH concentration associated with weight gain remains a focus of debate.

Aim: The aim of this review was to assess studies that evaluated the relationship between anthropometric measures and serum TSH concentration in euthyroid subjects.

Methods: Studies held on the Ovid MEDLINE database were searched and original articles published from 2000 to 2010 were included. The literature search was restricted to studies conducted in humans aged 18 years or older and written in English, Spanish, or Portuguese. Studies that evaluated the association between anthropometric measures and serum TSH within the normal range as the primary objective, as well as additional analysis, were included.

Results: A total of 29 studies met the inclusion criteria. Of the 29 studies, 18 showed a positive relationship between measures of adiposity and serum TSH. Despite the plausibility of this association, only two studies reported longitudinal findings. The influence of smoking on the association between serum TSH and anthropometric measures was evaluated in only three studies and remains unclear.

Conclusion: Thus, further longitudinal studies are needed to better understand the mechanisms by which TSH concentration might impact body weight.

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Introduction

Overt hypothyroidism is clearly related to body weight and greater adiposity (1), but the range of hormonal changes related to weight gain remains a subject of debate. Thyroid hormones affect many metabolic processes, and subclinical hypothyroidism has been associated with both hypertension (2) and hypercholesterolemia (3).

Among the several hormonal changes that occur in obesity, serum TSH concentration has been the focus of recent studies with conflicting results. The potential impact of minor changes in thyroid function on body weight and other anthropometric measures, especially in euthyroid subjects (4–6), has been investigated. Thus, the definition of the upper limit of normal serum TSH range has been under intense debate in the literature (7, 8). It has been suggested that the upper limit of the normal serum TSH range be reduced to 2.5 mU/l (8), but a large epidemiologic study in a population with no evidence of thyroid disease, seronegative for thyroid autoantibodies, without history of thyroid medications, and normal on thyroid ultrasound, indicated a serum TSH value of 4.0 mU/l as the upper reference limit (7).

To our knowledge, there are no reviews focusing specifically on the association between changes in

anthropometric measures and serum TSH concentration among subjects with normal thyroid function or subclinical thyroid disease. Thus, the main objective of this review was to assess studies that evaluated the relationship between anthropometric measures and serum TSH concentrations.

Method

Search strategy

Articles held on the Ovid MEDLINE database were searched and original articles published from 2000 to 2010 were included. The last search was held on 05 May 2010. The following search terms were used: 'TSH' or 'thyroid-stimulating hormone' or 'thyrotropin' or 'thyroid-stimulating hormone' or 'hormone, thyroid-stimulating' or 'thyreotropin' or 'hormones, thyroid' or 'subclinical hypothyroidism' or 'hypothyroidism' or 'hyperthyroidism' or 'thyroid disease' and 'BMI' or 'body mass index' or 'obesity' or 'overweight' 'weight gain' or 'weight loss' or 'skinfold thickness' or 'waist-hip ratio' or 'abdominal fat'. Our search was restricted to studies conducted in humans aged 18 years or older and written in English, Spanish, or Portuguese

languages. Studies evaluating the association between anthropometric measures and serum TSH among subjects with normal thyroid function or subclinical thyroid disease were included. Articles that lacked information about the association between serum TSH and anthropometric measures were excluded. There were no restrictions regarding study designs or sample size.

Results

Figure 1 depicts the selection process for studies included in this review. A total of 29 studies met the inclusion criteria. These studies were conducted in several countries: five were conducted in United States; four in Italy; three in Korea and The Netherlands; two in Greece, Norway, and Spain; and one in each of the following countries: Australia, Brazil, Denmark, Germany, India, Japan, the Czech Republic, and Turkey.

A total of 56 630 subjects between the ages of 18 and 89 years participated in the studies reviewed. The study sample includes 33% males, 60% females, and 7% unreported gender. This preponderance of females could be explained by the higher prevalence of thyroid disease and obesity among women compared with men. The minimum reference value of TSH ranged from 0.17 to 0.5 mU/l, whereas the maximum reference value of TSH ranged from 3.5 to 5.5 mU/l.

