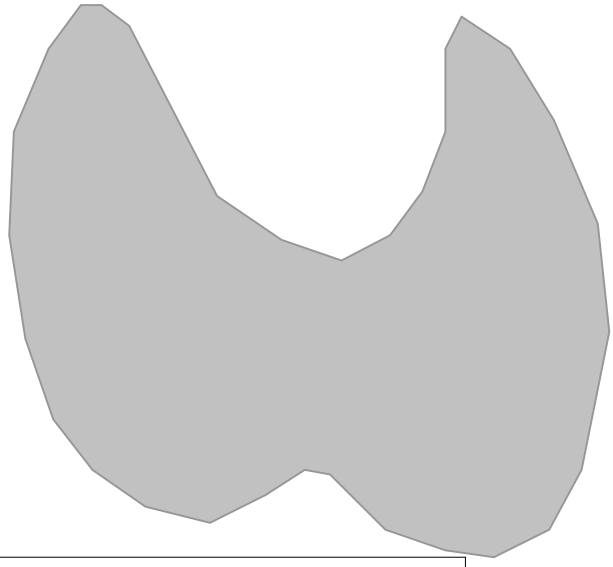
VALORES DE REFERENCIA DEL VOLUMEN TIROIDEO POR ECOGRAFÍA



TESIS DOCTORAL, 2005

FRANCISCO JAVIER MARAVALL ROYO

Departament de Medicina, Universitat de Barcelona

Director:

Dr. José Manuel Gómez Sáez

Departament de Medicina, Universitat de Barcelona.

Servei de Endocrinologia,

Ciutat Sanitària i Universitària de Bellvitge

JUSTIFICACIÓN GENÉRICA DEL TEMA UNITARIO

1.- INTRODUCCIÓN.

La determinación del volumen tiroideo es importante en el diagnóstico de las enfermedades tiroideas, para valorar estrategias terapéuticas y la eficacia de los tratamientos; así mismo es esencial en estudios epidemiológicos, para establecer la prevalencia de las enfermedades tiroideas, principalmente el bocio endémico y las áreas yododeficientes, y para elaborar programas preventivos, como la suplementación con yodo.

La exploración física es una técnica poco fiable para determinar el volumen tiroideo[1-3], y la prevalencia de bocio[4-6], pese a la utilización de métodos estandarizados, como la clasificación clínica de Perez et al.[7], de la Organización Mundial de la Salud, que es más cualitativa que cuantitativa.

Además, existe una gran variabilidad intra e interobservador, y depende también de la anatomía del cuello del paciente[8].

Existen diferentes técnicas para valorar el volumen tiroideo, como la gammagrafía con Tc99m[9], la tomografía computerizada por emisión de fotones[10], y la tomografía por emisión de positrones[11,12], pero tan sólo miden el volumen funcional, y además utilizan radiaciones ionizantes.

La tomografía axial computerizada[13] y la resonancia magnética[14] miden el volumen tiroideo con gran precisión, pero con un coste elevado.

La ecografía es una técnica precisa, y constituye la mejor alternativa, ya que es el método más simple y barato[2,9,12,15-17], y no tiene efectos adversos[15], sin embargo no es aplicable a bocios con extensión endotorácica[2,13,15,18,19].

Constituye hoy día, el método de elección para valorar el volumen tiroideo en estudios poblacionales, pero es preciso estandarizar la técnica, para minimizar los errores intra e inter-observador[20].

Por otra parte, el tamaño muestral de algunos estudios no siempre es representativo de la población estudiada. Por este motivo, se realizó un proyecto a nivel europeo (Thyro-Mobil), con el objetivo de evaluar el volumen tiroideo de la población escolar, y el nivel de yododeficiencia en diversos países.

Diversos factores están relacionados con la regulación del volumen tiroideo, y por tanto influyen en su variabilidad. Diferencias en la ingesta de yodo, los factores ambientales y las variables antropométricas[21,22] contribuyen a crear diferencias en los valores obtenidos en diferentes áreas geográficas[23].

En adultos residentes en áreas yodo-suficientes, o con yodo-deficiencia límite, algunos parámetros antropométricos y de composición corporal, especialmente la superficie corporal y la masa no grasa, han sido descritos como los mejores determinantes del volumen tiroideo[21,24,25].

Estas variables pueden contribuir a encontrar diferencias significativas de volumen tiroideo, en la misma área geográfica, en sujetos con patologías que cursen con modificación de la composición corporal, como es el caso de la diabetes mellitus. En pacientes con diabetes mellitus tipo 1 se han objetivado diferencias en la composición corporal, concretamente mayor masa magra, y menor masa grasa[26].

