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Assessment of subclinical hypothyroidism for a clinical score and thyroid peroxidase antibody: a comparison with euthyroidism grouped by different thyroid-stimulating hormone levels

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Abstract

Background: Subclinical hypothyroidism (SCH) might have many symptoms of hypothyroidism. The controversy appears to lower the level of thyroid-stimulating hormone (TSH) and group subjects with TSH of more than 3 or even 2.5 mIU/L as SCH subjects.

Objectives: To assess SCH subjects both clinically using Zulewski clinical score and biochemically and to evaluate whether the euthyroid subjects with high-normal TSH (HNT) have any clinical symptom or subnormal biochemical finding.

Methods: A prospective cross-sectional study of 233 subjects, 67 with SCH and 166 euthyroidism, was conducted. Euthyroid subjects were divided according to the level of TSH as HNT (>2.5 mIU/L) and low-normal TSH (0.5–2.5 mIU/L). The subjects were examined for clinical feature including Zulewski clinical score and biochemical evaluations including thyroid peroxidase antibody (TPO-Ab) titer. The comparisons between groups were assessed using independent sample *t* test, and correlations between variables were evaluated using Pearson correlation.

Results: A significantly higher clinical score and higher frequencies of symptoms were found in the SCH group compared to the euthyroid group. The most frequent symptom was fatigue. Euthyroid subjects with HNT were found to have higher TPO-Ab titers than those with low-normal TSH, $P < 0.05$. The Zulewski clinical score was positively correlated with TSH and TPO-Ab titer but negatively correlated with the FT4 level, $P < 0.05$.

Conclusions: Zulewski clinical score is higher in SCH subjects compared to euthyroid subjects and can aid in assessing SCH subjects. A significant correlation exists between Zulewski clinical score and each of the TSH, FT4, and TPO-Ab titer levels. The frequency of TPO-Ab positivity is high in SCH. Additionally, euthyroid with higher TSH levels has higher level of TPO-Ab titer but not higher clinical score.

Keywords: anti-thyroid peroxidase antibody; clinical feature; euthyroid; subclinical hypothyroidism; zulewski score

Subclinical hypothyroidism (SCH) is a mild form of thyroid failure. The presence of raised serum thyroid-stimulating hormone (TSH) in combination with a serum-free T4 level that is within the population reference range is sufficient to diagnose this condition [1]. SCH is more widespread than overt hypothyroidism, and so screening and early diagnosis

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are important [2]. There are risks of all-cause mortality, cardiovascular event, atrial fibrillation, left ventricular diastolic dysfunction, and pregnancy outcome in SCH, and a few studies revealed improvement after treatment with levothyroxine [3–6]. Thus, some physicians think that it is better to treat SCH subjects to prevent further elevation of serum TSH and its associated effect [7].

Although studies have revealed that SCH does not create a specific symptom, a substantial number of these patients complain of some hypothyroid features such as fatigue, muscle cramps, cold intolerance, depressive symptoms, reduced quality of life, cognitive function, and memory loss [8, 9]. Apart from biochemical results, the decision for treating such patients is determined by the physician's assessment of the clinical symptoms and risk factors. Therefore, the existence of a symptom-rating scale is important to assess the clinical feature and the potential effect of treatment. The clinical score can judge the individual severity of metabolic hypothyroidism [10]. For this purpose, a clinical score was set by Zulewski et al, who reevaluated the classically used hypothyroid clinical features in regard to current laboratory investigations [9].

The most common cause of SCH is autoimmune thyroiditis with its association of raised anti-thyroid peroxidase antibodies (TPO-Abs) [7]. This antibody can also be found in a number of euthyroid subjects; these subjects might be at a higher risk of developing SCH [10].

Additionally, previous study correlated the presence of this antibody with hyperprolactinemia [11]. Hyperprolactinemia is a usual finding in frank hypothyroidism, and mild prolactin elevation is found in SCH, particularly in those with higher TSH values [10, 12, 13]. A different mechanism is stated to be responsible for the development of hyperprolactinemia in hypothyroidism [14, 15].

