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Prevalence of thyroid function test abnormalities and anti-thyroid antibodies in an open population in Central México

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ABSTRACT

Objective. To examine the prevalence of abnormal thyroid function tests and positive anti-thyroid antibodies in two Central Mexican cities. **Material and methods.** Subjects 18 to 70 years old were randomly selected to participate in this survey. A questionnaire was given and blood samples were taken to measure TSH and free T4 levels as well as anti-TPO and anti-Tg antibodies. **Results.** The mean TSH level in subjects without existing thyroid disease was 1.72 mIU/L; 0.64 and 3.74 mIU/L were the 2.5th and 97.5th percentiles. The mean free T4 level was 1.02 ng/dL, and the 2.5th and 97.5th percentiles were 0.78 and 1.31 ng/dL, respectively. There was a 2.5% prevalence of former diagnosed thyroid diseases, 3.9% of individuals were sub-hypo, and 1.1% had overt hypothyroidism. Total hypothyroidism prevalence was 7.48% (when we considered TSH levels greater than 4.5 mIU/L), but it was 11.03% when diagnosed with TSH values greater than 3.5 mIU/L. Factors associated with hypothyroidism were older age, positive family background of thyroid disease, and positive anti-TPO and anti-Tg antibodies. Subclinical and overt hyperthyroidism were found in 1.7% of participants. **Conclusions.** Abnormal thyroid function test prevalence in this population was high, but few participants were aware of having a thyroid disease. The prevalence of positive anti-thyroid antibodies was high. More studies are necessary to elucidate the effects of thyroid abnormalities on other aspects of health status and quality of life.

Key words. Thyroid disease. Hypothyroidism. Hyperthyroidism. Anti-thyroid antibodies.

Prevalencia de alteraciones en las pruebas de función tiroidea y anticuerpos antitiroideos en población adulta del centro de México

RESUMEN

Objetivo. *Examinar la prevalencia de alteraciones en las pruebas de función tiroidea y anticuerpos anti-tiroideos en población abierta de dos ciudades de la región central de México.* ***Material y métodos.*** *Sujetos de 18-70 años de edad fueron seleccionados al azar en su sitio de trabajo e invitados a participar en el estudio, se aplicó un cuestionario y se tomaron muestras de sangre venosa para la medición de TSH, T4 libre y anticuerpos anti-peroxidasa tiroidea y anti-tiroglobulina.* ***Resultados.*** *El promedio de TSH en individuos sin antecedentes de enfermedad tiroidea fue de 1.72 mIU/L y los percentiles 2.5 y 97.5 se encontraron en 0.64 y 3.74 mIU/L, respectivamente. El promedio de T4 libre fue 1.02 ng/dL, con los percentiles 2.5 y 97.5 en 0.78 y 1.31 ng/dL, respectivamente. El 2.5% de la población estudiada tenía diagnóstico previo de enfermedad tiroidea, el hipotiroidismo subclínico se encontró en 3.9% de los participantes y el hipotiroidismo franco en 1.1%. La prevalencia de hipotiroidismo fue de 7.48% (TSH > 4.5 mIU/L) y de 11.03% con valores de TSH > 3.5 mIU/L. Los factores de riesgo asociados a hipotiroidismo fueron mayor edad, antecedentes familiares de enfermedad tiroidea y anticuerpos anti-tiroideos positivos. El hipertiroidismo subclínico y franco se encontró en 1.7% de los participantes.* ***Conclusiones.*** *La prevalencia de anormalidades en las pruebas de función tiroidea en la población estudiada es alta; sin embargo, pocos sujetos estudiados sabían del diagnóstico; la presencia de anticuerpos anti-tiroideos es alta. Se necesitan más estudios para conocer los efectos de los niveles anormales de hormonas tiroideas en la calidad de vida de las personas afectadas debido a los síntomas inespecíficos que causan.*

Palabras clave. *Enfermedades de la tiroides. Hipotiroidismo. Hipertiroidismo. Anticuerpos anti-tiroideos.*

INTRODUCTION

Thyroid disorders are the second most common endocrine disease in the general population, and the availability of highly sensitive and specific assays has permitted an extensive detection of abnormal thyroid function tests that allow thyroid disorder detection even in subclinical stages.