Existen pocos estudios sobre el volumen tiroideo y la yoduria en pacientes con diabetes mellitus tipo 1, especialmente en adultos.

En niños, algunos estudios muestran que el volumen tiroideo se correlaciona con variables antropométricas y la excreción urinaria de yodo[27,28], si bien otros autores no logran confirmar estos hallazgos[29].

Bianchi et al.[30] objetivan que una proporción considerable de adultos con diabetes mellitus tipo 1 tiene alteraciones en el volumen tiroideo determinado por ecografía, pese a la inexistencia de disfunción tiroidea.

Sin embargo, los criterios de selección de estos estudios fueron heterogéneos y no aportan datos sobre la composición corporal, además el estudio del volumen tiroideo se ve interferido por la elevada prevalencia de autoinmunidad contra el tiroides, presente en los pacientes afectos de diabetes mellitus tipo 1.

Los pacientes con enfermedades tiroideas con frecuencia presentan alteraciones en el peso corporal, ingesta, consumo de oxígeno y termogénesis. Los mecanismos por los cuales las hormonas tiroideas desarrollan un papel en la regulación del balance energético son complejos y no están bien esclarecidos[31].

Diversos factores están relacionados con la regulación del peso corporal, entre ellos la leptina, una proteína de 167 aminoácidos codificada por el gen *ob*[32]. Desde que se halló el déficit de leptina en ratones genéticamente obesos (ob/ob), existe una evidencia creciente de que la leptina juega un papel importante en la regulación de la ingesta y la termogénesis, y que sus concentraciones se correlacionan con el índice de masa corporal, y particularmente con los depósitos de grasa[32,33].

La leptina ejerce diversos efectos sobre hormonas hipotalámicas, y no sólo tiene un papel sobre la regulación de la eficiencia metabólica, sino que también contribuye a la adaptación del organismo a la inanición[34].

Las hormonas tiroideas y la leptina influyen sobre aspectos similares de la homeostasis corporal; se ha objetivado la existencia del efecto directo de la T_3 sobre la secreción de leptina[35-37], y la presencia de disfunción tiroidea en pacientes con déficit de leptina y con anormalidades en el receptor de la leptina sugieren que la leptina y el eje hipófiso-tiroideo están estrechamente relacionados[38].

Por este motivo no es sorprendente la existencia de diversos estudios, en animales y humanos, que investigan la relación entre leptina y disfunción tiroidea[39-46], si bien con resultados discordantes; en pacientes con enfermedades tiroideas, algunos estudios no encuentran correlaciones significativas entre la función tiroidea y las concentraciones de leptina[40-42,45], mientras que otros sí[35,43,44,46-48].

No obstante, poco se conoce sobre la relación entre el eje hipófiso-tiroideo y la leptina, en estudios poblacionales en sujetos sanos.

2.- OBJETIVOS DEL ESTUDIO.

Los objetivos de nuestro estudio fueron:

- Establecer valores de referencia del volumen tiroideo, y sus determinantes, en sujetos adultos sanos.
- Determinar el grado de yododeficiencia en una zona de Cataluña no estudiada previamente.
- Comparar el volumen tiroideo en pacientes con diabetes mellitus tipo 1 y sujetos normales, y analizar si las diferencias están en relación con variaciones en variables antropométricas y de composición corporal.
- Estudiar la relación entre el eje hipófiso-tiroideo y la leptina, en adultos sanos, ya que ambos juegan un papel relevante en la regulación fisiológica de la homeostasis energética.

3.- MATERIAL Y MÉTODOS.

3.1.- SUJETOS SANOS:

Los sujetos sanos fueron reclutados de la población de L'Hospitalet de Llobregat, de manera aleatoria se seleccionaron 880 personas del censo de 1996 (280,000 habitantes), de edades comprendidas entre los 15 y los 70 años, y se estratificaron por edad y sexo. Los sujetos fueron invitados a participar en el estudio mediante carta y llamada telefónica, y en caso necesario se les informó verbalmente en sus domicilios.

Se realizó la historia clínica, siendo rechazados aquellas personas con enfermedad tiroidea conocida, personal o en familiares de primer grado, así como con enfermedades crónicas (cardíacas, renales o hepáticas), o bajo tratamiento con fármacos con efecto sobre el funcionalismo tiroideo, y aquellos que no hubiesen residido al menos durante cuatro años en L'Hospitalet de Llobregat.