Recently, a controversy developed about the TSH level in SCH subjects [7, 14]. Euthyroid subjects with a serum TSH level of more than 3 mIU/L have higher TPO-Ab titers and higher rates of progression to overt hypothyroidism, although their TSH is within the reference limit [12]. Thus, reducing the upper limit of the normal TSH reference range from 5 to 3 or even 2.5 mIU/L has been suggested, and this affects the number of cases defined as SCH [12, 13, 16].

As subjects with SCH develop frank hypothyroidism at a rate of 5% every year and euthyroid subjects have a risk of developing SCH, it is valuable to recognize the subjects at risk [14, 17]. SCH subjects with high titers of anti-TPO antibodies are more likely to progress to overt hypothyroidism [2].

Until now, no study exists on the clinical and biochemical evaluation of SCH and euthyroid subjects in Sulaymaniyah city, Iraq; and to the best of our knowledge, prospective studies comparing SCH to euthyroid subjects or comparing euthyroid subjects with various TSH statuses for clinical and biochemical basis are scant. Few studies exist worldwide to assess SCH subjects for Zulewski clinical score.

The present study aimed to assess the frequency of clinical signs and symptoms, TPO positivity, and hyperprolactinemia in SCH subjects in Sulaimaniyah city and compare them with euthyroid subjects to find the relationship between the Zulewski clinical score and serum FT4, TSH, and TPO-Ab levels and to know whether Zulewski clinical score is helpful in the diagnosis of SCH subjects; evaluate whether euthyroid subjects with high-normal TSH (HNT) have a higher frequency of clinical symptoms, TPO-Ab positivity, and hyperprolactinemia than euthyroid subjects with low-normal TSH; and find the subjects who have risk factor for developing SCH (higher TPO-Ab), in whom more frequent follow-up with the thyroid function test was needed.

Methods

Patients

A total of 252 study subjects were evaluated prospectively for biochemical and clinical parameters from June 2017 to February 2018; the flow diagram of the studied participants is shown in **Figure 1**. The required sample size was calculated from the standard deviation of TSH (2.015) and frequency of clinical symptoms in SCH subjects from the previous studies, which indicated the requirement of at least 62 participants with 5% margin of error at 95% confidence intervals.

The study subjects included those who visited Shar Hospital/Sulaimaniyah city for their health check-up. Normal healthy hospital employees, friends, and relatives were also included. These subjects were sent for thyroid function tests and other required investigations, asked about hypothyroid symptoms, and examined for signs of hypothyroidism. After exclusion of 19 subjects, who had at least one of the exclusion

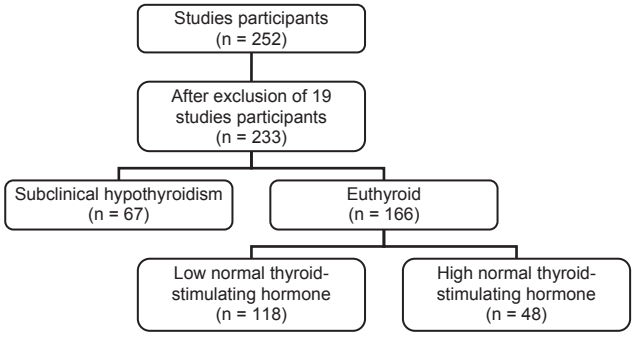

Figure 1. Flow diagram of the studied participants.

criteria, the subjects were separated into 2 groups by their serum TSH level from blood that was drawn by the researcher. The groups included 67 SCH subjects (SCH defined as having 2 laboratory readings of elevated serum TSH and normal serum FT4 level that had to be 2 weeks apart) and 166 euthyroid subjects (normal TSH and FT4 levels); the euthyroid subjects were further divided into euthyroid subjects with HNT (TSH > 2.5 mIU/L) and euthyroid subjects with low-normal serum TSH (TSH value of 0.5–2.5 mIU/L).

