



Original/Otros

Prevalence of autoimmune thyroiditis and thyroid dysfunction in healthy adult Mexicans with a slightly excessive iodine intake

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Abstract

Objective: the purpose of this study was to evaluate the prevalence of autoimmune thyroiditis and thyroid dysfunction in healthy individuals with no previously known thyroid disease, in an urban area of Mexico City.

Subjects and methods: the study was conducted on volunteers with no known thyroid disease. We recruited 427 subjects among the hospital’s medical and administration personnel. All underwent thyroid ultrasound (US) and TSH, free T4 (FT4), total T3 (TT3), thyroid anti-peroxidase (TPOAb) and anti-thyroglobulin (TgAb) antibodies were measured. Hypoechoogenicity and thyroid volume were determined by US. Urinary iodine (UI) excretion was also measured.

Results: the frequency of autoimmune thyroiditis was 8.4% (36/427) and women were most commonly affected than men (11.6 vs. 4.3% respectively, $P=0.008$); when including cases of atrophic thyroid, the frequency increased to 15.7% (67/427). Clinical hypothyroidism was detected in 1.2% (5/427) and it was sub-clinical in 5.6% of individuals. A goiter was present in 5.9% (25/427) of volunteers. Median UI was 267 $\mu\text{g/L}$, (IQR 161.3 – 482.5).

Conclusions: in spite of our study’s limitations, the frequency of autoimmune thyroiditis is clearly elevated in the studied population. Further studies are necessary in order to define the prevalence of autoimmune thyroid disease as well as the current iodine nutritional status in our country.

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Key words: *Thyroiditis autoimmune. Iodine intake. Thyroid dysfunction. Urinary iodine. Thyroid volume.*

PREVALENCIA DE TIROIDITIS AUTOINMUNE Y DISFUNCIÓN TIROIDEA EN ADULTOS MEXICANOS SANOS, CON UNA INGESTIÓN DE YODO LEVEMENTE EXCESIVA

Resumen

Objetivo: el objetivo del presente estudio fue evaluar la prevalencia de tiroiditis autoinmune y disfunción tiroidea en individuos sanos sin enfermedad tiroidea conocida, de un área urbana de la ciudad de México.

Material y métodos: el estudio se realizó en voluntarios sin enfermedad tiroidea conocida. Se reclutaron 427 individuos entre personal médico y administrativo del hospital. A todos se les realizó ultrasonido (US) tiroideo, TSH, T4 libre (FT4), T3 total (TT3), anticuerpos anti-peroxidasa tiroidea (TPOAb) y anti tiroglobulina (TgAb). Dentro de la evaluación por US se incluyó la hipocogenicidad y el volumen tiroideo. También se midió la excreción urinaria de yodo (UI).

Resultados: la frecuencia de tiroiditis autoinmune fue de 8,4% (36/427), las mujeres fueron más afectadas que los hombres (11,6 vs. 4,3%, respectivamente, $P=0,008$), cuando se sumó la tiroides atrófica, esta frecuencia se elevó al 15,7% (67/427) de los estudiados. El hipotiroidismo clínico fue detectado en el 1,2% (5/427) y el subclínico en el 5,6%. El hipertiroidismo clínico solo se observó en el 0,5% (2/427) y el subclínico en el 1,9%. El bocio se identificó en el 5,9% (25/427) de los voluntarios. La mediana de la UI fue de 267 $\mu\text{g/L}$, RIQ (161,3 – 482,5).

Conclusiones: a pesar de las limitaciones de nuestro estudio, es clara la frecuencia incrementada de tiroiditis autoinmune en la población estudiada. Son necesarios más estudios que definan tanto la prevalencia de enfermedad tiroidea autoinmune como el estatus nutricional de yodo actual en nuestro país.

