



Age Impact on TSH Profile in A Portuguese Population

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Abstract

Objective: The measurement of plasma Thyrotropin (TSH) is the most sensitive screening test for primary thyroid disorders. Our main goal was to study the association of TSH with age and gender in a Portuguese population without evidence of thyroid disease.

Methods: Cross-sectional and longitudinal study conducted in an Endocrinology Department. For the former, we identified the latest TSH measurements in 981 patients from the reference population, aged 19-94. For the latter, we observed serum TSH variations in 268 patients, aged 40-86, with a minimum of 5 years of follow-up.

Results: The mean age was 67.5 years and the mean serum TSH was 1.82mU/L. We found a positive correlation between TSH and age in this population ($p < 0,001$). Mean serum TSH was significantly higher in females than in males (1.99 vs. 1.78). Age significantly increased the means and the 97,5th centile of TSH. In the cross-sectional analysis, TSH increased by 0.014 mU/L for every year of age. In the longitudinal model, mean serum TSH in the cohort increased by 0.23mU/L at 13-year follow-up. The intra-individual TSH variation was statistically significant after 15 years of follow-up.

Conclusion: The findings are consistent with previous studies that report TSH increase with age. Nevertheless, our observations show that most results are included in the normal reference range, so an age specific reference interval of serum TSH is debatable. We also established a minimum follow-up period in order to perceive a significant change in TSH intraindividual.

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Introduction

The measurement of plasma Thyrotropin (TSH) is the commonly accepted and most sensitive screening test for primary thyroid disorders [1]. In most cases, the result will be within the normal range and no further testing is indicated. It is important to understand that normal ranges are calculated based on the 2.5th to 97.5th percentiles of the distribution of values measured in the population tested. Individuals with TSH values in the lowest and highest 2.5% of this distribution are outside the range, and these values are considered abnormal.

Multiple studies have examined associations of age, race, sex, BMI, dyslipidemia, glycemic control, kidney function and smoking with thyroid function [2-5].

In 2002, Hollowell et al [6] investigated TSH distribution in a representative sample of the US population from the National Health and Nutrition Examination Survey III (NHANES III) and reported that TSH levels were greater in females, in caucasians and increased with age. The 2.5th and 97.5th percentiles of TSH were 0.45 and 4.12 mIU/L, respectively.

More recently, the Thyroid Epidemiology, Audit and Research Study (TEARS) revealed consistent findings on the association between age and TSH [7]. In this study, the 2.5th centile of TSH decreased with age and the 97.5th centile increased with age, particularly on those over 70 years. Also, they reported that patients with diabetes had higher TSH concentrations. Contrary to NHANES III, males presented greater TSH values.

In populations with mild iodine deficiency, aging is associated with increased TSH concentrations with no change in free T4, which can mimic Subclinical Hypothyroidism (SH) [8-11]. Various studies have reported the prevalence of SH to be 3-12% in the general population [12]. However, the prevalence increases with age, and is about 10% in women older than 70 years and is somewhat lower in men [13,14]. Based on these data, some authors recommend the adoption of age-specific reference ranges for TSH [15,16]. One suggested approach is that the upper limit of the thyrotropin range should be raised to 7 mIU/L among individuals aged 80 years and older [17]. Observational data have shown no increased risk of cardiovascular or neurocognitive events in individuals with thyrotropin levels of 4.5 to 6.9 mIU/L who are followed up without treatment [18]. This change could reduce confusion about thyrotropin interpretation and lead to a reduction in unnecessary levothyroxine prescriptions and monitoring. Moreover, a recent study found no benefit of levothyroxine on thyroid-related symptoms in older persons with SH, defined as thyrotropin levels between 4.6 and 19.9 mIU/L [19]. At the same time, a large meta-analysis suggested no harm associated with TSH <10 mIU/L regarding cardiovascular events or mortality [20,21].

Our main goal is to study the association of TSH with age in a Portuguese adult population without evidence of thyroid disease.