The inclusion criterion was normal healthy adults in the age range of 17–70 years. Exclusion criteria included those who have serum TSH <0.5 mIU/L or TSH >10 mIU/L, those with abnormal FT4, those who were previously diagnosed as having a thyroid problem, presence of a thyroid nodule, those already on any sort of treatment for thyroid disease, inpatients and those with any chronic disease (e.g., diabetes) or those with severe acute illnesses, and those with any medical, physiological, or pharmacological cause of hyperprolactinemia.

The study obtained approval from the Ethical Committee of the College of Medicine, University of Sulaimani (meeting no. 51 on 23/5/2017). The written informed consents were taken from all study participants. A detailed questionnaire was filled out for each participant. The questionnaire contained sociodemographic status (age, height, weight, waist circumference, and lifestyle), history of systemic diseases, thyroid disease, drug, and surgical history. The subjects were examined for Zulewski clinical score [9] by the authors, which included 14 symptoms and signs of hypothyroidism. After assessment of the Zulewski score, the form was filled out by the authors and the sums of the score were calculated later for each participant. Apart from Zulewski signs and symptoms, the patient was asked for other common hypothyroid symptoms that included fatigue, muscle cramp, menstrual disturbance, cold intolerance, memory loss, alopecia, hirsutism, and galactorrhea.

Laboratory measurement and reference ranges

The participants were asked to fast on the day of investigations and to come in the morning at 9–11 am for blood drawing. The blood samples were centrifuged, and the serum was separated; the sera were analyzed for FT3, FT4, and TSH. A part of the serum was separated and stored at deep freeze at −70°C. Anti-TPO antibody and serum prolactin were determined on the stored serum sample. All biochemical tests were analyzed by the recent immunoassay method, which is electrochemiluminescence immunoassay, with the use of the same type of kits from Roche Diagnostics GmbH, Germany, and using the same device the Cobas e 411 analyzer (Hitachi High-Technologies Corporation, Germany). The data were analyzed with running of quality control.

The FT3, FT4, and TSH have a reference range of 2.0–4.4 pg/ml, 0.93–1.70 ng/dl, and 0.27–4.2 mIU/L, respectively, in the laboratory they were analyzed in. Prolactin up to 15 ng/ml for males and up to 23 ng/ml in females and TPO-Ab up to 34 IU/ml were regarded as normal.

Term definition

Subjects with subclinical hypothyroid were defined as subjects who had elevated TSH (>4.2 and up to 10 mIU/L) in the presence of FT4 within the reference range. Subjects with euthyroid were defined as subjects with TSH and FT4 within the reference range. Subjects with euthyroid with low-normal TSH were defined as euthyroid subjects with TSH values of 0.5–2.5 mIU/L. Subjects with euthyroid with HNT were euthyroid subjects with TSH values of 2.5–4.2 mIU/L. Subjects with hyperprolactinemia were defined as having a prolactin level of more than the upper limit for males and females. Subjects with thyroid peroxidase positivity were defined as having TPO-Ab above 34 IU/ml.

Statistical method

Test of normality was done using the Kolmogorov–Smirnov test. The variables that had normal distribution were presented with mean (standard deviation) and variables that were not within normal distribution were presented with median (range). The percentages of clinical symptoms, TPO-Ab positivity and hyperprolactinemia were assessed between groups using the chi-square test. The median values of the TPO-Ab level, s.TSH, s.FT4, s.prolactin, and clinical score were analyzed for each different group, and the median values were compared between the groups by the Man–Whitney *U* test. $P < 0.05$ was regarded as statistical significance. The normally distributed variables were compared using the independent sample *t* test. The associations between skewed and normally distributed variables were assessed using Spearman's correlation and Pearson correlation, respectively. The pairwise exclusion was used for missing value.