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Palabras clave: *Tiroiditis autoinmune. Ingestión de yodo. Disfunción tiroidea. Yodo urinario. Volumen tiroideo.*

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Introduction

Thyroid dysfunction is one of the most common endocrine disorders, but its prevalence and incidence according to the epidemiological studies conducted in various parts of the world, differ significantly¹. These variations hinge on each study's selected population, the age and gender of the included subjects, the different definitions applied to each dysfunction and every population's iodine intake. The population's iodine intake is one of the most relevant environmental factors associated to thyroid dysfunction and autoimmunity². The relationship between the iodine intake and the risk of developing thyroid disease is very close and dysfunction occurs in association with extreme nutritional iodine status; the risk is therefore present with both high and low intakes³. In the past few years, several studies have reported excessive dietary iodine intake in different populations as well as the subsequent abnormalities in thyroid function, with an increased incidence and prevalence of autoimmune thyroiditis and hence, an increase in hypothyroidism^{4,7}. The Mexican government has only conducted one national screening of urinary iodine (UI) in children under 12 years of age and in non-pregnant women between the ages of 12 and 49, as part of the 1999 National Nutrition Survey (ENN-1999); however, the reported results only reflected the presence or lack of iodine deficiency in children between the ages of 5 and 12, 91.5% had a UI > 100 µg/L and were not deficient. But among non-pregnant women between 12 and 49 years of age, the median UI was 281 µg/L⁸. According to the WHO database on UI per nation, Mexico has a median UI of 235 µg/L calculated on the basis of the last reports and is thus classified as a country with a more than adequate iodine intake and in which the risk of iodine-induced hyperthyroidism and autoimmune thyroid disease is present in susceptible groups⁹.

The purpose of this study was to evaluate the prevalence of autoimmune thyroiditis and thyroid dysfunction in healthy individuals with no known thyroid disease, in an urban area of Mexico City.

Subjects and methods

This is a cross-sectional study with non-probabilistic sampling, that included healthy volunteers over the age of 18, with no previous personal history of thyroid disease and not currently pregnant or lactating. They were recruited among the administrative, nursing and resident personnel in our hospital. All volunteers signed an informed consent form to participate in the study. They answered a questionnaire on their family history in terms of thyroid disease, their personal pathological history and comorbidities, and their use of drugs or contact with iodinated contrast media for radiological procedures. Volunteers that had been ex-

posed to iodinated products or substances within the previous 12 weeks were excluded from the study.

A thyroid ultrasound was performed on all participants with portable equipment and a 7.5 MHz lineal transducer; the procedure was conducted by a single investigator (AFR) to avoid inter-observer variations. The US evaluation was obtained at the beginning of every thyroid examination, before the operator had access to the volunteer's information. The volume of each thyroid lobe was calculated with the formula (mL): width x height x length x 0.52 and the sum of both lobe measurements equals the thyroid volume⁶. Ultrasound gain was adjusted to maintain constant operating conditions and until the lumen of the internal jugular vein and the carotid artery were free of echoes. Whether the thyroid gland's echogenicity was normal or decreased was determined by comparing the brightness of the thyroid echoes with that of the surrounding neck muscles. Thyroid hypoechogenicity was graded as follows: grade 1 or mild when compared to normal thyroid tissue, grade 3 or marked, referred to echogenicity similar to that of the sternocleidomastoid muscle. Changes in echo pattern intermediate to grade 1 and 3 were classified as moderate, grade 2¹⁰. Echogenicity was considered decreased, only if it was diffuse and the gland was completely compromised; focal echogenicities were not taken into account.

Nodular changes exceeding 5 mm were considered thyroid nodules and depending on their number, a solitary nodule was defined as > 5 mm in diameter in a thyroid of normal volume; multiple nodules were present if ≥ 2 thyroid nodules were detected and measured > 5 mm in diameter, in a gland of normal volume. There is no data in the literature on the reference values of the thyroid volume in the adult Mexican population, so a goiter was defined as a thyroid volume above 18.7 mL in men and 15.3 mL in women. This definition derives from a group of 235 individuals with no thyroid disease or family history of thyroid disease, no anti-thyroid antibodies, no goiter or nodules; the collected data in these individuals had an abnormal distribution and the goiter definition was obtained from the results' 97.5th percentile.