Subclinical thyroid disease is defined as normal serum thyroid hormone levels along with elevated serum TSH levels in the case of subclinical hypothyroidism (sub-hypo) or low serum TSH levels in the case of subclinical hyperthyroidism (sub-hyper).

Sub-hypo prevalence differs among different studies; in England, Turnbridge, *et al.*,[1] found that 7.5% of women and 2.8% of men had abnormal TSH values above 6 mIU/L. Hollowell, *et al.*,[2] used the National Health and Nutrition Examination Survey (NHANES) III study sample population and found a 4.3% prevalence of TSH levels above 4.6 mIU/L. Canaris, *et al.*,[3] reported an 8.5% prevalence, but this study included people who were taking drugs that affected thyroid function tests and in Japan, Takeda, *et al.*,[4] determined a prevalence of 3.1%. In Latin-American countries, Londoño, *et al.*,[5] reported a prevalence of 18.3% and in México, Garduño-García, *et al.*,[6] determined a prevalence of 8.3%.

Sub-hypo patients are usually asymptomatic or have subtle symptoms (asthenia, muscular pain, fluid retention, hair loss, dry skin, mood disorders, etc.) that are frequently overlooked; thus, the diagnosis is delayed. Sub-hypo has been associated with increased coronary heart disease,[7] and heart failure[8] risk, mildly reduced glomerular filtration rate,[9] and cognitive dysfunction in the elderly;[10] however, is unclear whether thyroid hormone treatment would be beneficial.[11]

Overt hypothyroidism is defined as TSH levels greater than 10 mIU/L and low FT4 levels. It is associated with multiple symptoms and signs that are related to thyroid hormone deficiency, which affect quality of life and biochemical parameters such as increased low density lipoprotein cholesterol levels, and its prevalence vary between 0.1 to 2%.[1-4]

Sub-hyper prevalence varies between 0.7 and 12.4% depending on the TSH cut-off value[2,4] and is associated with a higher risk for low bone density, hip fracture,[12,13] atrial fibrillation,[14] and dementia.[15] Treatment is recommended in elderly patients because of increased risks of atrial fibrillation, osteoporosis, and bone fractures.

Clinical hyperthyroidism is defined as TSH levels less than 0.1 mIU/L and FT4 levels above the reference range and is associated with symptoms and signs related to hormone excess, and its prevalence is reportedly between 0.3-0.5%.[2,4]

Some factors are related to higher thyroid disease frequency, such as iodine content in the diet, age, presence of circulating anti-thyroid antibodies, family background, and drug intake, such as amiodarone and lithium.

There have been few studies performed in México regarding thyroid disease prevalence in the open population, and none of the studies have focused on the prevalence of both thyroid function test abnormalities and thyroid antibodies. Thus, the aim of this study was to investigate the prevalence of thyroid function test abnormalities and the presence of thyroid peroxidase and thyroglobulin antibodies as autoimmune thyroid disease markers in the general population in Querétaro (Central México).

MATERIAL AND METHODS

Sample design

This is a cross-sectional study that included 362 randomly selected 18 to 70-year-old individuals and that was performed in two Central Mexican cities (Querétaro and San Juan del Río). Participants were invited to participate within their work setting. There was a 6% rejection rate, mainly because they could not participate at the time of intervention. All of the participants signed the informed consent, and the project was approved by the Medical School Bioethics Committee (Universidad Autónoma de Querétaro). This study follows the Helsinki Declaration for human research studies.

A questionnaire was applied to obtain information such as age, gender, family history of thyroid disease, medical history, and presence of symptoms related to hypo- or hyperthyroidism;[3,16] and also some symptoms seen more often on the clinical practice and referred by the patient were included such as headache and hair loss. Physical examination was performed and included weight (with light clothes and without shoes), height, blood pressure measurement, (after resting at least 5 min, 2 measurements were obtained, the average was used for analysis) and thyroid palpation (by an endocrinologist). Blood samples were obtained by venipuncture to measure FT4, TSH, anti-thyroglobulin and anti-thyroid peroxidase antibody levels.

Laboratory tests

Free T4 and TSH levels were measured using a chemiluminescent high-sensitivity method with a lower TSH detection level of 0.001 mIU/L. We used controls and standard calibrators with 6 points, and both assays were performed in duplicate at each point in the curve every day before the measurements were performed.