Multiple regression analysis was performed to predict Zulewski clinical score as a dependent variable from predictor variables (age, body mass index (BMI), waist circumference, TSH and TPO-Ab titer). The variables not normally distributed were transformed and skewness corrected. The multiple regression analysis was performed on transformed variables.

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Results

From 233 participants, 67 were defined as SCH subjects and 166 were defined as euthyroid subjects. The euthyroid subjects were further subdivided into euthyroid with low-normal TSH (LNT) patients (n = 118) and euthyroid with HNT patients (n = 48). The frequency of SCH among normal subjects who volunteered for the study was 14.79%.

Sociodemographic status for the study participants is shown in **Table 1**. The median age is 31.5 years with an age range of 18–70 years; 80.69% of the participants were female.

The comparison of characteristics and biochemical and clinical data between SCH and euthyroid subjects is shown in **Table 2**. Mean and median TSH in SCH subjects were 6.23 (±1.69) and 5.89 (6.54), respectively, while in euthyroid subjects, those were 2.03 (±0.89) and 1.95 (4.09), respectively. When the types of menstrual disturbances were assessed, the rate of heavy menstrual period among SCH groups was found to be highest when compared to that among euthyroid subjects, $P < 0.001$.

There were no statistically significant differences in sex and age between SCH and euthyroid groups. The serum TSH and TPO values were significantly higher in the SCH group compared to those in the euthyroid group, with a significantly higher rate of TPO positivity among SCH subjects. However, hyperprolactinemia was comparable between the 2 groups, and the difference in prolactin levels was not significant. Regarding the clinical data, the SCH group had a significantly higher frequency of hypothyroid symptoms and Zulewski score than euthyroid subjects ($P < 0.05$). When each component of the Zulewski clinical score was analyzed individually, paresthesia was the most frequent symptom (50.7%), followed by dry skin (28.4%), increased weight (26.9%), and constipation (25.3). Among the physical signs of Zulewski, slow movement was the most frequent sign (20.9%).

The TPO-Ab titer and Zulewski score were compared between SCH and euthyroid subjects in 2 different age groups: age less than 50 years and age more than 50 years. These comparisons are shown in **Figures 2** and **3**, respectively. Unlike younger age group, no significant differences exist between Zulewski score between SCH and euthyroid subjects in the age group of more than 50 years. When parameters were compared between the 2 different age groups of the same thyroid status, apart from lower FT3 and prolactin in the older age group; $P = 0.05$, no significant differences in other parameters were observed between the 2 age groups.

In **Table 3**, a comparison between euthyroid with LNT and HNT is demonstrated. There is higher TPO positivity in HNT in comparison to LNT, but the difference is not statistically significant. The TPO titer and TSH are significantly higher, and FT4 is significantly lower in the HNT euthyroid group compared to that in the LNT euthyroid group. The differences in clinical data between the 2 groups are not statistically significant, and Zulewski score is the same for both groups.

When TPO-positive and negative subjects were compared, no significant difference was observed between them in sex, prolactin level, and hyperprolactinemia. However, when clinical parameters were examined between the 2 groups, the occurrences of goiter, menstrual disturbance, and cold intolerance were higher in the TPO-positive group than those in the TPO-negative group ($P < 0.05$).

Correlations between most of the variables were assessed using Spearman's correlation; some of these correlations are demonstrated in **Table 4**.