Anthropometric measures used in the studies included BMI (4–6, 9–30), body weight (15, 31, 32), waist circumference (9, 14, 15, 23, 29, 33), waist–hip ratio (9, 15), hip (23), body fat percentage (13, 15, 17, 21, 23, 29, 32), subcutaneous (9, 15, 21, 27) and central (21) fat, and fat mass index (fat mass (kg)/height (m)²) (29).

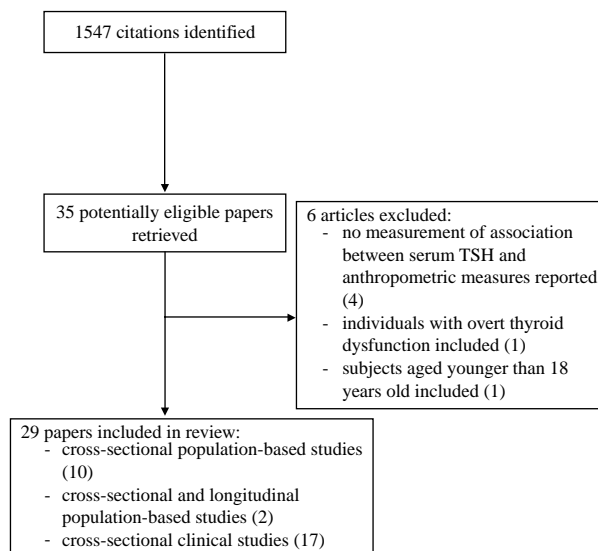


Figure 1 Flow chart of process for selection of eligible studies examining the association between body mass index (BMI) and serum TSH concentrations within the normal range.

Although race is known to be associated with serum TSH concentration (34) and adiposity (35), this demographic factor was not reported in 87.8% of participants. However, as most of the studies were performed in European countries, the majority of subjects were probably Caucasian.

Clinical studies

Of the total studies, 17 were based on clinical samples (see [Supplementary Table 1](#), see section on [supplementary data](#) given at the end of this article), 11 of which found to have a positive association between serum TSH concentration and measures of adiposity (10–12, 17, 18, 21, 22, 27, 30, 32). Of the 11 studies, seven included only obese or overweight subjects.

The highest correlation coefficient in the association between BMI and serum TSH was found in studies that included only euthyroid obese women ($r=0.44$, $P=0.01$) (18) or morbidly obese men and women ($r=0.91$; P value <0.001) (12).

The coefficient correlation in studies performed among obese women was twice greater than the coefficient correlation found in the study performed among obese males ($r=0.22$, $P<0.05$) (17).

None of the studies evaluated the association between measures of adiposity and serum TSH according to skin color.

Population-based studies

Results of population-based studies are shown in [Supplementary Table 1](#). Of the twelve studies, seven found a positive association between serum TSH and measures of adiposity (4, 6, 15, 20, 24, 26, 31).

Both cross-sectional and prospective findings were reported in two studies (6, 31). The first of these found a positive association between BMI and serum TSH only among non-smokers in both cross-sectional and longitudinal analysis (6). The other study found a positive association between body weight and serum TSH concentrations among men and women (31).

The largest population-based study was carried out in Norway and involved 27 097 euthyroid subjects. In this Norwegian study, BMI was positively associated with serum TSH ($\beta=0.41$, $P<0.001$ for women; $\beta=0.48$, $P<0.001$ for men) (4).

Three studies evaluated the association between measures of adiposity and serum TSH according to smoking status (4–6). Nyrnes *et al.* (6) found a positive association between BMI and serum TSH only among non-smokers. Makepeace *et al.* (5), however, failed to find any association with smoking status. In contrast, Asvold *et al.* (4) found a positive and statistically significant association between BMI and serum TSH among both non-smokers and smokers. In men,

however, this association was stronger among current smokers ($\beta=0.81$, $P<0.001$) than non-smokers ($\beta=0.32$, $P<0.001$).

