

Research Article

Predictors of Serum TSH in a Healthy Adult Sample of the Lebanese Population

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Abstract

Purpose: Measuring thyroid-stimulating hormone (TSH) is essential for diagnosing and monitoring thyroid diseases. The aim of this study is to determine the factors predicting TSH variability.

Materials and Methods: Plasma TSH, free T3 (FT3), total T3 (TT3), free T4 (FT4), anti-peroxidase antibodies (TPOAb) and anti-thyroglobulin antibodies (TgAb) were measured in 301 healthy Lebanese adults (198 women and 103 men) aged 18 to 65 years. Measurements were performed on the Cobas Roche automate. Age, sex, Body Mass Index (BMI), arterial blood pressure and the presence of dyslipidemia were collected from the population.

Results: The mean age of the population was 38.98 ± 13.28 years and the mean BMI $25.36 \pm \text{kg/m}^2$. There was no correlation between TSH and FT4, while a positive correlation was found between TSH and TT3, FT3, TPOAb and TgAb (respectively $p < 0.001$, $p = 0.002$, $p < 0.0001$ and $p < 0.0001$). TSH was not associated with age or gender but was positively correlated with BMI ($p = 0.053$) and systolic blood pressure ($p = 0.03$). In a multiple linear regression analysis, the independent predictors of TSH were FT4, FT3 and TPOAb. In addition, FT4, TPOAb, and dyslipidemia were independently associated with the TSH 97.5th percentile.

Conclusion: Our study showed that the main predictors of TSH are FT4, FT3 and TPOAb. This finding supports the role of TSH in enhancing T3 production as well as the main role of TPOAb in predicting the rise in TSH.

Keywords: TSH; Predictors; Lebanese; Healthy; Adults

Introduction

TSH (Thyroid stimulating hormone) is the most sensitive marker for assessing the thyroid status and is considered by the American Thyroid Association (ATA) as the most helpful test for screening thyroid dysfunction [1].

Serum TSH secretion is pulsatile [2] and exhibits a diurnal variation with a nocturnal peak leading to intraindividual TSH variations depending on the time of blood withdrawal during the day [3,4]. Serum TSH is also affected by acute stress [5] and varies according to age [3,6,7], sex [3,7], BMI [8] and iodine status [9]. TSH increases with BMI [10,11], is higher in females [12] and elderly people [12]. Some studies have also reported an increased prevalence of hypertension [13] and dyslipidemia [14] with the increase in TSH levels. Finally, the presence of antithyroid antibodies, either thyroid peroxidase antibodies (TPOAb) [15,16] or thyroglobulin antibodies (TgAb) [16], is associated with higher TSH values, with a stronger relationship with the former [15].

No previous studies were conducted in the Middle East to establish factors that can influence the variability of TSH. The aim of this study was to identify predictive factors of TSH variation in a healthy adult sample of the Lebanese population.

Materials and Methods

Population

This is a cross-sectional study conducted on a sample of Lebanese subjects aged between 18 and 65 years. Recruitment was done between November 2020 and January 2021 based on volunteering among healthy hospital employees and visitors. Were excluded from the study: subjects with a personal history of thyroid disease or clinical goiter, or with any recent acute stress (hospitalization or acute infection within the last month) or chronic diseases (such as hepatic or renal disease), as well as subjects on medication that can affect thyroid tests (such as levothyroxine, oral contraceptives, estrogen replacement therapy, glucocorticoids or biotin) or pregnancy.

On the day of sampling, height in meter (m) and weight in kilogram (kg) of all participants were measured. Height was measured without shoes using a wall mounted tape. Weight was measured without shoes and with light clothes on using a calibrated scale (Soehnle Professionals).

Body mass index (BMI) was calculated as weight (in kilograms) divided by the squared value of height (in meters) and expressed in kg/m^2 . BMI was divided into 3 subclasses: underweight for a BMI $< 18 \text{ kg/m}^2$, normal weight for a BMI between 18 and 25 kg/m^2 , overweight for a BMI between 25 and 30 kg/m^2 , and obese for a BMI superior

to 30 kg/m². Systolic and diastolic arterial pressures were taken in a sitting position after 5 minutes of rest.

