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Increase in Thyrotropin Is Associated with an Increase in Serum Prolactin in Euthyroid Subjects and Patients with Subclinical Hypothyroidism

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Abstract

Background: Prevalence and clinical significance of hyperprolactinemia in subclinical hypothyroidism have been reported in few studies. The upper limit of the normal range for TSH used to diagnose subclinical hypothyroidism is a matter of controversy. Some experts believe that the upper limit of the normal TSH range should be reduced from 4.2 to 2.5 mIU/L. Some evidence suggests a positive relationship between TSH > 2.5 mIU/L and cortisol as an indicator of metabolic stress. With this view prolactin as a stress hormone can be elevated in TSH >2.5 in comparison to TSH< 2.5. Hence the aim of this study was to evaluate the relationship between TSH and prolactin levels in the TSH range <10.

Methods: This cross-sectional study was performed on apparently healthy subjects with TSH<10 mIU/L. Subjects with the age of 18 to 35 years were enrolled. The sera were analyzed for prolactin, FT3, FT4, TSH, TPO-Ab and Tg-Ab.

Results: From the total number of 519 participants, in 65 subjects (12.5%) TSH was < 2.5. Seventy-nine subjects (15.2%) had TSH: 2.5-4.2 and 375 (72.3%) of the participants had TSH> 4.2 mIU/L. The mean age, weight and BMI of subjects in the three TSH groups were not significantly different. In the three TSH groups, the prevalence of hyperprolactinemia was zero, 3.8 and 30.7%, respectively. There was a positive and significant correlation between prolactin and TSH levels (r=0.613).

Conclusion: Hyperprolactinemia is common in patients with subclinical hypothyroidism (30.7%) and there is a positive correlation between TSH and PRL in subjects with TSH<10 mIU/l.

Keywords: Thyrotropin, Prolactin, Hypothyroidism

Conflicts of Interest: None declared
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Introduction

Hyperprolactinemia is the most prevalent hypersecretion syndrome in hypothalamic-pituitary axis. It has many

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↑What is "already known" in this topic:
Subclinical hypothyroidism is a common state, with a prevalence of 3-15% in adult populations. Upper limit of the TSH normal range, used to diagnose subclinical hypothyroidism, is a matter of controversy. Some experts believe that the upper limit of the normal range for TSH should be reduced from 4.2 to 2.5 mIU/L. Some evidence suggest a positive correlation between TSH > 2.5 mIU/L and cortisol as an indicator of metabolic stress. With this view, prolactin as a stress hormone can be elevated in TSH >2.5. Hence the aim of this study was to evaluate the relationship between TSH and prolactin levels in TSH range <10.

→What this article adds:
Hyperprolactinemia is common in patients with subclinical hypothyroidism (30.7%) and there is a positive correlation between TSH and PRL in subjects with TSH<10 mIU/l. It seams this relationship hold in the TSH range of 4.3-10 mIU/l, but not below, however this finding requires further scientific and practical evaluation.

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different causes, including medications, hypothyroidism, renal failure, and pituitary disorders. The release of prolactin from the lactotrope cells in the anterior pituitary depends on the dual regulation of hypothalamic peptides delivered through the hypothalamic-hypophyseal portal vessels. The dominant inhibitory s ignal prevents prolactin secretion by dopamine. The stimulatory signal of the hypothalamus increases the secretion of prolactin hormones through thyrotropin-releasing hormones (TRH) (1).

While the prevalence of hyperprolactinemia is reported to be 39% in overt hypothyroidism, its prevalence and clinical significance are unclear in subclinical hypothyroidism (SCH), and few studies have addressed these phenomena. Evidence shows that the rate of hyperprolactinemia is controversial in SCH and varies from 8% to 34% (2-5).

The prevalence of SCH is increasing due to the widespread use of laboratory tests to assess thyroid function. SCH or mild hypothyroidism is a common state, with a prevalence of 3-15% in adult populations (2, 6-8). Generally, SCH is more common in women than in men and in elderly than young people (2, 6). This syndrome, defined as an elevated serum TSH level with normal levels of free thyroxine (FT4) and free triiodothyronine (FT3). Since the definition of SCH is based on an increase in TSH level beyond the upper limit of normal, the cut-off point of upper TSH normal range plays a key role in determining the prevalence of this condition. Laboratories determine the normal range of TSH by determining cut-off points for the upper limit and lower limit of normal. The upper limit of normal TSH range is controversial. Some experts believe that the upper limit of normal TSH range should be reduced from 4.5-5 (current cut-off) to 2.5 mIU/L. In support of this hypothesis, careful follow-up of individuals with high normal TSH levels (>2.5) has demonstrated that TSH levels can predict overt hypothyroidism. Some evidence suggests a positive relationship between TSH level above 2.5 mIU/L and serum cortisol level in young healthy people, while an increase in cortisol is suggestive of metabolic stress in these subjects (9). In response to physiological or physical stress, the hypothalamic-pituitary-adrenal (HPA) axis activates and secretes stress hormones such as cortisol and prolactin (10).