A fasting (no less than 8 hrs.) venous blood sample was obtained from all volunteers, between 0700 and 1000 hrs; after centrifugation, serum was placed in aliquots and frozen at -20°C until processing. Urine samples for UI determinations were obtained in only 11% of volunteers; these individuals were chosen by simple randomization. Samples were collected in 100 mL urine collection containers before noon, transferred into 5 mL vials and frozen at -20°C until processing. The epidemiological criteria used to evaluate the iodine nutritional status based on the UI were as follows: < 99.0 µg/L reflected a deficient intake, 100.0 to 199.0 µg/L reflected an adequate intake and > 300.0 µg/L suggested an excessive iodine intake¹¹.

Thyroid disease diagnostic criteria

Thyroid hormone reference values were obtained from the 2.5th and 97.5th percentiles in 282 individuals with no thyroid disease or family history of thyroid disease, no anti-thyroid antibodies and no goiter or thyroid nodules¹². Dysthyroidism was defined according to the following criteria: clinical hypothyroidism was diagnosed if the TSH was > 4.88 mIU/L and FT4 < 10.21 pmol/L (< 0.79 ng/dL); subclinical hypothyroidism was diagnosed with a TSH > 4.88 mIU/L and FT4 between 10.21 and 25.64 pmol/L (0.79 – 1.99 ng/dL); clinical hyperthyroidism was diagnosed with a TSH < 0.71 mIU/L and FT4 > 25.64 pmol/L (1.99 ng/dL) and/or TT3 > 2.70 nmol/L (1.75 ng/mL); subclinical hyperthyroidism was diagnosed with a TSH < 0.71 mIU/L, FT4 between 10.21 and 25.64 pmol/L (0.79 – 1.99 ng/dL) and TT3 between 1.30 and 2.70 nmol/L (0.84 – 1.75 ng/mL). Autoimmune thyroiditis (AT) was diagnosed if the TPOAb and/or TgAb were abnormally elevated and the thyroid's diffuse hypoechoogenicity was \geq grade 2 (moderate or marked); the separate presence of any of these findings were not considered diagnostic of AT^{6,13}. Another manifestation of thyroid autoimmune disease included the diagnosis of autoimmune atrophic thyroiditis, and included individuals with a thyroid volume < 5.0 ml regardless of the presence or lack of abnormally elevated anti-thyroid antibodies^{6,14,15}.

Laboratory analysis

The concentrations of FT4, TT3, TPOAb and TgAb were measured in serum by radioimmunoassay (RIA). FT4 had an analytical sensitivity of 0.65 pmol/L (0.05 ng/dL) and a normal range of 10.21 to 25.64 pmol/L (0.79 – 1.99 ng/dL), the intra-assay coefficient variation (CV) was < 8.15% and the inter-assay CV was < 14.9%. The TT3 assay had an analytical sensitivity of 0.15 nmol/L (0.09 ng/mL) and a normal range of 1.30 to 2.70 nmol/L (0.84 – 1.75 ng/mL), an intra-assay CV < 8.3% and an inter-assay CV < 10.1%; TgAb had an analytical sensitivity of 2.0 IU/mL and values below 30 IU/mL were considered normal, the intra-assay CV was < 8.3% and the inter-assay CV was < 12.8% (RIA-gnost® FT4, RIA-gnost® T3, TGAB ONE STEP®; Cisbio Bioassays France). The assay used for TPOAb had an analytical sensitivity of 1.9 IU/mL and values below 100 IU/mL were considered normal, the intra-assay CV was < 9.31% and the inter-assay CV was < 12.4% (Anti-hTPO RIA KIT Izotop® Budapest, Hungary). TSH was determined by immunoradiometric assay (IRMA) with an analytical sensitivity of 0.005 mIU/L and a normal range between 0.71 to 4.88 mIU/L; the intra-assay CV was < 4.0% and the inter-assay was < 3.5% (Turbo TSH ¹²⁵I IRMA KIT® Izotop Budapest, Hungary).