All participants signed an informed written consent, and the study was approved by the Ethics Committee at Hôtel-Dieu de France university hospital, Beirut, Lebanon (CEHDF1524).

Biological Analysis

For all the subjects enrolled in the study, fasting blood samples were collected at the laboratory of the authors' institution between 8 and 10 am, then were centrifuged on the day of collection, and the resulting serum frozen at -20°C for <2 months before biochemical measurements: TSH, free T4 (FT4), free T3 (FT3), and total T3 (TT3), Thyroid antibodies (TPOAb and TgAb). Measurements were performed on the fully automated Cobas Core electrochemiluminescence (ECL) technology immunoassay system (Roche Cobas e411). The respective reference ranges defined by the manufacturer for TSH, FT4, FT3, TT3, TPOAb, and TgAb are defined as 0.27- 4.2 µIU/mL, 12-22 pmol/L, 3.1 - 6.8 pmol/L, 1.3 - 3.1 nmol/L, < 34 IU/mL and < 115 IU/mL. For all the biological parameters the coefficient of variation is less than 8%.

Statistical Analysis

The distribution of the biological values (TSH, FT4, FT3, TPOAb and TgAb) was checked using Shapiro-Wilk (SW) tests and visual inspection of the quartile-quartile (Q-Q) graphics. Native variables with a skewed distribution were expressed as a median value with an interquartile interval (quartile 1 - quartile 3) and the 95% distribution interval (percentile 2.5 - percentile 97.5). Correlations between the quantitative variables were estimated by the Spearman correlation coefficient for variables departing from normality, and by the Pearson correlation coefficient otherwise, including log-transformed variables. 95% Confidence intervals (95% CI) for Spearman's rho were derived by bootstrapping based on 10,000 samples. The Student test, the Mann-Whitney test, the Chi-square test were used as appropriate. TPOAb and TgAb antibodies' levels, reported initially as <5 and <10 respectively, were considered to be equal to 5 and 9 respectively. In the multivariate analyses, a primary model of multiple linear regression was done to study the correlation between Ln (TSH) and the different independent variables. Model calibration used Cox-Snell R², Cook distances and the studentized residuals. An additional quantile regression model was used to study the variations of percentile 2.5, percentile 50 (median) and percentile 97.5 with the independent factors. All statistical analyses were performed using IBM SPSS (IBM Corp; SPSS Statistics for Windows v26.1, Armonk, NY, USA).

Results

Baseline Anthropometric and Socioeconomic Characteristics of the Sample

The sample consisted of 301 subjects, 103 men and 198 women (respectively 34.2% and 65.8%). Most of the participants were recruited from Beirut and Mount Lebanon areas (34.9% and 51.8% respectively). Demographic, anthropometric, and clinical characteristics of the sample, and according to sex are shown in (Table 1). The mean age was 39.0 ± 13.4 years, comparable in males and females (p=0.95). Men had a higher BMI (27.1 ± 4.7 vs 24.5 ± 4.6 Kg/m², p<0.001), had more frequently hypertension and dyslipidemia (p=0.07 and p=0.037 respectively). 29 subjects reported to have