With this view prolactin as a stress hormone can be elevated in TSH >2.5 mIU/L in comparison to TSH< 2.5 mIU/L in apparently healthy adults. Hence the aim of this study was to evaluate the relationship between TSH and prolactin levels in TSH range <2.5, 2.6 -4.2 and 4.3-10 mIU/L in a population of young, healthy adults.

Methods

This cross-sectional study was performed between November 2018 and August 2020, on healthy volunteers who referred for checkups and those who had been referred with a diagnosis of subclinical hypothyroidism to the endocrinology clinic in Zahedan, Southeastern Iran. Subjects with a minimum age of 18 years and a maximum of 35 years were continuously enrolled in the study by consecutive sampling. Participants with at least one of the exclusion criteria were excluded. Exclusion criteria were: age <18 or age >35 years; previously diagnosed thyroid problem or thyroid treatment, any thyroid nodule, ischemic heart disease, diabetes mellitus, neurologic diseases, acute illnesses, psychological problem, history of smoking (<1 year ago), using drugs affected on prolactin level or thyroid function test and oral contraceptive. Women with a history of pregnancy or lactation within the last year were also excluded from the study.

A questionnaire with these data was completed for each participant. The questionnaire contained sociodemographic status (age, lifestyle, sleep duration per 24 h, job), drug history, past medical and surgical history, history of thyroid disease or treatment for thyroid disease, history of stress or psychiatric disease.

Height in standing position using a stadiometer and body weight with minimal clothes using a digital scale was determined. Body Mass Index (BMI) was calculated as weight in kilograms, divided by height in square meters. Blood pressure in a sitting position after 15 minutes of rest with a manual sphygmomanometer was evaluated.

After obtaining the consent of the participants and measuring their height and weight, a physician evaluated the health status of the participants and study eligibility. All blood samples were taken between 8:00 and 9:00 AM; in the fasting state, three hours after waking up, after a 15-minute waiting period to avoid any stress-induced changes in PRL. Serum was stored at −70 C until hormone analysis was performed. The sera were analyzed for prolactin, FT3, FT4, TSH, TPO-Ab and Tg-Ab. The data were analyzed by running of quality control. Intra-assay and inter-assay imprecision for all analytes averaged less than 5%. FT4, FT3 and TSH using immunochemoluminescent assays by an automated analyzer were measured. The FT3, FT4, and TSH had a reference range of 2.3-4.2 pg/ml, 0.8-1.8 ng/dl, and TSH: 0.4-4.2 mIU/L, respectively, in the lab they were analyzed in. Participants with abnormal FT4 or FT3, TSH < 0.4 mIU/L or TSH > 10 mIU/L were excluded.

Finally, 519 subjects were included in the study. Participants were separated according to their TSH levels to three groups: TSH <2.5, TSH; 2.5-4.2 and TSH: 4.3-10.

Serum samples of patients with normal thyroid function or subclinical hypothyroidism who fulfilled the above criteria were evaluated to measure serum prolactin levels. Serum prolactin were measured by chemoimmuno luminance (CLIA) method. Coefficients variation of prolactin was 2.4%. The normal ranges of serum prolactin were 4–25 ng/mL in females and 4–20 ng/mL in males.

Serum samples of patients with hyperprolactinemia were assessed for macroprolactinemia using the polyethylene glycol (PEG) precipitation test to eliminate macroprolactin.The diagnosis of macroprolactinemia was made if post-PEG prolactin levels was less than 40% of pre-PEG prolactin (11).

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments. The Zahedan University Ethics Committee for Human Studies approved the protocol. All participants provided informed consent.