Anti-thyroglobulin (Tg-Ab Assay) and anti-thyroid peroxidase antibodies (TPO-Ab Assay) were measured with the AxSYM® Microparticle Enzyme Immunoassay (MEIA) by Abbott Diagnostics. The lower detection limit was 2 IU/mL for the Tg-Ab assay and 1 IU/L for the TPO-Ab assay. The coefficient of variation was less than 6.6% and 6.5%, respectively. We used controls and calibrators as quality control procedures: positive control contained defibrinated human plasma positive for anti-TPO in phosphate buffer with protein stabilizers; negative control contained also defibrinated human plasma to yield the following concentration ranges: negative control 0.0 to ≤ 2.0 IU/mL and positive control 40-110 IU/mL these controls were tested once each day of use. The standard calibrators were determined with different concentrations that contained defibrinated human plasma positive for anti-TPO in phosphate buffer with protein stabilizers were: calibrator A contained a 0.0 IU/mL concentration; calibrator B 8.0 IU/mL; calibrator C 20.0 IU/mL; calibrator D 100.0 IU/mL; calibrator E 400 IU/mL; and calibrator F 1000 IU/mL; the calibrators are referenced to the internationally recognized NIBSC Anti-thyroid Microsome Serum (66/387). Also for anti-Tg antibodies we used negative and positive controls the first one had not anti-Tg plasma and the last contained defibrinated human plasma positive for anti-Tg with protein stabilizers to yield the following concentration ranges: negatives control less than 25 IU/mL, positive control 90 to 210 IU/mL. The standard calibrator had different concentrations: standard A 0.0 IU/mL; standard B 25 IU/mL: standard C 125 IU/mL; standard D 250 IU/mL; standard E 500 IU/mL, and standard F 1,000 IU/mL; these calibrators are referenced to the World Health Organization Thyroglobulin Autoantibodies 1st International Reference preparation (65/93). Both calibration curves and positive and negative controls were determined according to the suggested method and were found within the recommended range.

Definitions

Subclinical hypothyroidism was defined as TSH level between 4.5 to 10 mIU/L and normal FT4 level; however, some population studies have determined that the 97.2th percentile for TSH level was 3.5 mIU/L when patients with nodules, antibodies and use of drugs that affect thyroid function were excluded.[4,17] Overt hypothyroidism was defined as TSH level higher than 10 mIU/L plus low FT4 level, subclinical hyperthyroidism was defined as TSH level between 0.1 and 0.4 mIU/L and normal FT4 level, and overt hyperthyroidism was diagnosed by TSH level less than 0.1 mIU/L and high FT4 level.[11]

The questionnaire was done according to the individual symptoms described by Canaris[3] and Zulewski.[16]

Statistical analysis

The sample size was calculated with the Epi Info program; the sample was calculated for an expected thyroid function test abnormality frequency of 5% and a minimum sample size of 203 individuals was calculated. The descriptive analysis was performed using mean and standard deviation for continuous variables with a normal distribution, median and interquartile interval was used for those variables with a non-normal distribution, and nominal variables were expressed as percentages. Means comparison was performed using Student's t-test for quantitative variables with a normal distribution, and the Mann-Whitney U test and Wilcoxon tests were used for those with a skewed distribution. The χ^2 and Fisher's exact test were used with qualitative variables. Statistically significant differences were considered if the p value was less than 0.05. The confidence intervals were calculated at 95% (95% CI), and risk was calculated using the Odds Ratio (OR). The statistical analysis was performed with the SPSS statistical package version 12.0 (SPSS Inc. 233 South Wacker Drive, 11th Floor Chicago, IL 60606-6412, USA).

RESULTS

In total, 362 participants were included in this study, 164 (45.3%) were females and 198 (54.7%) males; the mean age was 37.7 ± 12.1 years, 9 participants (7 women) had a previous diagnosis of hypothyroidism and were taking levothyroxine; one had Graves' disease and was treated with radioac-

Table 1. Demographic and clinical characteristics of all the participants.