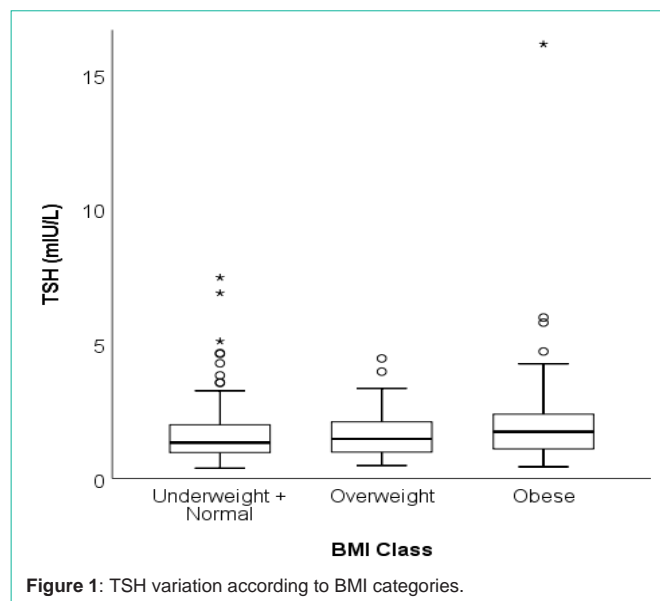


Figure 1: TSH variation according to BMI categories.

Table 1: Demographic, anthropometric and clinical characteristics of the total sample, and according to sex.

	Total Sample n=301	Men n=103	Women n= 198	P value
Age, years (SD)	38.98 (13.28)	39.06 (13.60)	38.94 (13.14)	0.95
BMI, Kg/m ² (SD)	25.36 (4.80)	27.09 (4.74)	24.46 (4.59)	<0.001
Underweight/Normal	52.8%	36.9%	61.1%	<0.001
Overweight	30.6%	43.7%	23.7%	
Obesity	16.6%	19.4%	15.2%	
SBP, mmHg (SD)	11.76 (1.36)	12.21 (1.34)	11.52 (1.31)	<0.001
DBP, mmHg (SD)	7.51 (1.07)	7.86 (1.13)	7.33 (0.99)	<0.001
Hypertension (%)	8.6	12.6	6.6	0.07
Dyslipidemia (%)	9.6	14.6	7.1	0.037

SBP and DBP are systolic and diastolic blood pressure, respectively. Continuous variables are expressed as mean +/- standard deviation (SD), categorical variables are expressed as frequency.

dyslipidemia of which 14 were treated by hypolipidemic agents and 26 reported to be hypertensive of which 21 treated by antihypertensive drugs.

Biological Parameters (TSH, FT4, FT3, and TT3)

The median and interquartile range (Q1-Q3) of the biological variables in the total sample and according to sex are shown in (Table 2). There was no significant difference in TSH and FT4 values between men and women (p= 0.494 and p=0.308 respectively). However, men had significant higher FT3 and TT3 values than women (p<0.001 and p=0.043 respectively).

Relationship between TSH and Other Variables

TSH was positively correlated with BMI (Spearman's rho 0.112, 95% CI -0.002; 0.222, p=0.053) but not with age (Spearman's rho -0.021, 95% CI -0.132; 0.095, p=0.723). Median TSH values were not influenced by gender (1.42 (IQR 1.03-2.25) for men vs 1.42 (IQR 0.94-2.08) for women, p=0.494). Figure 1 depicts TSH values across BMI categories, with medians (IQR) of 1.33 (0.95; 2.02), 1.47 (0.98; 2.1) and 1.74 (1.1; 2.4)µIU/mL respectively in normal/underweight, overweight, and obese BMI subjects. There was no correlation between TSH and FT4 (Spearman's rho -0.053, 95% CI

Table 2: Biological values in the total sample and according to sex.

	Total Sample	Men	Women	P value
TSH, $\mu\text{IU/mL}$	1.42 (0.99; 2.11)	1.42 (1.03; 2.25)	1.42 (0.94; 2.09)	0.494
FT4, pmol/L	14.8 (13.72; 16.53)	14.82 (13.79; 16.75)	14.79 (13.7; 16.46)	0.308
TT3, nmol/L	1.71 (1.56; 1.93)	1.8 (1.6; 1.96)	1.69 (1.55; 1.91)	0.043
FT3, pmol/L	4.53 (4.16; 5.01)	4.77 (4.36; 5.22)	4.46 (4.05; 4.88)	<0.001
TPOAb, IU/mL	6.93 (4; 10.19)	6.57 (4; 10.36)	7.16 (4; 10.11)	0.64
TgAb, IU/mL	10.18 (9; 14.95)	9 (9; 12.3)	10.31 (9; 17.8)	0.043

Data are expressed as median and its interquartile range (Q1–Q3)

Table 3: Multiple linear regression with TSH as a dependent variable.