Urinary iodine was measured by spectrophotometry with the kinetic microplate method based on the Sandell-Kolthoff reaction and results were expressed in μ g/L. They were processed in the Laboratorio de Bioquímica Nutricional, del Instituto de Nutrición de Centroamérica y Panamá (INCAP)/International Resource Laboratories for Iodine Network (IRLI)-Guatemala.

This study was approved by the Ethics Committee of the *Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán”*.

Statistical analysis

Nominal categorical variables are presented as frequencies and proportions. The distribution of continuous numerical variables was determined with the Kolmogorov Smirnov and Shapiro-Wilk tests; those with an abnormal distribution are reported as medians and interquartile ranges (IQR).

Group comparisons were established with Fisher's exact T test and the Mann Whitney U test, depending on the case. A $p < 0.05$ was considered significant in all statistical analyses and we used the SPSS 15.0 statistics software package (Chicago IL, USA).

Results

Four hundred twenty-seven (427) medical and non-medical personnel from the Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán” volunteered for the study. Over 50 % of participants were originally from central Mexico and reflect the type of population seen in our hospital; all volunteers had lived in Mexico City for at least the previous 6 months.

The studied population was young, with a median age of 26 and ranging between 18 and 67. Only 11.7% were above the age of 40 and women predominated over men (56.4%/43.6%). The characteristics of the entire population are described in table I.

Structural abnormalities of the thyroid detected by US were scant; 39 (9.1%) subjects had nodules, mostly single. Only 6 volunteers had more than one nodule (1.4%), 31 (12.9%) were female and 8 (4.3%) were male ($p = 0.002$). Due to the nodules characteristics by US, a fine-needle biopsy guided by US was recommended to 7 volunteers but only 6 accepted. Cytopathology results fulfilled the Bethesda system category II [16] criteria. All goiters detected by US were diffuse and none were multinodular. Most of the individuals with goiter were female, 19 (7.9%) and only 6 (3.2%) were men ($p = 0.06$). Thyroid volume in our population was higher in males (median 10.6 mL IQR 8.8 – 12.9) than in females (median 8.1 mL IQR 6.2 – 10.5), $p = 0.001$. Two individuals, one female and one male, were found to have thyroid hemiagenesis

(0.47%), lacking the left lobe and isthmus; both subjects underwent thyroid ^{99m}Tc scintigraphy to confirm the ultrasound findings and exclude the presence of ectopic tissue.

Ninety point eight percent (90.8%) of all participants were euthyroid, 175 males (94.1%) and 213 (88.3%) females, p = 0.007. The thyroid dysfunctions detected in our population are summarized in table II. Urinary iodine excretion was determined in 48 volunteers and the median UI value was 267 µg/L, (IQR 161.3 – 482.5).

Discussion

In this study, we found a group of individuals with similar characteristics to those reported in large thyroid epidemiological studies^{17,18}; however our group's average age is lower, which highlights some of our findings, that tend to increase with age of individuals. The presence of autoimmune thyroiditis was similar to that found in other studies although most of these were conducted in children and hence its prevalence was higher^{13,19}; the frequency was also higher than that in

Table I
Characteristics of the total population (n=427)

