Original Article

# Thyroid Disorders and the Prevalence of Antithyroid Antibodies in Shiraz Population

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**Abstract**

**Background and Objectives:** Thyroid dysfunction is a common health problem affecting millions of patients worldwide. Autoimmune thyroid disorders are among the most common autoimmune disorders. In this population-based study, we assessed the prevalence of abnormal thyroid function, antithyroid antibodies and the probable relationship between them in Shiraz, southern Iran.

**Methods:** Serum thyrotropin (TSH) was determined in 981 subjects (66.8% female and 33.2% male; mean age: 39.1 ± 14.3 years), who were selected with stratified random sampling. Because of the preponderance of females over males, we performed the statistical analyses using sex-weighted data (50% for each sex). Also, antithyroid peroxidase antibodies (TPOAb), and antithyroglobulin antibodies (TgAb) were measured in two random subgroups of 376 and 537 patients respectively). Thyromegaly detected on physical examination.

**Results:** In this cross-sectional study, 8.1% of participants had elevated serum TSH level and 3.4% had low serum TSH level. A statistically significant relationship was found between gender and thyromegaly and TSH values. Positive TPOAb and positive TgAb were detected in 17% and 5.1% of participants respectively. In addition, a significant relationship was observed between elevated TSH levels and positive results for both antibodies. Detectable levels of thyroid antibodies correlated with female sex, while no correlation was observed between detectable levels of thyroid antibodies and thyromegaly.

**Conclusion:** Thyroid disorders, especially elevated TSH level, are common. It seems that autoimmune mechanisms are strongly involved in the etiology of hypothyroidism in this area.

**Keywords:** TgAb, Thyroid dysfunction, TPOAb, TSH

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## Introduction

Clinical and subclinical thyroid diseases are quite common disorders which can have important consequences, especially in the elderly population.[1–4]

Several studies have demonstrated that the prevalence of thyroid disorders varies with regional iodine intake, age, gender, ethnicity and geographical area.[5–8]

The results of Whickham survey conducted more than two decades ago in England revealed the prevalence of thyroid dysfunction as 6.6% in adult population.[9]

In the third National Health and Nutrition Examination Survey (NHANES III) in the United States, hypothyroidism was found in 4.6% and hyperthyroidism in 1.3% of the total population.[10]

After introduction of iodized salt, autoimmune thyroid diseases were detected more frequently especially in iodine sufficient areas.[11–14]

Prior to the national iodine repletion program, Iran was also considered as an iodine-deficient country. However, a recent study showed no iodine deficiency in Iran.[15] Up to now, no population-based studies have been carried out in Iran using thyroid examination and sensitive assays for serum thyroid stimulating hormone (TSH) and thyroid autoantibodies. Therefore, the present survey was conducted in order to provide data on this issue.

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## Subjects and Methods

This study was carried out on a group of individuals aged 15 or more living in urban areas of Shiraz, southern Iran. The study was conducted during spring 2008 by the Endocrine Research Center of Shiraz University of Medical Sciences, Shiraz, Iran.

We used a multistage-stratified random sampling method to select participants from our society. There are 8 regions in Shiraz. From each region, 150 families were randomly selected based on postal codes. From each family, one person aged 15 years or more was invited to come to the Endocrine Research Center in Namazee Hospital between 8:00 and 9:00 am while fasting for 12 hours. A total number of 996 individuals out of 1200 invited subjects agreed to participate in the study.

The individuals with a history of thyroid or pituitary diseases, those taking medications affecting TSH level, and pregnant women were excluded from the study. Also, all the participants were ambulatory with no acute diseases which could interfere with the measured variables.

After applying the exclusion criteria, 981 subjects were included in the survey. The excluded subjects consisted of pregnant women (n = 2), those with previous thyroidectomy (n = 2), and those who were receiving replacement therapy with levothyroxine (n = 3) or other medications such as steroids, anticonvulsants or amiodarone

which could affect the thyroid function test (n = 8).

After explaining the research objectives to the participants, they completed a questionnaire including anthropometric characteristics, medical history, and the medications they take.

Thyroid examination was performed by the endocrinologist. Thyroid size was assessed using the palpation method and classified into grades 0 – 2 according to the classification of WHO/UNICEF/ICCIDD.[16]

The primary objective was to determine the prevalence of thyroid dysfunction and antithyroid antibodies in participants. The secondary objective was to determine any relationship between thyroid function and lipid profile or BMI.

Twenty milliliters of venous blood was obtained from each subject. After centrifugation the samples were sent to endocrine research laboratory for measurement of TSH and lipids. Thyroid autoantibodies, TgAb and TPOAb were also measured in 537 and 376 randomly selected participants respectively.

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (code No. 86-3432). Informed consents were obtained from the participants and those with abnormal thyroid function tests were referred to an endocrinologist for further management.