	Unstandardized Coefficients		p-value	95.0% Confidence Interval	
	B	Std. Error		Lower Bound	Upper Bound
Constant	1.053	0.677	0.121	-0.280	2.385
Ln(FT4)	-0.778	0.243	0.001	-1.256	-0.301
TT3	0.163	0.115	0.158	-0.064	0.391
FT3	0.127	0.061	0.040	0.006	0.247
Ln(ATG)	0.052	0.034	0.134	-0.016	0.119
Ln(ATPO)	0.130	0.038	0.001	0.055	0.205
Age	-0.001	0.003	0.741	-0.006	0.004
Sex	-0.027	0.068	0.690	-0.160	0.106
Hypertension	-0.086	0.112	0.444	-0.307	0.135
Dyslipidemia	-0.005	0.104	0.962	-0.209	0.199
BMI	0.010	0.007	0.146	-0.003	0.023

Variables whose distribution deviates significantly from statistical normality (Figures QQ, Shapiro-Wilk tests) were log-transformed to normalize their distribution, and incorporated into the regression in a logarithmic form

Table 4: 97.5th quantile regression analysis with TSH as a dependent variable.

Parameter	Coefficient	Std. Error	p-value	95% Confidence Interval	
				Lower bound	Upper bound
(Intercept)	12.398	2.0333	0.000	8.396	16.400
FT4	-0.415	0.0878	0.000	-0.587	-0.242
TT3	-0.951	0.6335	0.134	-2.198	0.296
FT3	0.394	0.3384	0.245	-0.272	1.060
ATPO	0.079	0.0032	0.000	0.073	0.085
ATG	-0.003	0.0017	0.076	-0.006	0.000
Age	-0.026	0.0138	0.059	-0.054	0.001
BMI	0.067	0.0364	0.066	-0.005	0.139
Sex	0.391	0.3692	0.290	-0.335	1.118
Hypertension	-0.984	0.6129	0.109	-2.191	0.222
Dyslipidemia	-2.582	0.5693	0.000	-3.703	-1.462

Sex: 0 for males, 1 for females

Hypertension: 0 for no hypertension, 1 for the presence of hypertension

Dyslipidemia: 0 for absence of dyslipidemia, 1 for the presence of dyslipidemia

-0.171; 0.066, $p=0.357$) whereas a positive correlation was observed between TSH and TT3 (Spearman's rho 0.215, 95% CI 0.099; 0.324, $p<0.001$), FT3 (Spearman's rho 0.182, 95% CI 0.068; 0.295, $p=0.002$), TPOAb (Spearman's rho 0.205, 95% CI 0.087; 0.317, $p<0.001$), and TgAb (Spearman's rho 0.211, 95% CI 0.094; 0.321, $p<0.001$). TSH was higher in subjects with positive thyroid antibodies (median 2.16 (1.38-3.2) versus 1.37 (0.94-1.91) $\mu\text{IU/mL}$ respectively, $p<0.001$).

Finally, TSH was correlated with systolic blood pressure (Spearman's rho 0.125, 95% CI 0.013; 0.231, $p=0.031$) but not with diastolic blood pressure (Spearman's rho 0.075, 95% CI -0.040; 0.184, $p=0.197$). TSH was not significantly different in subjects with dyslipidemia compared to those without (median 1.42 (1.00-2.10) versus 1.34 (0.99-2.54) $\mu\text{IU/mL}$ respectively, $p=0.902$).