Variables	Total (n=427) N (%)	Males (n=186) n (%)	Females (n=241) n (%)	P [§]
Age*	26 (24 – 30)	25 (24 – 28)	26 (24 – 36)	0.001
Family history of thyroid disease	59 (13.8%)	23 (12.4%)	36 (14.9%)	0.482
BMI(Kg/m ²)	24.20 (22.10 – 27.36)	24.33 (22.46 – 27.18)	24.04 (21.70 – 27.55)	0.321
TPOAb (IU/L) [†]	39 (9.1%)	10 (5.4%)	29 (12.0%)	0.018
TgAb (IU/L) [†]	45 (10.5%)	10 (5.4%)	35 (14.5%)	0.002
TPOAb/TgAb [‡]	54 (12.6%)	14 (7.5%)	40 (16.6%)	0.005
TT3 (nmol/L)*	1.91 (1.67 – 2.13)	1.95 (1.70 – 2.19)	1.89 (1.65 – 2.08)	0.067
FT4 (pmol/L)*	15.83 (13.13 – 18.66)	17.85 (15.06 – 20.59)	14.16 (12.25 – 16.82)	0.0001
TSH (mIU/L)*	2.0 (1.27 – 2.85)	1.87 (1.20 – 2.79)	2.05 (1.33 – 2.97)	0.069

*Values are medians and interquartile ranges.

[†]Significant values of antibodies.

[‡]Significant TPOAb and/or TgAb values.

[§]Fisher's exact test and Mann-Whitney U.

BMI: Body mass index, TPOAb: Anti-thyroid peroxidase antibodies, TgAb: Anti-thyroglobulin antibodies, TT3: total T3, FT4: Free T4, TSH: Thyrotropin.

Conversion to MS units: FT4: ng/dL = pmol/L/12.87; TT3: ng/mL = nmol/L/1.536.

Table II
Dysthyroidism in the studied population

Variables	Total n= 427 (%)	Males n= 186 (%)	Females n= 241 (%)	P*
Autoimmune thyroiditis	36 (8.4)	8 (4.3)	28 (11.6)	0.008
Atrophic thyroiditis	31 (6.6)	3 (1.6)	28 (11.6)	0.0001
Thyroid hypoechogenicity	140 (33.0)	31 (16.6)	109 (45.2)	0.0001
Subclinical hypothyroidism	24 (5.6)	7 (3.8)	17 (7.1)	0.203
Clinical hypothyroidism	5 (1.2)	1 (0.5)	4 (1.7)	0.393
Subclinical hyperthyroidism	8 (1.9)	3 (1.6)	5 (2.1)	1.000
Clinical hyperthyroidism	2 (0.5)	0	2 (0.8)	0.507

*Fisher's exact test

other studies in children^{15,20}. There are similar studies that take into account both autoimmune and atrophic thyroiditis; if we include both entities in our studied population, 15.7% of individuals had these characteristics, a similar number to that reported in the literature (15.6% - 19.5%)^{6,7,14}. Atrophic thyroiditis refers to the end-stage of destructive autoimmune thyroiditis²¹. The frequency of thyroid hypoechogenicity was also high and notably different between genders; it was more common in females as also reported in studies evaluating geographic areas with normal or excessive iodine intake^{14,22} but greater than that reported in areas with iodine deficiency²³. It is currently clear that decreased thyroid echogenicity is a strong predictor of autoimmune thyroid disease¹⁰.