	All subjects	Females	Males	p value
n (%)	362 (100)	164 (45.3)	198 (54.7)	
Age, yr	37.7 ± 12.1	36.8 ± 11.8	37.9 ± 12.3	0.37†
SBP, mmHg	119.5 ± 16.2	114.4 ± 15.5	123.9 ± 15.5	< 0.001†
DBP, mmHg	80.9 ± 11.3	76.9 ± 9.4	84.4 ± 11.7	< 0.001†
BMI (m/kg^2)	26.4 ± 4.8	25.7 ± 5.1	27 ± 4.5	0.009†
TSH mIU/L, median (IIQ)	1.58 (1.2-2.2)	1.63 (1.1-2.1)	1.56 (1.2-2.3)	0.73*
Free T4 ng/dL	1.02 ± 0.19	1.02 ± 0.16	1.02 ± 0.21	0.82†
Family thyroid diseases, n (%)	29 (8)	19 (11.4)	10 (5.2)	0.003‡
Previous thyroid diseases, n (%)	9 (2.48)	7 (4.2)	2 (1)	0.09‡
Previously diagnosed with hypothyroidism, n (%)	9 (2.5)	7 (77.8%)	2 (22.2%)	0.058‡
Subclinical hypothyroidism, n (%)	14 (3.9)	7 (4.2)	7 (3.6)	0.79‡
Overt hypothyroidism, n (%)	4 (1.1)	4 (2.4)	0 (0)	0.04‡
Subclinical hyperthyroidism, n (%)	4 (1.1)	2 (1.2)	2 (1.0)	0.87‡
Overt hyperthyroidism, n (%)	2 (0.6)	0 (0)	2 (1.0)	0.50‡
Positive anti-TPO antibodies, n (%)	34/359 (9.4)	19 (11.6)	15 (7.8)	0.27‡
Positive anti-TG antibodies, n (%)	48/359 (13.4)	20 (12)	28 (14.5)	0.54‡

F: female. M: male. † Student's t test. * Mann-Whitney Wilcoxon. ‡ Chi square.

tive iodine, and 29 participants (8%) reported a family history of thyroid disease (Table 1).

The mean TSH value after excluding patients with abnormal levels was 1.72 mIU/L, the 2.5th percentile was 0.64 mIU/L and the 97.5th percentile was 3.74 mIU/L. The mean FT4 level was 1.02 ng/dL; the 2.5th percentile 0.78 ng/dL and the 97.5th percentile was 1.31 ng/dL. These levels were not different when individuals with positive antibodies were excluded. The mean TSH level was 1.68 mIU/L, the 2.5th percentile was 0.66 and the 97.5th percentile was 3.71 mIU/L. The mean FT4 levels was 1.02 ng/dL, the 2.5th percentile was 0.8 and the 97.5th percentile 1.31 ng/dL.

Excluding the participants who had abnormal levels, there was no difference in the mean TSH levels when males and females were compared (1.58 ± 0.63 *vs.* 1.70 ± 0.68, p = NS). TSH and free T4 levels without excluding participants with thyroid disease and positive antibodies are demonstrated in table 1. We determined that two people had thyroid nodules by physical thyroid gland examination.

Sub and overt hypothyroidism

In this sample, 14 (3.9%) individuals had TSH levels between 4.5 and 10 mIU/L, they were significantly older (45.3 ± 11.1 *vs.* 36.6 ± 12 yrs. p = 0.008), and had higher BMI (26.1 ± 28.6 p = 0.01), but there was no significant differences in other clinical variables (Table 2).

Patients with TSH levels greater than 10 and normal free T4 levels can be diagnosed as subclinical hypothyroidism; one patient had a TSH level of 13.45 mIU/L with a low-normal free T4 level. This patient was a 52 year old woman who had 8 hypothyroidism-related symptoms and anti-thyroid antibodies present. In total, four (1.1%) participants had TSH values higher than 10 mIU/L (overt hypothyroidism), all of whom were females. They had a more frequent family background of thyroid disease (50 *vs.* 7.6% p = 0.03), had more hypothyroidism symptoms compared with the normal TSH group (7 *vs.* 3); dry skin, headache, hair loss, and bradykinesia, were present more frequent in patients with sub-hypo and hypothyroidism compared with the group of patients with normal thyroid function tests (Table 3); also this group of patients were older (44.3 ± 5.6 *vs.* 36.6 ± 2.0), had higher BMI, waist circumference, anti-TPO prevalence (100 *vs.* 6.4%, p < 0.001), and anti-TG antibodies (100 *vs.* 10.4%, p < 0.0001) (Table 2).