Table 1. Sociodemographic state of the study participants

Parameter	Frequencies, n (%)
Age (years)†	31.5 (52)
Age range (years)	18–70
Sex	
Female	188 (80.69)
Male	45 (19.31)
Body mass index‡	27.28 [4.84]
Waist circumference (cm)‡	84.88 [12.14]
Smoker (yes%)	20 (8.6)
Education	
Educated	155 (90.1)
Illiterate	17 (9.9)
Work	
Student	34 (14.8)
No work	67 (29.1)
Employee	85 (37)
Free work	44 (19.2)
Marital status	
Married	138 (60)
Single	88 (38.3)
Divorced	4 (1.7)
Exercise	
Rarely	99 (44.4)
Some time	82 (36.8)
Daily	42 (18.8)

All non-descriptive data are presented as number (%)
†The parameters not normally distributed are expressed as median (range)
‡The normally distributed data are expressed as mean [±SD]
SD, standard deviation

Table 2. Characteristics of SCH and euthyroid subjects according to biochemical and clinical data. Bold numbers indicate significant *P*

Parameters	SCH (n = 67), mean (±SD)	Euthyroid (n = 166), mean (±SD)	*P*
Age (years)†	34 (52)	31 (53)	0.368
Sex (female)	85.1%	78.9%	0.281
Marital status (married)	68.3%	56.9%	0.289
BMI (kg/m^2)‡	27.95 [4.35]	27.00 [5.01]	0.183
Waist circumference (cm)‡	86.77 [13.19]	84.12 [11.66]	0.202
Biochemical data			
TSH (mIU/L)†	5.89 (6.54)	1.95 (4.09)	**<0.001**
FT4 (ng/dl)†	1.15 (11.35)	1.23 (1.22)	**<0.001**
FT3 (pg/ml)‡	3.39[±0.46]	3.43[±0.39]	0.733
TPO-Ab titer (IU/ml)†	15.22 (606)	6.64 (504.6)	**<0.001**
Prolactin (ng/ml)†	17.29 (45.13)	15.01 (48.43)	0.283
TPO positivity	43.8%	10.2%	**<0.001**
Hyperprolactinemia	27%	28%	0.873
Zulewski score†	3 (5)	2 (6)	**<0.001**
Clinical data			
Goiter	15.1%	4.9%	**0.017**
Menstrual disturbance	51.2%	39.7%	0.193
Decreased appetite	29.8%	19.9%	0.126
Fatigue	80.3%	58.2%	**0.002**
Muscle pain	62.3%	38.9%	**0.002**
Memory loss	50.8%	43%	0.304
Alopecia	46.6%	40.4%	0.42
Hirsutism	24.5%	22.1%	0.723
Cold intolerance	37.3%	23.8%	**0.05**
Galactorrhea	3.6%	1.9%	0.473

†The parameters not normally distributed are expressed as median (range), and the groups were compared using the Mann–Whitney test
‡The normally distributed data are expressed as mean [±SD], the comparison between groups are analyzed using independent sample *t* test, all non-descriptive data are presented as %, and chi-square is used to find significance for frequencies
BMI, body mass index; FT3, free triiodothyronine; FT4, free thyroxine; SCH, subclinical hypothyroidism; SD, standard deviation; TPO-Ab, anti-thyroid peroxidase antibody; TSH, thyroid-stimulating hormone

Pearson correlations were assessed for normally distributed data. There was a significantly negative correlation between age and each of the FT3 and prolactin hormone levels (age and FT3: $r = -0.247$, $P = 0.03$; age and prolactin: $r = -0.274$, $P < 0.001$). However, significant correlations were not observed between prolactin and TSH or TPO. The pairwise exclusion was used for missing value.

A multiple regression analysis was run to predict Zulewski clinical score from age, BMI, waist circumference, TSH level, and TPO-Ab titer. All non-parametric variables were transformed (either log or square root transformation), and the skewness was corrected. The multiple regression model statistically significantly predicted Zulewski clinical score ($F = 5.58$, $P < 0.001$, and adjusted $R^2 = 0.125$). TSH and BMI added statistically significantly to the prediction ($P < 0.001$ and $P < 0.05$, respectively). TSH has a regression coefficient of 0.361 and a standard error of 0.108.