### Measurements

Body mass index (BMI) was calculated as kg/m$^2$. Serum concentrations of TSH and TgAb were measured by immunoradiometric assay (IRMA). The serum concentration of TPOAb was measured using radioimmunoassay (RIM) (IMMUNOTECH – BECKMAN Coulter Company – Prague). In addition, serum concentrations of total cholesterol, triglycerides, and HDL cholesterol were determined by cholesterol oxidase/peroxidase method, direct detergent method, and glycerol phosphate oxidase/peroxidase method respectively (Biosystems S.A. Costa Brava 30, Barcelona Spain). Besides, low density lipoprotein cholesterol (LDL-C) concentration was calculated according to the Friedwald formula.

Normal ranges, intra-assay and inter-assay coefficients of variation for the tests are as follows:

- TSH: 0.3 – 5.2 mIU/L ; 3.75%; 5.7%;
- TPOAb: < 40 IU/ml ; 12.4%; 12.5%;
- TgAb: < 40 IU /ml ; 10.4%; 10.2%;
- Total cholesterol: up to 200mg/dl; 1.1%; 1.9%;
- HDL-C: up to 35mg/dl, 0.8%; 1.3 %;
- Triglycerides: up to150mg/dl; 1.7%; 2.6%;

### Statistical analyses

All the statistical analyses were performed using SPSS statistical software (version 16) and data were expressed as means ± SD.

Chi-square test was used for comparison of categorical variables. Moreover, student's t-test was used for continuous variables with normal distribution, while Mann-Whitney U test was used for those with a skewed distribution (e.g. TSH).

Besides, for the purpose of age adjustment the participants were divided into four age groups: 15 – 28 years (n= 268), 29 – 39 years (n = 256), 40 – 50 years (n = 232), > 50 years (n = 225). Due to the preponderance of female subjects in this study, statistical analyses were performed on sex weighted data. Logistic regression analysis was performed and P value < 0.05 was considered as statistically significant.

## Results

In this cross-sectional study, 655 out of 981 participants (66.8%) were female and 326 out of 981 participants (33.2%) were male. The mean age of the study subjects was 39.13 ± 14.36 years and the mean TSH concentration was 3.02 ± 5.98 mIU/L (95% CI: 2.62 to 3.41). Elevated TSH levels and low TSH values were found in 8.1% and 3.4% of the participants respectively. Among those with increased serum TSH, 5.7% had levels between 5.2 – 10 mIU/L and 2.4% had values greater than 10 mIU/L.

The mean value of BMI was 25.88 ± 4.54 kg/m$^2$ without any significant difference between the two sexes (P = 0.3). Results revealed no significant relationship between abnormal TSH levels and BMI (OR: 1.50, 95% CI: 0.90 – 2.47, P = 0.1).

According to the study findings, 21.7% and 1.9% of the participants had grade I and grade II thyromegaly respectively. In addition, a statistically significant relationship was found between thyroid enlargement and female gender (OR: 5.40, 95 % CI: 1.55 – 18.86, P = 0.003) and also elevated TSH levels (OR: 1.91, 95% CI: 1.15 – 3.15, P = 0.01).

Furthermore, positive TPOAb was found in 17% of the participants (22.8% of females and 11.7% of males), while positive TgAb was detected in 5.1% (7.7% of females and 2.9% of males). Also, a significant relationship was observed between elevated TSH levels and positive results for both antibodies (P = 0.001, r = 0.147 for TgAb and r = 0.329 for TPOAb). The population's characteristics regarding TPOAb and TgAb are summarized in Table 1 and Table 2.

Detectable levels of thyroid autoantibodies was not correlated to thyromegaly (P = 0.3 for TPOAb and P = 0.4 for TgAb).

After age and sex adjustment, the prevalence of high levels of TSH in women was about two times more than men. In addition, abnormal TSH concentrations, positive thyroid autoantibodies and thyroid enlargement were associated with female gender. Elevated TSH values were more prevalent in age groups 2 and 3. But, there was no association between low TSH levels or thyromegaly and age of subjects (Table 3).

The results also revealed no significant relationship between the mean levels of lipid profile components and TSH concentrations, neither in subjects with normal lipid profile nor in those with hyperlipidemia.

Mean levels of lipid profile components, the rate of lipid abnormalities and their relationship with elevated TSH levels are summarized in Tables 4 and 5, respectively.

Statistical analyses were also performed on the data of the 537 randomly selected individuals for whom at least one of the antithyroid antibodies was measured. In this subgroup, positive rates for TgAb and TPOAb were 5.1% and 13.7% respectively. Again, a significant relationship was found between positive results for these antibodies and higher TSH levels and female sex, but not with thyromegaly . The mean value of TSH level in this subgroup was 2.47 ± 2.81 mIU/L.