Multiple Linear Regression and Quantile Regression

A multiple linear regression analysis using Ln (TSH) as a dependent variable is shown in (Table 3). Only TPOAb, FT4, and FT3 were found to be independently associated with TSH ($p=0.001$, $p=0.001$ and $p=0.04$ respectively). A quantile regression analysis with TSH as a dependent variable was performed, taking 2 thresholds, the first one for the 2.5th percentile, and the second one for the 97.5th percentile (Table 4). For the 2.5th percentile cut-off, none of the predictors influenced the variation of TSH 2.5th percentile. For the 97.5th percentile cut-off, FT4, TPOAb, and the presence of dyslipidemia were independent predictors associated with TSH 97.5th percentile ($p<0.0001$ for the 3 variables), while age, BMI and TgAb values tended but did not reach statistical significance ($p=0.06$, $p=0.07$, $p=0.08$ respectively).

Discussion

The current study found an independent relationship between TSH and both FT3 and TPOAb while a negative independent correlation was noted between TSH and FT4. The negative association between TSH and FT4 is expected and explained by the negative feedback exerted by FT4 on the pituitary gland. In fact, TSH increases when FT4 decreases and vice versa in order to maintain a state of euthyroidism [17]. FT4 is then converted by type 1 and 2 deiodinases into FT3, which is the most active hormone at the receptor level [17]. The positive correlation we observed between TSH and FT3 was only described in a previous study performed on adults and was shown to be age dependent since when TSH levels increase, the FT3/FT4 ratio increases until age 40, but not in the older age groups [18]. Another pediatric study [19] demonstrated that both obese and non-obese children had elevated TSH and FT3, without an increase in FT4. This positive association between TSH and FT3 could be explained by the preferential effects of TSH on deiodinase stimulation, secretion and FT3 metabolism [19], a finding that is attenuated with the aging process. In addition, and similarly to previous studies [15,16,20], a positive relationship was found in the current study between TSH and the prevalence of TPOAb and TgAb, even if this independent association was only noted for TPOAb. Tipu et al, [20] found in an adult Pakistani population that TSH is higher in subjects who had positive antibodies compared to those who had negative ones. Also, a Saudi study [21] showed higher TSH levels when both antibodies are positive whereas in two other studies [15,22], this association was only found for TPOAb. Finally, Roos et al, [15] and Li [16] et al, showed that subjects with positive thyroid antibodies at baseline developed with time thyroid dysfunction more commonly than seronegative subjects.

We found a positive correlation between TSH and BMI, as well as a significant increase in TSH values among the 3 BMI classes (normal, overweight, and obese). BMI was also an independent predictor of the 97.5th percentile of TSH even if this association was at the limit of significance. A positive correlation between TSH and BMI was described mainly in obese subjects [23]. In addition, the loss of more than 10% of weight in 98 women over a duration of 6 months was followed by a significant decrease in TSH [24]. Finally, data analysis of 14 cohorts (from Europe, US, Australia, and South America) with 55,412 individuals with TSH levels within the normal range demonstrated that BMI did not differ between the lower (0.45–

1.49 mIU/L) and the higher TSH quartile (3.50–4.49 mIU/L) [25] suggesting that at least in non-obese subjects TSH did not differ within the reference intervals. The link between TSH and BMI is explained by the effect of leptin on TSH [23]. Leptin is shown to regulate the expression and secretion of Thyroid releasing hormone (TRH) via the stimulation of paraventricular nuclei and arcuate nucleus [10]. In addition, leptin increases the conversion of pro-TRH to TRH through an action on the activity of pro-hormones convertases (PC) 1/3 and 2 [10]. The subsequent increase in TSH secretion leads to an increase in FT4 level, which in turn induces thermogenesis and basal metabolism limiting further weight gain [10]. TSH is also shown to have a role in adipocyte differentiation and adipose tissue expansion, *in vitro* and *in vivo*, by binding to its receptors on adipocytes [23].