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Statistical analyses

The study variable described with descriptive statistics, like frequency, percentage and mean with standard deviation (SD) in normal and median with range and quartile in non-normal distributed variable. The normality of variables assessed with Shapiro–Wilk test and graphical approaches, like histogram and Q-Q plot. The mean difference of numerical variable in three TSH groups analyzed with One-way ANOVA and Kruskal-Wallis H test in normal and non-normal distributed variable, respectively. Also, Post-hoc comparison conducted based-on Bonferroni correction and we used Mann–Whitney U test in non-normal distributed variable. We used of Chi square and Fisher's exact test for testing the association between two categorical variables. The correlation between numerical variable assessed with Pearson and Spearman correlation coefficient in normal and non-normal distributed variable, respectively. The P-value lower than 0.05 considered statistically significant. All of analysis conducted with STATA v14 software.

Results

Out of 603 participants, 84 were excluded after the exclusion criteria were applied. This resulted in a final sample 519 subjects, of which 13.7% were men. The mean age of study participants was 26.4 years. Table 1 describes the demographic and biochemical characteristics of the study participants. Among all participants in the study, 22.7% of subjects had hyperprolactinemia, which was more common in women than men (24.1% vs 14.1%), a statistically significant difference (p:0.038).

As shown in Table 2, of the total number of participants in the study, for 65 subjects (12.5%) TSH was less than 2.5. Seventy-nine subjects (15.2%) had TSH: 2.5-4.2 and 375 (72.3%) of participants had TSH> 4.2 mIU/L. The mean of age, weight and *BMI* in the three TSH groups were not significantly different (p>0.05). Also, the mean of FT3 and FT4 values did not differ significantly between the three TSH groups (p>0.05). The prevalence of hyperprolactinemia in the three TSH groups was statistically significant (p<0.001), so that in the three TSH groups the prevalence was zero, 3.8 and 30.7%, respectively. The

Table 1. The socio-demographic and biochemical characteristics of the study participants

Variable	Mean (SD) Number (%)
Total number	519
Age (years)	26.4 (4.4)
Sex	
Male	71 (13.7)
Female	448 (86.3)
Marital status	
Married	474 (91.3)
Single	45 (8.7)
Work	
Student	20 (3.9)
Employee	66 (12.7)
No work	383 (73.8)
Free work	49 (9.4)
Smoker	
Yes	34 (6.6)
No	485 (93.4)
Exercise	
Rarely	440 (84.8)
Sometime	55 (10.6)
Regular	24 (4.6)
BMI (Kg/m2)	24.0 (2.8)
Systolic Blood Pressure (mmHg)	113.7 (12.2)
Diastolic Blood Pressure (mmHg)	69.4 (8.0)
Sleep duration per 24 h (hours)	7.6 (3.2)
TSH (mIU/L)	6.1 (2.5)
FT4 (ng/dl)	1.2 (0.33)
FT3 (pg/ml)	3.4 (1.4)
Anti-TPO titer (IU/ml) [a]	19.0 (1 to 2000)
Anti-Tg titer (IU/ml) [a]	71.0 (8 to 6500)
Positive Anti-TPO (>16 miu/l)	128 (24.7)
Positive Anti-Tg (>100 miu/l)	69 (13.3)
Prolactin (µg/l)	21.1 (12.1)
Hyperprolactinemia	118 (22.7)

a Median [range] of original data.

Table 2. Comparison between groups in demographic and biochemical data

Variable	Group A (TSH<2.5) (n=65)	P value [a]	Group B (TSH: 2.5-4.2) (n=79)	P value [b]	Group C (TSH: 4.3-10) (n=375)	P value [c]	P value [d]
Age (years)	26.2 (4.3)	1.0	26.5 (4.2)	1.0	26.4 (4.5)	1.0	0.915
BMI (Kg/m^2)	23.9 (2.6)	0.249	24.3 (2.5)	1.0	24.1 (2.9)	0.253	0.140
FT4 (ng/dl)	1.15 (0.33)	0.359	1.24 (0.35)	1.0	1.24 (0.33)	0.143	0.135
FT3 (pg/ml)	3.69 (3.73)	0.422	3.35 (0.51)	1.0	3.33 (0.51)	0.172	0.159
Anti-TPO titer (IU/ml) *	9.0 (5.5-13.5)	0.650	9.0 (4.0-14.0)	0.002	12.0 (6.0-23.0)	0.010	0.001
Anti-Tg titre (IU/ml) *	54.0 (34.0-76.5)	0.616	55.0 (42.0-76.0)	0.016	67.0 (39.0-92.0)	0.006	0.003
Prolactin (ng/ml)	11.2 (5.4)	1.0	12.3 (5.9)	<0.001	24.7 (12.0)	<0.001	<0.001
Hyperprolactinemia; n (%)							
In total	0 (0.0)	0.252***	3 (3.8)	<0.001**	115 (30.7)	<0.001**	<0.001**
In Male	0 (0.0)	0.266***	3 (20.0)	0.693***	7 (14.9)	0.583***	0.451***
In female	0 (0.0)	NA	0 (0.0)	<0.001***	108 (32.9)	<0.001**	<0.001**