When the frequency of Zulewski score level was assessed between SCH and euthyroid subjects, it was found that the number of SCH subjects with the intermediate score (3–5) that is suggestive of mild hypothyroidism was 42%, while 80% of euthyroid subjects had a normal score (of less than 3). The subject with SCH has 2.9 time (odds ratio = 2.89) higher risk of having abnormal Zulewski score (intermediate score).

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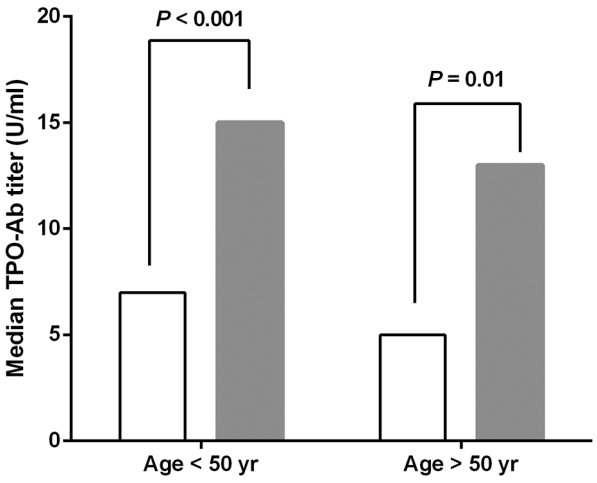

Figure 2. Comparison of median TPO-Ab titer on euthyroid (white bars) and subclinical hypothyroidism (gray bars) between 2 different age groups.

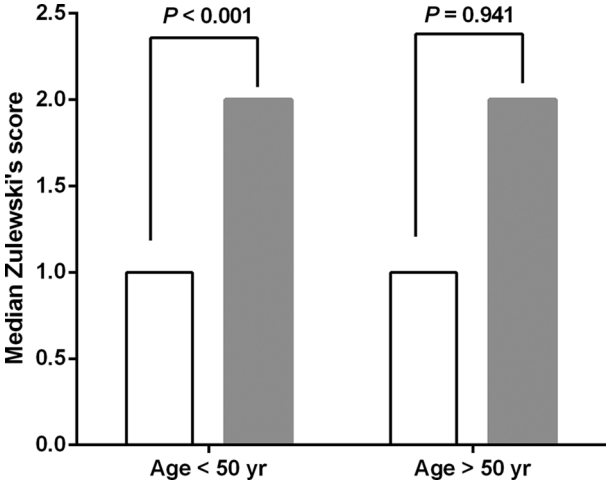

Figure 3. Comparison of median Zulewski score on euthyroid (white bars) and subclinical hypothyroidism (gray bars) between 2 different age groups.

Table 3. Characteristics, laboratory findings, and Zulewski scores among the 2 euthyroid groups with different TSH levels. Bold numbers indicate significant *P*

Parameter	Euthyroid with LNT (TSH 0.5–2.5) (n = 118)	Euthyroid with HNT (TSH > 2.5) (n = 48)	*P*
Age† (years)	30 (52)	33 (52)	0.373
BMI‡	26.99 [4.96]	27.23[5.12]	0.782
Waist circumference‡	84.13 [±11.92]	84.69 [±10.76]	0.812
Biochemical data			
TSH (mIU/L)†	1.6 (2.17)	3.15 (1.7)	**<0.001**
FT4 (ng/dl)†	1.24 (1.22)	1.21 (0.64)	**0.046**
FT3 (pg/ml)‡	3.48 [±0.39]	3.26 [±0.39]	**0.08**
TPO-Ab titer (IU/ml)†	5.81 (265.6)	10.23 (504.6)	**0.036**
Prolactin (ng/ml)†			
TPO positivity	14.8 (48.43)	15.54 (35.77)	0.986
Hyperprolactinemia	9 (7.6%)	8 (17.4%)	**0.065**
	37 (31.4%)	9 (20.5%)	0.365
Zulewski score†	2 (7)	2 (7)	0.149