## Discussion

In this population-based study, high and low serum TSH levels were found in 8.1% and 3.4% of the participants, respectively. In addition, TPOAb and TgAb were positive in 17% and 5.1% of the subjects, respectively. The study results revealed a significant relationship between the presence of antibodies (alone or in com-

**Table 1.** The study population's characteristics based on TPOAb.

| | TPOAb - | TPOAb + | P-value |
|---|---|---|---|
| **Gender ( % )** | | | 0.007 |
| Female | 43.3% | 62.9% | |
| Male | 56.7% | 37.1% | |
| **BMI (kg/m$^2$)** | 25.32 ± 4.10 | 25.97 ± 4.24 | 0.5 |
| **TSH (mIU/L)** | 2.08 ± 1.63 | 4.37 ± 4.14 | 0.001 |
| Data are given as means ± SD; TSH: Thyroid stimulating hormone, BMI: Body mass index. | | | |

**Table 2.** The study population's characteristics based on TgAb.

| | TgAb- | TgAb+ | P-value |
|---|---|---|---|
| **Gender ( % )** | | | 0.01 |
| Female | 46.1% | 70.4% | |
| Male | 53.9% | 29.6% | |
| **BMI (kg/m$^2$)** | 25.36 ± 4.31 | 26.52 ± 4.96 | 0.4 |
| **TSH (mIU/L)** | 2.37 ± 2.65 | 4.21 ± 4.55 | 0.01 |
| Data are given as means ± SD; TSH: Thyroid stimulating hormone, BMI: Body mass index. | | | |

**Table 3.** Adjusted values for odds ratio and 95% confidence interval for abnormal TSH concentrations, positive antithyroid antibodies and thyroid enlargement.

| | High TSH ( > 5.2mIU/L) | Low TSH (< 0.3mIU/L) | Positive TPOAb ( > 40Iu/ml) | Positive TgAb ( > 40Iu/ml) | Thyromegaly |
|---|---|---|---|---|---|
| **Age category (year), (n = no. of participants)** | | | | | |
| 15 – 28 (n = 268) | 1 | 1 | 1 | 1 | 1 |
| 29 – 39 (n = 256) | 3.74 (1.71 – 7.63) | 0.66 (0.23 – 1.91) | 1.84 (0.64 – 5.29) | 3.92 (1.14 – 13.33) | 0.36 (0.05 – 2.29) |
| 40 – 50 (n = 232) | 2.14 (1.10 – 4.16) | 0.86 (0.28 –2.62) | 0.47 (0.20 – 1.14) | 2.07 (0.72 – 5.95) | 0.24 (0.04 – 1.47) |
| > 50 (n = 225) | 1.53 (0.81 – 2.89) | 1.18 (0.34 – 4.04) | 0.52 (0.21 – 1.25) | 1.61 (0.59 – 4.40) | 0.37 (0.05 – 2.43) |
| **Sex** | | | | | |
| Male | 1 | 1 | 1 | 1 | 1 |
| Female | 1.93 (1.16 – 3.19) | 1.21 (0.58 – 2.51) | 2.22 (1.26 – 3.91) | 2.91 (1.24 – 6.84) | 5.07 (1.48 – 17.35) |
| TSH: Thyroid stimulating hormone; TPOAb: Antithyroid peroxidase antibody; TgAb: Antithyroglobulin antibody; Data are OR, 95% CI. | | | | | |

bination) and elevated TSH levels. Also, abnormal thyroid function and positive thyroid autoantibodies were significantly related to female sex.

Furthermore, a significant relationship was observed between thyroid enlargement and elevated TSH levels. However, regarding the secondary end points no correlation was found between TSH values, BMI, and lipid profile parameters.

Our findings are consistent with several other population-based studies. For instance, the study performed in Colorado showed that 9.5% of the population had TSH values > 5 mIU/L and 2.2% had TSH concentrations lower than 0.3 mIU/L.[1] Also, Tunbridge et al. conducted a longitudinal study in England which showed that 7.5% of women and 2.8% of men of all ages had serum TSH values greater than 6 mIU/L.[9]

Besides, Kasagi et al. reported high and low TSH values in 6.5% and 2.8% of their examinees, respectively.[17]

However, the prevalence of abnormal TSH levels for our participants was higher than some other reports. For instance, Busselton study in Australia showed elevated TSH levels and low TSH levels in 5.6% and 0.64% of the population, respectively.[18] Moreover, Okamura et al. reported high and low TSH values in 4.5% and 0.9% of Japanese subjects, respectively.[19] Yet, another study performed in the Netherlands reported high TSH levels in 4.4% and low TSH levels in 1.2% of the participants.[20]

Inconsistent estimates of thyroid dysfunction prevalence may be related to the discrepancy of iodine intake in the areas involved and different definitions for disease state.