In total, 16 participants (3.6%) had TSH levels between 3.5 and 4.5, they were older (46.8 ± 11.4 *vs.* 36.3 ± 11.8, p = 0.002), and 2 (12.5%) had positive both antibodies.

The prevalence of new and former subclinical and overt hypothyroidism as a cutoff for subclinical hypo-levels of 3.5 and 4.5 mIU/L is summarized in table 4. In total, 50% of individuals with sub-hypo were positive for anti-TPO antibodies *vs.* 6.1% in euthyroid participants.

Table 2. Comparison of clinical and biochemical characteristics among euthyroid and hypothyroid subjects.

	Normal TSH	TSH 4.5-10 mIU/L	TSH >10 mIU/L	p value*
n (%)	330 (91.2)	14 (3.9)	4 (1.1)	
Age, yr (SD)	36.6 (12.0)	45.3 (11.1)	44.3 (5.6)	0.014
Symptoms n (SD)	3.1 (2.8)	5.2 (4.1)	7 (5.9)	0.001
SBP, mmHg (SD)	119.0 (15.9)	129.4 (17.2)	116.8 (22.3)	0.058**
DBP, mmHg (SD)	80.6 (11.2)	88.9 (11.4)	76.3 (11.1)	0.02**
BMI, m/kg^2 (SD)	26.1 (4.6)	28.6 (3.9)	35 (13.1)	< 0.001
Waist circumference, cm (SD)	88.7 (13.37)	94.3 (14.2)	107.4 (27.4)	0.009
Family history of thyroid diseases, n (%)	25/328 (7.6%)	1/14 (7.1%)	2/4 (50%)	0.03
TSH mIU/L, (SD)	1.73 (0.8)	5.9 (1.2)	21.6 (6.13)	< 0.001
Free T4 ng/dL, (SD)	1.02 (0.13)	0.92 (0.16)	0.67 (0.12)	< 0.001
Positive anti-TPO antibodies, n (%)	23/341 (6.7%)	7/14 (50%)	4/4 (100%)	< 0.001
Positive anti-TG antibodies, n (%)	37/341 (10.8%)	7/14 (50%)	4/4 (100%)	< 0.001
Glucose mg/dL, (SD)	90.8 (22.9)	99.6 (37.4)	102.3 (19.2)	0.26

* We used ANOVA or Pearson chi square. ** When we controlled for age the difference between groups was no longer significant.

Table 3. Comparison of symptoms in euthyroid, sub-hypo and hypothyroid subjects.

Symptom	Normal TSH (n = 330)	TSH > 4.5 (n = 14)	Hypothyroidism (n = 4)	p value*
Fatigue	42.4% (140)	61.5% (8)	75% (3)	0.18
Paraesthesia	19.8% (65)	30.8% (4)	25% (1)	0.61
Dry skin	23.7% (78)	57.1% (8)	75% (3)	0.001
Constipation	23% (76)	42.9% (6)	50% (2)	0.11
Myxdema	4.3% (14)	14.3% (2)	25% (1)	0.41
Short term memory loss	23.6% (78)	28.6% (4)	50% (2)	0.44
Cold intolerance	14.8% (49)	35.7% (5)	25% (1)	0.09
Bradykinesia (slow movements)	1.5% (5)	7.1% (1)	25% (1)	0.001
Depression	15.9% (52)	28.6% (4)	25% (1)	0.41
Other symptoms†				
Headache	18.2% (60)	35.7% (5)	75% (3)	0.005
Hair loss	26.8% (88)	42.9% (6)	75% (3)	0.047

* Chi square. † Symptoms not described in references.

Sub and overt hyperthyroidism

Sub-hyper and overt hyperthyroidism were present in 6 (1.7%) participants. Of these participants, two (0.6%) individuals had overt hyperthyroidism with a TSH value less than 0.1 mIU/L, and 4 (1.1%) participants had a TSH value between 0.1-0.4 mIU/L (sub-hyper). There were no differences in the prevalence between females and males (Table 1). All of these patients had hyperthyroidism symptoms but had not been previously diagnosed.