All variance were compared between the groups using ANOVA and Pos-Hoc with Bonferroni correction. p-value < .05 was regarded as significant.
[a]. p value between A and B groups. [b]. p value between B and C groups. [c]. p value between A and C groups. [d]. p value between three groups.
*Median (IQR) of non-parametric data between the groups were compared using Kruskal–Wallis H test and Mann–Whitney U test. ** P-value based-on Chi-square test.
*** P-value based-on Fisher exact test.

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Table 3. Correlations between prolactin and other variables among study participants

		Age	Weight	BMI	TSH [a]	FT4	FT3	Anti-TPO [a]	Anti-Tg [a]
Prolactin	Correlation coefficient	-0.018	-0.037	0.005	0.613	0.054	-0.054	0.130	0.112
	P-value	0.682	0.403	0.903	<0.001	0.216	0.216	0.003	0.011

Pearson correlation was used for correlation between prolactin and all normally distributed variables.
aSpearman's correlation is used for correlation between prolactin and non-parametric variables.

prevalence was significantly higher in the C group than the other two groups (p<0.001). The serum prolactin level in the C group (TSH: 4.3-10) was significantly higher than the other two groups (Fig. 1).

As shown in Table 3, no significant correlation was found between prolactin levels with age, weight, BMI, FT4 and FT3 (p>0.05). While there was a positive and significant correlation between prolactin and TSH value (r=0.613; p<0.001) (Fig. 2).

Discussion

In the present study, we examined serum prolactin in three groups of subjects based on their TSH levels. These data indicate that the serum prolactin level is elevated in 30.7 percent of patient with subclinical hypothyroidism and there was a positive and significant correlation between prolactin and TSH.

Various degrees of hyperprolactinemia have been reported in patients with overt hypothyroidism. However, the results vary regarding the prevalence and extent of hyperprolactinemia in patients with SCH. In a study of 66 patients with SCH, Meier et al. reported the prevalence of hyperprolactinemia to be 19% (12). Also, Notsu et al. measured the prolactin level in 15 healthy individuals (control group) and 74 patients with Hashimoto's thyroiditis (42 cases of euthyroid, 18 cases of SCH, and 14 cases of overt hypothyroidism). In this study, the prevalence of hyperprolactinemia was reported to be 42% in patients with overt hypothyroidism, 11% in patients with SCH, and 14% in patients with euthyroidism (13). Similar findings were reported in a study by Goel et al., in which 8% of patients with SCH had hyperprolactinemia. Also, a positive correlation was reported between TSH and prolactin levels (3). In another study from India, hyperprolactinemia was reported in 42.19% of patients with overt primary hypothyroidism and 34.93% of patients with SCH. In this study, a positive relationship was reported between prolactin and TSH levels, especially TSH levels above 7.5 (4). In another study from Iran on 481 patients with SCH, 20.4% had hyperprolactinemia (5).

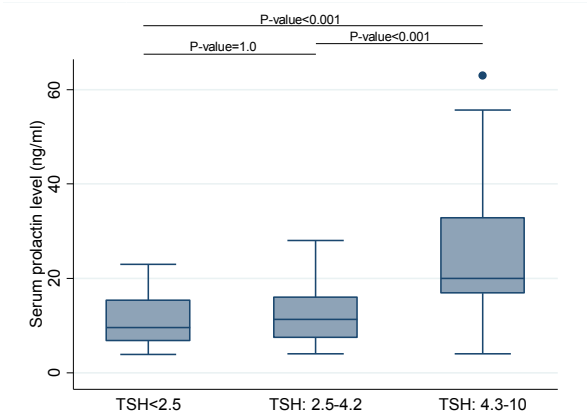

Fig. 1. Distribution of prolactin level in three group subjects.