No se objetivaron diferencias entre la muestra inicial, y los sujetos que finalmente participaron en el estudio, en relación a la edad y el sexo.

Doscientas noventa y dos personas fueron estudiadas, pero 24 fueron excluidas: seis por disfunción tiroidea no diagnosticada previamente, y 18 por bocio nodular descubierto al realizar la ecografía. Finalmente, 268 sujetos sanos fueron analizados, 134 hombres y 134 mujeres, cuya distribución por sexo y edad fue representativa de la población de L'Hospitalet de Llobregat.

3.1.- PACIENTES AFECTOS DE DIABETES MELLITUS TIPO 1.

Entre 1993 y 1997 todos los pacientes recientemente diagnosticados de diabetes mellitus tipo 1, y controlados en nuestro Servicio, fueron incluidos en un estudio de prevalencia e influencia de la autoinmunidad tiroidea durante los primeros años de evolución de la enfermedad[49]. El diagnóstico de diabetes mellitus tipo 1 se realizó de acuerdo con la presencia de los criterios clásicos de insulinodependencia[50], datos inmunológicos (presencia de anticuerpos anti-glutámico ácido descarboxilasa en el 75'4 %, anti-tirosinfosfatasa en el 49'2 %, y uno o ambos marcadores inmunológicos en el 81'5 %), y la determinación de la reserva de la secreción de insulina (niveles de Péptido C inferiores a 1 nmol/L tras estímulo con glucagón[49].

Todos fueron instruidos en la realización de ejercicio físico, y dieta entre 1,500 y 2,500 Kcal, según sus características antropométricas. Todos fueron tratados con una pauta de tratamiento insulínico intensivo, con el objetivo de alcanzar concentraciones de glucosa y HbA1c cercanos a la normalidad.

En 1999, la cohorte inicial de pacientes (n = 111) menores de 40 años que continuaron el seguimiento en nuestra Unidad fueron invitados a participar en el estudio sobre el volumen tiroideo, y 83 aceptaron. Siete fueron excluidos por estar previamente diagnosticados de patología tiroidea autoinmunitaria (6 con hipotiroidismo primario, 1 con enfermedad de Graves-Basedow), y 11 por tener anticuerpos antiperoxidasa tiroidea positivos.

Finalmente 65 pacientes (36 hombres y 29 mujeres) fueron analizados. Ninguno tomaba fármacos con efecto conocido sobre la función tiroidea.

Todos los sujetos sanos y los pacientes fueron informados sobre el propósito del estudio y dieron voluntariamente su consentimiento para participar en el estudio. El estudio fue aprovado por el comité ético del Hospital.

3.3.- MÉTODOS.

Todos los sujetos que participaron fueron interrogados sobre el consumo de sal yodada, tabaco (cigarrillos/día) y alcohol (gramos/día), y el número de gestaciones en las mujeres.

Se determinó el peso, la talla, el índice de masa corporal (peso/talla^2), y el cociente cintura/cadera. El área de superficie corporal (ASC) se calculó mediante la fórmula[51]: $ASC = Peso^{0'425} \times Talla^{0'725} \times 71'84 \times 10^{-4}$ (Peso en Kg, y talla en cm).

Se evaluó clínicamente el volumen tiroideo de acuerdo con la clasificación de Pérez[7].

Se determinó la TSH plasmática (límites normales 0'48 – 4'36 mU/L) mediante un ensayo enzimoinmunométrico específico (Elypse), los anticuerpos antiperoxidasa tiroidea mediante radioinmunoensayo (Bio Code, Izasa, Lieja, Bélgica), y la excreción urinaria de yodo, en muestras de orina reciente en sujetos sanos y en orina de 24 horas en sujetos con diabetes mellitus, mediante el método de Benotti et al.[52].

La HbA1c se determinó por cromatografía líquida de alto rendimiento (HA 8140, Menarini Diagnostics, Florencia, Italia)

La determinación de la leptina se realizó mediante un RIA (Linco Research, St Charles, MO, USA), que utiliza leptina humana recombinante (HR-leptina), con un antisuero dirigido contra la HR-leptina. El límite de detección del ensayo fue de 0'5 ng/mL. Los coeficientes de variación intra e inter-ensayo fueron del 7 y 8 % respectivamente. El RIA para leptina no tiene reacción cruzada con la proinsulina, insulina o glucagón humanos.