†The parameters not normally distributed are expressed as median (range), and the groups are compared using the Mann–Whitney test
‡The normally distributed data are expressed as mean [±SD], the comparison between groups is analyzed using the independent sample *t* test, all non-descriptive data are presented as %, and chi-square is used to find significance for frequencies
BMI, body mass index; FT3, free triiodothyronine; FT4, free thyroxine; HNT, high-normal TSH; LNT, low-normal TSH; SD, standard deviation; TPO-Ab, anti-thyroid peroxidase antibody; TSH, thyroid-stimulating hormone

Discussion

In this study, SCH subjects were reported to have 1-point higher Zulewski clinical scores than euthyroid subjects. A good correlation between the Zulewski clinical score and TSH was observed as well, and TSH positively predicted Zulewski score. This finding is supported by previous studies including Colorado [18], Swiss [9], Reuter [19], and Cooper [20], in which the SCH group more frequently presented with hypothyroid symptoms than euthyroid subjects. The Colorado study also revealed a clear correlation between a number of symptoms and elevated TSH [18]. Zulewski et al found an

Table 4. Correlation between studied variables using Spearman correlation

Correlations	Age (years)	TSH level (mIU/L)	FT4 level (ng/dl)	Median TPO-Ab titer (IU/ml)	Zulewski' score
Age (years)		0.027	–0.240**	0.126	0.158*
TSH level (mIU/L)	0.027		–0.275**	0.319**	0.287**
FT4 level (ng/dl)	–0.240**	–0.275**		–0.203**	–0.149*
Median TPO-Ab titer (IU/ml)	0.126	0.319**	–0.203**		0.200**

*Correlation is significant at the 0.05 level (2-tailed)
**Correlation is significant at the 0.01 level
FT4, free thyroxine; TPO-Ab, anti-thyroid peroxidase antibody; TSH, thyroid-stimulating hormone

obvious correlation between the score and FT4 and TSH in SCH subjects [9]. However, a study by Goel et al. showed no significant difference in clinical presentation between the SCH group and the euthyroid group [21]. In this study, fatigue, muscle cramp, and cold intolerance were the most frequent symptoms in SCH. In a study of SCH women by Kong et al. [22], the most frequent symptom was fatigue (83%). Although the percentage of some clinical symptoms, especially fatigue, was also high in euthyroid subjects in the present study, these clinical features were significantly higher in SCH subjects than in euthyroid subjects.

In the present study, a higher mean TPO-Ab titer was found in SCH subjects than that in euthyroid subjects with a similarly higher rate of TPO positivity among the SCH group. The mean TPO value among TPO-positive subjects was 190.88 IU/ml (±170.59). We reported 10.2% TPO positivity among the euthyroid group. This is in accordance with the study by Roos et al. who evaluated 2394 euthyroid subjects for TPO positivity, of which 8.4% were TPO positive [23].

In our study, higher titers of TPO-Ab and lower serum FT4 level were detected in euthyroid subjects with HNT compared to those with LNT. This might suggest that the presence of higher TPO-Ab titer is in part responsible for the decrease in FT4 and its concomitant increase in s.TSH, even if the TSH is within the reference normal limit. This could be supported by the finding of a positive correlation between TPO-Ab titer and TSH level and a negative correlation between TPO-Ab titer and FT4 level demonstrated in the present study, which is in line with previous studies [23, 24]. The study of Roos et al documented a higher prevalence of TPO positivity among the higher quartile for TSH in the euthyroid range [23]. In a study by Li et al., a significantly higher TSH value was reported in patients who were positive for both TPO-Ab and thyroglobulin antibody than in populations with negative antibodies or only 1 positive antibody [25].