Anti-TPO antibodies were positive in 16.7% of patients, and anti-TG antibodies were present in 33.3% in individuals with TSH levels below 0.4 mIU/L.

Thyroid antibodies

Thyroid peroxidase antibodies were found in 34 (9.5%) participants, and thyroglobulin antibodies were found in 48 (13.4%) participants; 29 (8.01%) subjects were positive for both antibodies. Patients who were positive for both antibodies were older, and had higher TSH levels than subjects without or just anti-Tg or anti-TPO (Table 5). To have positivity for both antibodies was the most important risk factor associated with TSH higher than 4.5 mIU/L (OR 26.1 IC95 9.0-75 p = 0.0001).

Table 4. Prevalence of thyroid function test abnormalities.

Diagnosis	n	(%)
Subclinical hypothyroidism TSH > 4.5-10 mIU/L	14	(3.9)
Subclinical hypothyroidism TSH > 3.5-10 mIU/L	27	(7.4)
Overt hypothyroidism TSH > 10 mIU/L	4	(1.1)
Previous hypothyroidism diagnosis	9	(2.48)
Total subclinical and overt hypothyroidism TSH > 4.5	27	(7.48)
Total subclinical and overt hypothyroidism TSH > 3.5	40	(11.03)
Subclinical hyperthyroidism TSH 0.1 to 0.4 mIU/L	4	(1.1)
Overt hyperthyroidism TSH < 0.1 mIU/L	2	(0.6)
Total subclinical and overt hyperthyroidism	6	(1.7)

Table 5. Clinical and thyroid function test characteristics in participants with and without anti-thyroid antibodies.

	No antibodies (n = 306)	Anti-Tg antibodies (n = 19)	Anti-TPO antibodies (n = 5)	Both antibodies (n = 29)	p value ANOVA
Age (yrs)	36.4 ± 11.7	42.9 ± 12.0	39.8 ± 10.3	42.2 ± 12.8	0.01
TSH (mIU/L)	1.7 ± 0.97	1.9 ± 1.1	1.8 ± 1.40	5.84 ± 7.03	< 0.0001
Free T4 (ng/dL)	1.02 ± 0.14	1.09 ± 0.35	1.10 ± 0.13	0.96 ± 0.37	0.07

DISCUSSION

Information about thyroid disease prevalence in México is scarce, and few studies have been performed to assess the prevalence of thyroid function test abnormalities in an open population in Central México.

In this study, we determined that 7.48% of population had TSH values higher than 4.5 mIU/L, and 11.03% were ≥ 3.5 mIU/L in subjects ≥ 18 years old. These results are similar to those reported by Garduño-García, *et al.*,[6] (8.3%) but lower than those reported in 2,401 healthy subjects attending the Hospital General de México by Hurtado-López, *et al.*,[18] where high TSH levels were found in 21.5% of patients; however, in their report, there was no information on their TSH values or other demographic data.

The NHANES III study[2] was performed in subjects with no antecedents of thyroid disease, they found hypothyroidism in 4.6% (0.3% clinical and 4.3% subclinical), and hyperthyroidism in 1.2% (0.5% clinical and 0.7% subclinical) of participants with a TSH reference range of 0.45-4.12 mIU/L and mean values of 1.4 mIU/L. The Colorado study[3] that was performed in people attending a state fair, determined that 9.5% had TSH values ≥ 5.01 mIU/liter and 2.2% had TSH values ≤ 0.3 mIU/liter. These differences in thyroid disease prevalence may be related to sampling methodology, TSH cut point level, geographic variations and differences in iodine intake.

Few studies have been performed in the Latino population to evaluate normal TSH levels. In Brazil, Rosario, *et al.*,[17] determined TSH ranges (2.5-97.5th percentiles) of 0.43-3.24 mIU/L and mean values of 1.52 mIU/L, but in México, reference TSH values are lacking; thus, it is important to perform a larger study in different geographical areas of Mexico in people who are not taking thyroid drugs to evaluate the normal TSH values within our population.