La composición corporal se determinó mediante impedanciometría[53], utilizando la fórmula facilitada por el fabricante (Holtain BC Analyser, Londres, RU), obteniendo el valor del agua corporal total (en L), la masa no grasa (en Kg), la masa grasa (en Kg), y el porcentaje de masa grasa. La precisión de esta técnica en la determinación de la masa grasa es de ± 3 %.

El mismo radiólogo realizó todas las ecografías, determinando la ecogenicidad, y el volumen tiroideo según el método de Brunn et al.[16], con el mismo ecógrafo,

utilizando una sonda de 7’5 MHz (Toshiba Sonolayer SA 250); la variabilidad intraobservador fue del 10 %, y el error del 11 %. Los sujetos fueron examinados en decúbito supino, con el cuello en hiperextensión.

Se realizaron planos longitudinales y transversales, y el volumen de cada lóbulo se calculó multiplicando la longitud máxima x el grosor máximo x la anchura máxima x 0’479. El volumen tiroideo se obtuvo de la suma de ambos lóbulos, y el istmo no fue incluido. Los nódulos inferiores a 10 mm se incluyeron en el cálculo del volumen tiroideo.

Cada paciente con diabetes mellitus fue apareado con un sujeto control procedente del grupo de población sana, del mismo sexo y edad (± 2 años).

4.- JUSTIFICACIÓN DEL TEMA UNITARIO.

En el primer trabajo se muestran los valores del volumen tiroideo ecográfico, en una población adulta no yododeficiente, y se han elaborado unas tablas en las que se distribuyen los valores por sexos e intervalos de edad, lo cual permite establecer valores de referencia del volumen tiroideo para nuestra población. Estos datos son extrapolables a otras zonas no deficientes en yodo, ya que son similares a otros estudios en poblaciones europeas.

En el segundo trabajo se estudian los determinantes del volumen tiroideo en esta población, mostrando las correlaciones con la edad, el sexo, y variables antropométricas, biológicas y de composición corporal, siendo la superficie corporal el determinante principal. El análisis demuestra que en las zonas yodosuficientes, la yoduria no es un factor importante en el volumen del tiroides.

En el tercer trabajo se demuestra que el volumen tiroideo de los pacientes con diabetes mellitus tipo 1 es mayor que en sujetos sanos, y que se debe a diferencias en la composición corporal, especialmente la masa no grasa y el área de superficie corporal.

En el cuarto trabajo se describe la correlación entre las variables antropométricas, biológicas y de composición corporal, con el volumen tiroideo y la leptina, y la diferente regulación de estos parámetros en hombres y mujeres.

TRABAJOS PUBLICADOS

F. J. Maravall [1]
N. Gómez-Arnáiz [1]
A. Gumá [2]
R. Abós [3]
J. Soler [1]
J. M. Gómez [1]

Reference Values of Thyroid Volume in a Healthy, Non-iodine-deficient Spanish Population

Abstract

Our aim was to assess reference values of thyroid volume by ultrasonography in healthy adult subjects. We conducted an epidemiological cross-sectional study where 880 subjects were randomly selected from the town census of L'Hospitalet de Llobregat after being invited to participate in our study directly by mail and phone call. We made a clinical history of each subject and determined serum thyrotropin, antiperoxidase antibodies, urinary iodine excretion and thyroid volume by ultrasonography. Subjects with thyroid disease were excluded. We finally studied 268 representative subjects. The reference thyroid volume was median 7.31 ml, mean 8.22 ml (Confidence Interval: 7.75 – 8.69ml). In men: median 9.19 ml, mean 9.87 ml (CI: 9.09 – 10.65 ml); in women: median 6.19 ml, mean 6.57 ml (CI: 6.22 – 9.92 ml) ($p < 0.0001$). We grouped the subjects into decades, and found that thyroid volume was different ($p = 0.0034$) in males because the younger group had lower volume. We did not find any differences among age groups in women. The mean of the urinary iodine excretion was 154.23 µg/l. We have determined reference values of thyroid volume measured by ultrasonography in our iodine non-deficient population and prepared tables that distribute thyroid volume by sex and age.