The frequency of hyperprolactinemia in the SCH group of the present study is 27%, which is approximately near to the finding of 20.4% by study in Iran [26]. In a study in India, 34.93% of SCH subjects had hyperprolactinemia. However, when hyperprolactinemia was evaluated among the SCH groups with higher TSH (> 7.5), the percentage of hyperprolactinemia was raised to 49% [11]. Other studies reported lower rates of hyperprolactinemia (19% and 8%, respectively) [10, 21]. We found a comparable result of hyperprolactinemia between SCH and euthyroid subjects, which is inconsistent with other studies in which a higher rate of hyperprolactinemia was reported in SCH patients compared to euthyroid subjects. The difference in the study subjects and TPO-positive subjects in various studies might be responsible for this, and the presence of a higher record of hyperprolactinemia in previous studies might also be due to their inclusion of those with higher TSH values in their studies. A small percentage of our study's participants have TSH values more than 7.0 mIU/L. As stated by another study, hyperprolactinemia is higher at higher TSH levels [11].

When the relation between hormones and age was evaluated in this study, a significant negative correlation between age and each of the FT3, FT4, and prolactin was found, which suggests lower hormone levels with advancing age and low thyroid hormone secretion leads to a compensatory increase in TSH release from the pituitary. This supports a higher TSH reference range that is commonly seen in the elderly. Although when parameters of the 2 age groups with the same thyroid status were compared, significant differences between variables were not observed apart from lower FT3 and prolactin in the older age group.

In agreement with a study done in Iran [27], significant correlations between TPO titer and TSH were revealed. No relation between prolactin and TSH was found in the present study. This is inconsistent with studies by Sharma et al. and Goel et al., who showed a positive correlation between TSH and prolactin levels [11, 21]. No significant differences were found between sex of TPO-positive and TPO-negative groups. However, a study by Roos et al. reported higher TPO positivity in females [23].

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Conclusion

This study suggests that hypothyroid symptoms, especially fatigue, muscle pain, and cold intolerance, are present in a large fraction of SCH subjects when compared with euthyroid subjects. The Zulewski hypothyroid score correlated well with the TSH level, and SCH subjects presented with a higher score than euthyroid subjects. The frequency of TPO-Ab positivity is high (43.8%) in SCH subjects and the presence of TPO-Ab is significantly associated with an increase in TSH level. There is no significant difference in the prolactin level or hyperprolactinemia between SCH and euthyroid subjects. Additionally, euthyroid subjects with HNT levels have a higher level of TPO-Ab titer than euthyroid subjects with the low-normal TSH, with no difference in the clinical parameters between the 2 groups.

Because the study was performed prospectively, the number of study subjects was small; a larger sample size can give more accurate results. Another shortcoming of this study is that we did not check the subject's serum for vitamin D deficiency, as vitamin D deficiency is common in this country (Iraq) [28, 29], and most of the hypothyroid symptoms are nonspecific; fatigue and muscle cramping are also common complaints of those with vitamin D deficiency.

This study recommended the use of the Zulewski clinical score along with biochemical tests for the assessment of SCH for severity and treatment decisions. It also recommended testing and follow-up of subjects with TSH within the high-normal level for TPO-Ab. This is especially important for early diagnosis of SCH, as the treatment in some cases of SCH is mandatory and prevents the risk of progression to overt hypothyroidism and its clinical consequences. Especially, treatment should occur in those who have cardiovascular risk factors and those who have unexplained menstrual disturbances. Treatment is also important in women who want to become pregnant and who might go undiagnosed because of non-specific thyroid symptoms; this is to decrease pregnancy outcome. A larger study is needed in the future with follow-up of the euthyroid subject with HNT level or those with positive TPO-Ab to know the frequency of progression to SCH among this group and to assess SCH patients who received treatment with Zulewski score to find whether the score reduced with treatment or was affected by the biochemical changes during follow-up.

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Conflict of interest statement. The authors have completed and submitted the International Committee of Medical Journal Editors Uniform Disclosure Form for Potential Conflicts of Interest. None of the authors disclose any conflict of interest.

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