There are controversies about when to screen an open population for subclinical thyroid disease. Uniform guidelines for thyroid disease screening using serum TSH levels have not been established; however, the populations that would benefit the most from this screening are women ≥ 60 years, subjects with previous exposure to thyroid gland radiation, subjects with previous thyroid dysfunction, surgery, autoimmune disease, and/or family history of thyroid disease.[19] Pregnant women in the first trimester may also benefit from universal screening.[20]

Serum TSH measurement is the most sensitive screening test for thyroid dysfunction, and for the diagnosis of subtle forms of hyper- and hypothyroidism, the laboratory reference range is usually chosen by determining the 95% confidence limits of a population of individuals free of known thyroid dysfunction.[21] However, there is controversy in the upper limit for TSH level and it has been suggested that when individuals with thyroid auto antibodies, goiter, or a strong family history of thyroid disease

are excluded, the 95% TSH reference range shrinks to 0.3-2.5 or 3.0 mIU/liter.[22]

Some studies have demonstrated that patients with TSH ≥ 3.5 mIU/L have more frequent hypothyroidism-related clinical symptoms. In this study, patients with TSH values above 3.5 mIU/L were more symptomatic; however, our results demonstrated that most of the patients with subclinical disease did not seek medical attention and did not pay attention to subtle clinical symptoms. Thus, further studies are necessary to understand the impact of these symptoms on quality of life, well-being and job performance. Also we included headache and hair loss as symptoms to be asked in the questionnaire due to we have observed that patients with hypothyroidism frequently complain of this symptoms, and when we did the statistical analysis we found there was difference between the patients with hypothyroidism and those who do not have abnormal thyroid tests, in consequence we think it is necessary to explore these symptoms in other clinical studies in order to confirm this finding based on clinical practice experience. Recent controlled trials administering levothyroxine failed to demonstrate any improvement in clinical symptoms and quality of life with levothyroxine administration in patients with sub-hypo and there is insufficient evidence that levothyroxine treatment improves the lipid profile, cardiac dysfunction or decreases fracture risk.[23,24] Shin, *et al.*,[25] demonstrated that levothyroxine treatment attenuated the decline in renal function in chronic kidney disease patients with sub-hypo.

The presence of both anti-thyroid antibodies preceded thyroiditis diagnosis and has been associated with subsequent hypothyroidism. In this study, positive TAbs results were associated with higher TSH values. This finding supports the recommendation to measure antibodies in patients with subclinical thyroid disease because these patients progress more rapidly to clinical hypothyroidism; progression to overt thyroid disease at one year was reportedly 2 to 5%, and the progression rate was proportional to baseline serum TSH concentrations and positive anti-thyroid antibodies.[26] Hollowell, *et al.*[2] reported a 10.4% prevalence of positive TgAb and 11.3% prevalence of TPOAb in the U.S. population. In this study, positive antibodies were more prevalent in women than in men, were increased with age, and TPOAbs were significantly associated with hypo or hyperthyroidism but TgAbs were not. At the core institutional laboratory we lack of radioimmunoassay methods to measure antithyroid-Ab, so an immunometric assay was used, most of the laboratories in México use this methodology which is easier to work as radioactivity is not needed, however we recognize that many reports had shown a high analytical variability with this methodology.[27,28]

There was also higher BMI and waist circumference in this group, which makes this group of patients more susceptible to metabolic consequences. Participants were younger than other populations studied because some studies suggest that aging is associated with increased serum TSH concentrations.[29]

Some of the study limitations are the small sample, participant age, localization in one geographic area, no thyroid gland ultrasound examination, the physical thyroid examination was performed by one expert only and no history of iodine intake or excretion was investigated.

In conclusion, this study demonstrates that subclinical thyroid disease prevalence with unspecific symptoms is high, and it is very important that the normal TSH reference range is standardized for the Mexican population to ensure that the results are accurate and reproducible in our population.

More studies need to be performed to describe thyroid disease incidence in our country.

ACKNOWLEDGMENTS

We thank the support of Merk-Serono for transportation, blood sample collection and the TSH and free T4 measurements.

We also thank Abbott diagnostics for donating the kits and controls to determine anti-TPO and anti-TG antibody presence, and thanks to Hospital Ángeles de Querétaro clinical laboratory, where the thyroid antibodies measurements were performed.

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Recibido el 13 de mayo de 2013.
Aceptado el 28 de febrero 2014.