The current study did not show a significant relationship between age and TSH. However, age was an independent predictor of the 97.5th percentile of TSH even if this relationship was only at the limit of significance. A physiological increase in TSH levels with age has been reported in several studies worldwide [3,12,26]. This increase was demonstrated in the NHANES III study [12] and has been shown to occur regardless of the presence of thyroid diseases, or to drug intakes that might affect TSH and/or FT4 levels [27]. The absence of a positive correlation between age and TSH in our study can be explained by the age limit of 65 of our participants or to the small size of our population.

Also, a difference in TSH values according to sex was not demonstrated in our study even though the prevalence of TPOAb and TgAb was higher in women than in men (16.2% in women vs 6.8% in men). The relationship between TSH and sex is controversial in the literature. Hollowell et al, [12] found that TSH concentrations greater than 4.5 mUI/L were more commonly observed in women than in men and this was attributed to a higher prevalence of thyroid antibodies in women than in men [20,28], whereas at the opposite the Scottish TEARS study [6] reported that males had significantly higher median TSH compared to females. A third study did not find an association between TSH and sex [29]. Finally, the WHICKHAM survey showed that TSH levels did not vary with age in males but increased markedly in females after the age of 45 years, a rise that was abolished when persons with thyroid antibodies were excluded from the sample [30]. This discrepancy between our data and the literature could be explained by the small size of the current sample, the younger age of the participants since the prevalence of autoimmune disease increases after the 4th decade [31] or to ethnic differences.

There was a positive correlation between TSH and systolic blood pressure in univariate analysis that faded out after adjustment for other covariates. An association between clinical thyroid dysfunction and hypertension has been previously reported in both hyperthyroidism [32,33] and hypothyroidism [32] but also in subclinical hypothyroidism [34]. In adults [13] as well as in children and adolescents [35], the prevalence of hypertension increases with the linear increase in TSH values within the normal reference range. Hyperthyroidism has been shown to increase pulse pressure [33], while hypothyroidism primarily increases diastolic blood pressure [36]. This relationship could be explained by a decrease in vascular compliance, or by an increase in renal vascular resistance secondary to hormonal changes. The reason for our results could be ethnic

differences between populations.

A relationship between mean log (TSH) and dyslipidemia was not observed in the study. However, dyslipidemia was independently associated with TSH 97.5th percentile. A positive correlation between TSH and lipid parameters was described in several studies [14,37,38] This finding is explained by the fact that FT4 increases lipolysis, and facilitates cholesterol hepatic clearance [17]. In addition, TSH within the reference normal range is associated with central obesity, hyperglycemia, insulin resistance and high blood pressure [14], and therefore is considered as a new marker in the evaluation of the cardiovascular risk.

The strength of the study lies in the fact that all the biological parameters of the thyroid workup were measured in the same laboratory and using the same measurement method. In addition, samples were collected in the morning, avoiding nycthemeral cycle fluctuations. However, the main limitations of the study are the sample size that is relatively small, and the cross-sectional nature of the study.

Conclusion

In a healthy Lebanese population, an independent positive association between TSH, TT3, and TPOAb was noted, while a negative relationship was observed with FT4. No significant independent relationship was found between TSH and age, gender, BMI, SBP, DBP, and dyslipidemia. TPOAb and the presence of dyslipidemia are also associated with the TSH 97.5th percentile, confirming the fact that TSH may be a helpful test in the diagnosis and follow-up of auto-immune thyroid diseases. Additional studies should be performed to clarify more precisely the role of each of these factors in TSH variations.

Ethics and Consent to Participate

All procedures followed were in accordance with the ethical standards of the ethics committee of Hôtel-Dieu de France on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study had the approval of the ethics committee of Hôtel-Dieu de France hospital (CEHDF1524). All participants signed a written informed consent to participate in the study.

Availability of Data and Material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors have nothing to disclose.

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Author Contributions Statement

DM and AA have performed most of the volunteers’ recruitment and have contributed to the redaction of the manuscript, EN has contributed to the redaction of the manuscript, GS has performed the statistical analysis and participated in the redaction of the manuscript, and MHGY has conceived and designed the study, and has wrote the

manuscript. All the authors have read and approved the final version of the paper.

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