Discussion

The published literature investigating the association between anthropometric measures and serum TSH within the normal range presents conflicting results. However, 17 of the 29 reviewed studies found a positive association between anthropometric measures and serum TSH, and the two longitudinal population-based studies showed a positive association between serum TSH concentration and BMI or body weight (6, 31).

The plausibility of this association has been discussed and could be mediated by TSH action directly stimulating preadipocyte differentiation, thus inducing adipogenesis (36, 37). Another hypothesis is that the association between serum TSH and body weight may be due to leptin (38). In agreement with the leptin hypothesis, a recent study in treated thyroid cancer patient found an increase in serum leptin after acute recombinant human TSH administration, which was proportional to adipose mass (39). Also, the highest correlations in the association between BMI and serum TSH concentration ($r=0.91$) was shown among morbidly obese participants (12). In line with these findings, Rotondi *et al.* (30) found higher values of serum TSH among euthyroid morbid obese subjects when compared with euthyroid normal-weight patients and morbidly obese subjects with hypothyroidism showed lower level of anti-TPO. Thus, the authors suggested that the raised serum TSH concentrations, especially in morbid obesity, may be independent of thyroid function.

The effects of excess body weight on thyroid could differ between lower grades of overweight and morbid obesity (30), which could in part explain the different findings reported by the reviewed studies, because these articles include people with different levels of overweight or obesity that could blur a possible effect of TSH. In addition, the variability in anti-TPO levels could also explain the discrepancy of results among the reviewed studies.

Among the reviewed studies, the maximum reference value of TSH ranged from 3.5 to 5.5 mU/l. As previously mentioned, the definition of the maximum reference value of the TSH range has been the subject of intense debate. Hamilton *et al.* (7) performed a population-based study with subjects without evidence of thyroid disease and suggested an upper reference limit of serum TSH of 4 mU/l. However, 18 of the 29 examined studies considered an upper-limit TSH value of over 4 mU/l. This variability in limits might explain the lack of association between BMI and TSH in 11 (5, 9, 13, 16, 19, 23, 25, 28, 29, 33, 40) of the 29 examined studies. Another source of discrepancy is the fact that almost half of the studies did not perform adjustment for potential confounders.

Limitations of the reviewed articles included the fact that most studies were conducted in a clinical setting, whereas only two reported a longitudinal design (6, 31). Furthermore, adjustment for potential confounders was also limited in the reviewed studies whereby 14 (9, 10, 13, 14, 16–19, 21–23, 27, 29, 30) of the 29 studies performed no such adjustments.

Age, sex, and smoking were the variables adjusted for. Sex and smoking are considered potential confounders as well as effect modifiers of the association between BMI and serum TSH. It is well known that the prevalence of thyroid disorders is higher among women than men (41). Consequently, participants in the reviewed studies were mainly women and the majority of reports evaluated the association between BMI and TSH adjusting by sex. Among those studies that performed analyses stratified according to sex, Dvorakova *et al.* (15) found a significant association between BMI and serum TSH only among women, whereas the other studies found no significant differences by sex.

Smoking is related to both serum TSH and BMI. Smokers have lower serum TSH concentration (42) and lower BMI than non-smokers (43). Of the 29 studies, four considered smoking a potential confounder, three of which performed analysis stratified according to smoking status. The results of these studies, however, were inconclusive. A study performed in Norway found a positive association between BMI and serum TSH only among non-smokers (6). In contrast, another study also performed in Norway found the same association among both non-smokers and smokers. Nevertheless, the association between BMI and serum TSH in men was stronger among current smokers than non-smokers (4).

In summary, despite the plausibility of the association between serum TSH within the normal range and anthropometric measures, almost half of the studies did not find a positive relationship. However, the findings from the large studies and the longitudinal investigations indicated a positive association. The influence of smoking on the association between serum TSH and anthropometric measures was evaluated in only three studies and remains unclear. Thus, further controlled longitudinal studies are needed to better understand the mechanisms by which TSH concentration might impact body weight.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-11-0261>.

Declaration of interest

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

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