The number of individuals with elevated anti-thyroid antibodies is remarkably similar to that reported in some studies⁴ or even superior²⁴. The presence of hypothyroidism was also significant when compared to thyroid epidemiological studies. Subclinical hypothyroidism is highly prevalent due to the different TSH normal cut-off points in the definition; we used a value of 4.88 mIU/mL but if a value of 4.5 mIU/L is used, the number of cases is 8.2% and significant in our study group's conditions^{4,17,18}. A research group in our country, recently reported a prevalence of subclinical hypothyroidism of 8.3% in a large sample of 3148 individuals from the country's central area and an average TSH of 2.49±1.42 mIU/L after excluding previously detected thyroid patients²⁵; in that study, the prevalence of clinical hypothyroidism was 1.87% (*personal communication*). Mentioning this study is important because although it had a different purpose, some of its data can be compared with our results, especially because it was conducted in the same region of Mexico and similar equipment was used to determine TSH (IRMA). Data amenable to comparison is similar in both studies but both studied populations are different to the Mexican-American cohorts reported in the National Health and Nutrition Examination Survey (NHANES III). In this survey, Mexican-Americans were in an intermediate position, between Whites and non-Hispanic Blacks in terms of thyroid dysfunction prevalence: clinical hypothyroidism 0.2%, subclinical hypothyroidism 3.9%, clinical hyperthyroidism 0.2% and subclinical hyperthyroidism 0.5%¹⁸. Median UI in the NHANES III in Mexican-Americans was 183.4 µg/L that interestingly, was above the median - 144.7 µg/L - but still within the limits of an optimal iodine intake²⁶. These findings allow us to infer that our results are due to excessive iodine intake, although UI was not measured in all subjects. In the past decades, there is a tendency in the USA towards a decrease in UI although the median UI still reflects an optimal iodine intake in the general population. Inadequate iodine intake has been, however, detected in pregnant females²⁷. This situation has also been detected in several industrialized countries such as France, Australia,

Ireland and the United Kingdom, in which iodine deficiency is reemerging after having been adequately controlled²⁸. In Latin America, the situation appears to be different since there are several reports reflecting a tendency toward excessive dietary iodine intake since the publication of ThyroMobil in 2004. Chile, Ecuador and Brazil were reported to have a median UI > 300 µg/L, although Chile was an exceptional case since 100% of individuals had a UI > 300 µg/L (median 540 µg/L). Venezuela, Paraguay, Honduras and Peru had UI levels between 200 and 299 µg/L, reflecting a more than adequate dietary iodine intake. Of the 13 countries studied, more than half had an excessive iodine intake²⁹. The ICCIDD regional coordinator's for Latin America last report showed that after studying 22 countries, 13 had a median UI > 200 µg/L but in 8 countries, a national survey had not been conducted within the previous 8 years and among these, was Mexico³⁰. Other non-nationwide studies conducted in the region have shown the same tendency, including Colombia³¹, Brazil⁶ and Peru³². This predisposition to excessive iodine intake in our region may possibly increase the rates of autoimmune thyroiditis and hypothyroidism in our populations; although there are few studies investigating the prevalence of these problems in the region, it seems this is occurring, as suggested by publications from Brazil^{6,7,14,19} and Chile³³.

The cases of hemiagenesis detected in our study were an unexpected finding since this is a rare congenital anomaly usually discovered after the development and discovery of thyroid disease. The prevalence of thyroid hemiagenesis in the normal population is 0.05 to 0.2%, its etiology is unclear although a genetic component has been suggested and its prevalence is increased in areas with iodine deficiency³⁴. In a similar study conducted in a population with excessive iodine intake, the frequency of hemiagenesis was increased to 0.5%, above that expected in a normal population¹⁹.

The discovery of nodules and goiters in our study primarily reflects our population's intake status³⁵ and coincides with the measurements obtained in the sample population that according to the ICCIDD/WHO, has a more than adequate iodine intake and agrees with the data registered in our country by the WHO⁹.

Our study has limitations to consider, particularly the fact that our group is relatively young and small, but this underscores the findings in this type of population. Another limitation is that UI levels were obtained in only a sample of the entire study population. However, our study provides important epidemiological data on thyroid dysfunction in our population and promotes the use of US as a diagnostic tool in the diagnosis of thyroid autoimmunity, data that will be helpful in future comparative studies in other populations.

In conclusion, albeit with some limitations in the studied population, this study demonstrates an increased frequency of autoimmune thyroiditis as well

as direct and indirect findings suggesting an increase in thyroid autoimmunity; this increase may perhaps, be associated to a more than adequate dietary iodine intake. Further and broader studies exploring these factors including urinary iodine excretion in our population are necessary.

Conflict of interest

The authors have no conflict of interest or financial or personal relationship to the study and declare receiving no funding or grant support.

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