Meanwhile, we also focused on the role of thyroid autoimmunity by measuring TPOAg and TgAb as sensitive autoimmune thyroid disease markers. The results obtained regarding positive antibodies in the study subjects were in accordance with many other previous studies, mostly from areas with iodine sufficiency.[19–23]

Notably, the results of the present cross-sectional study showed a positive relationship between the presence of thyroid autoantibodies and elevated TSH levels, which is in agreement with the previous studies. For example, Joseph et al. and Jensen, et al. reported that the presence of thyroid peroxidase antibodies was associated with higher TSH values. This association persisted even in normal TSH concentrations.[10,21,24,25]

Moreover, Whickham and Busselton follow-up surveys showed that the increasing levels of serum TSH in the presence of TPOAbs could predict the incidence of overt hypothyroidism.[11,26]

In contrast to the results of some previous studies such as Hollowell, et al. which reported no association between detectable TgAb and hypothyroidism, the results of our study showed this relationship for both antibodies.[10,24]

In this regard, Li, et al. conducted a study to identify the prevalence of thyroid autoantibodies in populations with different levels of iodine intake. They reported the high iodine intake as a risk factor for developing hypothyroidism and increased prevalence of positive TgAb.[27]

On the other hand, regarding the relationship between low TSH levels and thyroid autoantibodies, it has been reported that decreased TSH levels could be associated with positive TPOAb

**Table 4.** Mean concentrations of lipids in the 981 participants.

| Lipid concentrations (mg/dl) | Mean ± SD |
|---|---|
| Cholesterol | 200.49 ± 41.95 |
| Triglycerides | 157.5 ± 85.02 |
| HDL-C | 43.15 ± 10.21 |
| LDL-C | 125.79 ± 34.20 |

Data are given as means ± SD; HDL-C: High density lipoprotein, LDL-C: Low density lipoprotein.

**Table 5.** The prevalence of lipid abnormalities in the 981 participants and their relationship with elevated TSH levels.

| Lipid abnormalities (mg/dl) | Prevalence ( % ) | OR (95 % CI), P-value |
|---|---|---|
| Hypercholesterolemia ( > 200) | 48.4% | 1.5 (0.9 – 2.3), P = 0.07 |
| Hypertriglyceridemia ( > 200) | 26.7% | 1.46 (0.87 – 2.46), P = 0.14 |
| Low HDL-C ( < 40) | 42.8% | 1.05 (0.65 – 1.7), P = 0.8 |
| High LDL-C ( > 130) | 39.8% | 1.14 (0.71 – 1.82), P = 0.5 |

OR: Odds ratio; 95% CI: 95% Confidence interval; HDL-C: High density lipoprotein, LDL-C: Low density lipoprotein.

alone or none of the antibodies. The findings of the current study also showed no relationships in this regard.[24,27]

In this study, thyromegaly grade II was detected in 1.9% of the participants which was more frequent in women.

Interestingly, there was a significant relationship between thyroid enlargement and high TSH levels, but not with detectable thyroid autoantibodies. Thus, a palpable thyroid may be a marker for suspected autoimmune thyroid disease. However, it doesn't appear as an important clue to make such a diagnosis.

It is still controversial whether subclinical hypothyroidism is associated with hyper- cholesterolemia. Some previous studies reported that even the modest elevations of serum TSH levels contribute to the elevation of cholesterol level. However, the findings of the present study revealed no relationship between lipid profile changes and TSH concentration.[28–31]

Also, the results of our study showed no significant relationship between BMI and TSH levels.

The strength of this research was that the participants were selected randomly and the thyroid autoantibodies were measured by a sensitive assay method.

One of the limitations of the current study was that the history of thyroid disease and taking thyroid-related or other medications were self-reported and those subjects who had the history of previous thyroid disorders or were receiving medications with some effect on thyroid function tests were excluded from the study. In addition, because of its cross-sectional design, we could not include individual changes over time. Finally, we could not perform simultaneous measurement of urinary iodine as a marker of its intake. However, recent studies showed that there is no more iodine deficiency in Iran, including this area in Fars province.[15]

The results of this study revealed that thyroid disorders especially elevated TSH levels are common in our population. Also, it seems that autoimmune mechanisms can be strongly considered as important etiologic factors of hypothyroidism in this area. These findings suggest that TSH levels and thyroid autoantibodies are useful tools to identify the subjects at risk for developing overt hypothyroidism in future.

Now, several years after the execution of iodine repletion program in our country, it seems that some patterns of thyroid disorders have changed to those which are observed in iodine sufficient populations. However, further studies are recommended to be conducted in this regard within different age groups by simultaneous measurement of urinary iodine as a marker of iodine intake.

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