Materials and methods

We performed a cross-sectional and longitudinal analysis in order to analyze age-related changes in TSH levels. The study was conducted at the Endocrinology Department at Armed Forces Hospital, in Lisbon, from July 2019 to July 2020. All subjects attended the outpatient clinic for follow-up visits regularly, due to specific endocrine conditions, mainly type 2 diabetes. Patients were excluded based on the criteria below in order to

derive a reference cohort without thyroid disease:

- Any subject younger than 18 years at baseline.
- Any female subject pregnant at the time.
- Any subject who had ever been diagnosed with thyroid nodules, thyroid cancer, hyperthyroidism or hypothyroidism.
- Any subject who had been prescribed levothyroxine, metimbasol, propylthiouracil, amiodarone or lithium at any time.
- Any subject who had ever been treated with radioactive iodine.
- Any subject who had ever tested positive for thyroid antibodies.
- Any subject who had ever undergone thyroid surgery.

For the **cross-sectional study**, we identified the latest TSH measurements in 981 subjects from the reference population, aged 19-94. Student's t-test was used to compare the mean TSH between females and males. The relationship between age and TSH was analyzed using a linear regression model. The regression coefficient and 95% Confidence Interval (CI) were calculated. BMI was also measured to reduce potential for confounding. TSH measurements were grouped by 10-year age band and the means and percentiles were calculated for each age group. We used the one-way analysis of variance (ANOVA) to compare TSH distributions in different age groups.

For the **longitudinal analysis**, a subgroup analysis of the cross-sectional population was established. The changes in TSH were calculated for 268 subjects aged 40-86. As part of their annual consultation with the endocrinologist, they were routinely screened for TSH levels. Follow-up periods ranged from 5 to 20 years. Student's T-test was used to compare means.

We adopted the TSH reference interval provided by our manufacturer (0.35-4.9 mIU/L). All tests were carried out by the military analytical laboratory, excluding the possibility of laboratory-related bias. For measurement of TSH in human serum, the Chemiluminescent Microparticle Immunoassay (CMIA) was conducted. The test was performed on the Abbott ARCHITECT i2000 system.

All statistical analyses were performed using SPSS version 25.0. A *p*-value of less than 0.05 was regarded as statistically significant. The study was approved by the Health Ethics Committee at Armed Forces Hospital.

Results

Cross-sectional analysis

The cohort included 778 males and 203 females. The mean age was 67.5 years ± 12.4 and the mean serum TSH was 1.82 mIU/L ± 1.0 (min: 0.16 max: 6.9).

We found a positive correlation between TSH and age (*p*<0.001). TSH increased by 0.014 mIU/L for every year of age. The R² of 0.029 indicates that the linear model explains ~3% of the variability in thyroid function (shown in Figure 1).

A one-way ANOVA was conducted to compare TSH means in 5 age groups: 40s, 50s, 60s, 70s, 80s (Table 1). There was a significant difference at the *p*<0.001 level for the 5 groups. Post hoc comparisons using the Tukey HSD test indicated that the

mean score for the 40s and 50s were significantly different than the 70s and 80s.

Based on 10-year age groups, the mean TSH was 60% higher in 80-year-old adults than in 40-year-old adults (2.1 mU/L vs. 1.3 mU/L). The 97.5th centile shifted from 2.97 mU/L to 5.17 mU/L across these age groups (shown in Table 1). Age significantly increased the means and the centiles of TSH, however the main effect of age is seen at the 97.5th centile of TSH.

We found 11 TSH measurements (1,1%) higher than the reference interval in the cohort. The ages of those subjects ranged from 66 to 85 years. The percentage of subjects with TSH greater than 4.9mU/L was 0.8% in the 60s group, 1.4% in the 70s group and 3% in the 80s group. We also report 10 (1%) results below the inferior limit. All subjects were over 60 years of age.

Mean serum TSH was significantly higher in females than in males (1.99 vs. 1.78) with a $p < 0.05$. We presumed BMI as a possible confounder, however both groups presented a mean BMI of 29 kg/m². Age distributions were also similar in both groups.

Longitudinal analysis

The cohort included 268 subjects, with a mean follow-up period of 13 years \pm 4.5.