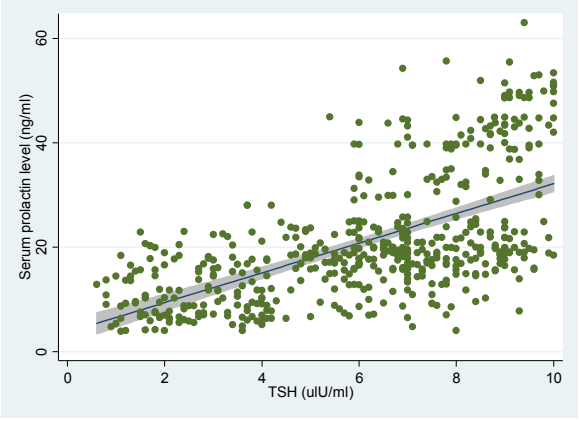

Fig. 2. The correlation between prolactin level and serum TSH of the participants.

The pathophysiological mechanism and leading cause of hyperprolactinemia in primary hypothyroidism is due to the effects of TRH (14). In this situation, TRH increases in response to decreased serum levels of circulating thyroid hormones. The increased TRH level causes thyrotropic and lactotropic cell hyperplasia, leading to high basal prolactin levels and an intensified prolactin response to intravenous TRH (12, 13, 15). Another factor that increases blood prolactin levels in patients with hypothyroidism is the reduced renal clearance. Decreased sensitivity of prolactin secretion to dopamine has also been observed in these patients, which may contribute to hyperprolactinemia (16). Also, estrogen may be an important factor. Evidence shows that the prevalence and degree of hyperprolactinemia are higher in women than men because estrogen increases the prolactin response to TRH (12).

In normal populations, the TSH distribution curve is skewed towards the lower limit of the normal reference range. The serum TSH distribution curve is not Gaussian and there is a tail end at the upper limits of normal TSH range. If the TSH distribution is generalized to be Gaussian, then the upper limit for the 97.5th percentile will be 2.5 mIU/L (17). As previously explained, the definition of SCH depends on the definition of the normal range of TSH. Most laboratories have now set the upper limit of normal TSH at 4.2-5, while some experts believe that it should be reduced to 2.5. This is because the sensitivity of laboratory tests has increased in recent years, and the study populations in the reference studies, used to determine the normal range of TSH, included people with thy-

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roid disorders, and most people with TSH levels of 3.5-4 were positive for thyroid antibodies (18-23). Also, some studies have shown that if these individuals are followed-up, most of them with TSH levels above 2.5 will progress to hypothyroidism in later years (24-26). On the other hand, the use of 2.5 mIU/L as the upper limit of normal for serum TSH will increase substantially the number of patients in the general population diagnosed with subclinical hypothyroidism.

Interestingly, a study suggest a positive relationship between TSH > 2.5 mIU/L and cortisol in apparently healthy young individuals. This study suggest that TSH levels > 2.5 mIU/L may be abnormal and herald a pathologic disorder (9). In response to any kind of stress, cortisol is produced and secreted by adrenal glands. On the other hand, both clinical and subclinical hypothyroidism can be associated with mild metabolic stress, and this may be another reason for the positive correlation between TSH and cortisol. Metabolic stress can increase the production and secretion of stress hormones. From this point of view, other stress hormones may also be increased as a result of metabolic stress in the upper half of the normal range. It is clear that prolactin secretion is dramatically affected by stress (10, 27). Therefore, there may be a positive relationship between TSH and PRL in upper normal range. But this study showed a positive relationship between TSH and serum PRL levels in patients with subclinical hypothyroidism. No relationship was found between prolactin and TSH in its normal range (< 4.2 mIU/L). This may be due to the fact that prolactin is not as sensitive to low stress levels as cortisol.

Conclusion

In conclusion, these data, demonstrate hyperprolactinemia is common in patients with SCH and there is positive correlation between TSH and PRL in subjects with TSH<10 mIU/l. It seams this relationship hold in the TSH range of 4.3-10 mIU/l, but not below, however this finding requires further scientific and practical evaluation. More prospective studies are needed in patients with untreated SCH to determine the impact of persistent hyperprolactinemia in these patients.

Acknowledgement

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Ethical approval

We conducted study procedures following the ethical principles of the research committee (either organizational or national). In addition, we respected the principles of the 1964 Helsinki declaration and its amendments. The ethics committee of the Zahedan University confirmed the study protocol. Informed consent was obtained from all participants.

Conflict of Interests

The authors declare that they have no competing interests.

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