At 13-year follow-up, the mean serum TSH concentration in the cohort increased from 1.75 to 1.98 mU/L, with a mean Δ TSH of 0.23 mU/L. A paired sample t-test was conducted to compare means from the same group at different times. Intraindividual TSH increments were observed after 6 years but were only significant after 11 to 15 years of follow-up (shown in Table 2).

Table 1: TSH means and percentiles among different age groups (n=981).

Decade	No. of subjects	Mean TSH (SD) (mIU/L)	2.5 th percentile (mIU/L)	97.5 th percentile (mIU/L)
20s	9	1.97	-	-
30s	9	1.72	-	-
40s	43	1.33 (0.63)	0.37	2,97
50s	198	1.64 (0.88)	0,44	4
60s	261	1.76 (0.92)	0,49	4,18
70s	288	1.91 (1.0)	0,45	4,39
80s	165	2.11 (1.19)	0,51	5,17
90s	8	1,95	-	-

Table 2: Longitudinal analysis of TSH variations in the cohort (n=268).

Follow-up period	No. of subjects	Mean baseline TSH (mU/L)	Mean follow-up TSH (mU/L)	Mean Δ TSH	p-value
5 ys	31	2.24	2.12	↓ 0.12	0.509
6-10 ys	96	1.68	1.79	↑ 0.12	0.199
11-15 ys	91	1.76	1.99	↑ 0.23	0.016
16-20 ys	50	1.58	2.23	↑ 0.64	0.000

Discussion

In this study of a cohort of individuals with no evidence of thyroid disease, serum TSH concentrations increased on average by 0.14 mU/L with each additional decade of age, which is consistent with previous findings on the association between age and TSH. Nevertheless, our observations show that most of the results are included in the normal reference range provided by our manufacturer. There was a significant increase in means and 97.5th percentiles across age groups, whereas for the 2.5th percentile there was no significant trend, in line with the study by Kahapola-Arachchige et al. [22].

Regarding 80-year-olds, merely 3% depicted a TSH between 4.9-6.5 mU/L so the relevance of an age-specific reference interval of serum TSH for this age group is debatable. Also, in adults aged 65 years and older, mild TSH elevations can normalize over time, highlighting the value of repeated assessments for clinical evaluations [23]. Nonetheless, all the mentioned studies admit that higher TSH concentrations in the elderly could be tolerated

without pharmacological intervention and we concur with that principle.

In the longitudinal analysis, we concluded that a significant change in TSH is detected after 11 to 15 years of follow up. Below that threshold, the variation is too subtle to be relevant. The shift in TSH distribution curves we observed in the present study is similar to that seen in the TEARS and NHANES III data [7,6].

The longitudinal and cross-sectional analyses each showed increasing TSH concentrations with age, although with a small discrepancy: in the former, mean TSH increased 0.23mU/L after 13 years, whereas in the latter the calculated increment was 0.18mU/L for the same time frame. Both are consistent with previous observations that the change in TSH during ageing is gradual, with increases in the order of 0.2-0.3 mU/L over a decade [15]. Concerning the mechanisms that could account for these results [16], many participants never had serum thyroid

antibody testing so, although unlikely, our results might reflect a higher prevalence of occult thyroid disease in older people.

As our linear model explains only 3% of the variability in TSH concentrations, we recognize other individual factors' influence on thyroid function. BMI, smoking status or gender are a few described in the literature [24]. Regarding gender impact on thyroid function, our findings support the results from the NHANES and the most recent KNHANES studies [16,9] that reported higher TSH concentration in females. We do not recognize the clinical value of this outcome.

The strengths of this study include adequate sample size to provide good statistical power and clinical relevance. Its major asset is that it includes both a cross-sectional and a longitudinal evaluation of the cohort, thus strengthening the reliability of the results. The main constraint of this study is the lack of fT4 levels to assess its relationship with TSH variations. Also, the number of subjects in each age group differs, with a relatively small sample size at the extremes of age (<30ys and >90ys). Lastly, the lack of data regarding iodine status for the Portuguese adult population could hinder the interpretation of the results.

Conclusions

In summary, this study supports previous evidence regarding TSH shift with age. At the same time, we have established a minimum period of follow-up in order to perceive a significant change in TSH concentrations intraindividual. Furthermore, the relevance of an age-specific reference range is debatable.

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