Key words
Thyrotropin · Antiperoxidase antibodies · Urinary iodine excretion · Iodine non-deficient · Cross-sectional study

Introduction

Determination of thyroid volume is important for the diagnostic of thyroid diseases and therapeutic strategies as well as in assessing treatment efficacy. It is also essential for epidemiological studies to establish the prevalence of thyroid diseases particularly in endemic goiter and iodine deficiency (ID) areas, and to plan prevention programs such as prophylactic iodine administration. Physical examination is not a reliable technique for determining thyroid volume [1 – 3] or goiter prevalence [4,5] despite the standardized methods used such as clinical goiter classification by Perez et al. [6] at WHO, which has the problem of being much more qualitative than quantitative. Results vary greatly between and among observers, and much depends on the patient's neck anatomy [7]. Different techniques do exist for determining thyroid volume such as Tc^{99m} scintiscan [8], single-photon emission computer tomography [9], and positron emission

Affiliation
[1] Endocrinology Service, Ciutat Sanitària i Universitària de Bellvitge, C/ Feixa Llarga s/n, L'Hospitalet de Llobregat, Barcelona, Spain
[2] Radiology Service, Ciutat Sanitària i Universitària de Bellvitge, C/ Feixa Llarga s/n, L'Hospitalet de Llobregat, Barcelona, Spain
[3] Clinical-Epidemiology Unit, Ciutat Sanitària i Universitària de Bellvitge, C/ Feixa Llarga s/n, L'Hospitalet de Llobregat, Barcelona, Spain

Correspondence
Dr. F. J. Maravall · c/ Paer Casanovas 37, 4° · C. 25.008 Lleida · Spain · Phone: +34 (973) 235192 · Fax: +34 (973) 248754 · E-Mail: javimarlleida@hotmail.com

Received 24 November 2003 · **Accepted after revision** 31 March 2004

Bibliography
Horm Metab Res 2004; 36: 645–649 © Georg Thieme Verlag KG Stuttgart · New York · DOI 10.1055/s-2004-825901 · oISSN 0018-5043

tomography [10,11], but these techniques measure functional volume and use ionizing radiations. CT scan [12] and magnetic resonance imaging [13] obtains a thyroid volume with a high level of precision, but it has an elevated cost. Ultrasonography is a precise technique and is the best alternative, being a simple method as well as being the cheapest [2,8,11,14,15] and has no adverse effects [14], but the method is not useful in goiter with substernal extension [2,12,14,16,17].

Several factors are known to be involved in the regulation of thyroid volume; they have an influence on its variability. The differences between iodine intake, environmental factors and anthropometrics attributes [18,19] may contribute to create many thyroid volume differences when measured in different geographical areas [20]. In addition, the sample size of different studies is not representative of the population studied. A European project was thus carried out in order to evaluate thyroid volume in a population of schoolchildren in connection with iodine deficiency levels in several European countries (Thyro-Mobil).

The aims of the present study were, first, to assess reference values of thyroid volume in a healthy adult population and to compare with previous epidemiological studies, and second, to assess the iodine deficiency degree in an area of Spain that had not previously been studied.

Materials and Methods

Subjects were recruited from L'Hospitalet de Llobregat, a town of 280,000 inhabitants. Eight hundred and eighty subjects were randomly selected from the town census (1996), all of whom were within 15 and 70 years old. They were classified according to gender and age, and were invited to participate in our study directly by mail and phone call, and finally by verbal information. All subjects were fully informed of the purpose of the study and gave their voluntary consent to take part in the investigation. The Ethics Committee at the Hospital approved the study. We made a clinical recording of every subject, refusing candidates with previous thyroid disease and first-degree family history of thyroid disease. Subjects recruited were in good health, had no chronic illness (heart, kidney, or liver failure), were not on medication affecting thyroid function, and had been living in the town for the last four years. There was no evidence of any differences between the initial sample and the subjects that participated in the study at the end regarding gender and age. After previous selection, 292 participants (33.18 %) were willing to enrol, but 24 were excluded – six due to unknown thyroid dysfunction (abnormal TSH), and eighteen due to previously undiscovered nodular goiter diagnosed by ultrasonography. Finally, 268 healthy subjects were analyzed, 134 men and 134 women; distribution by sex and age was representative of the L'Hospitalet de Llobregat population. All subjects were questioned about tobacco and alcohol consumption. Weight, height, body mass index (BMI), and waist-hip ratio (WHR) were determined. Thyroid size was estimated by palpation according to the Perez classification [6]. Plasma TSH within the normal range of 0.48–4.36 mU/l was confirmed by a specific two-site enzymoimmunometric assay (Elypse), and serum antithyroid peroxidase antibodies (TPO Ab) were determined by radioimmunoassay (Bio Code, Izasa, Liège, Belgium); values higher than 80 IU/ml were considered positive. Urinary iodine excretion (UIE) was measured in extemporary samples according to the method by Benotti et al. [21]. Thyroid volume was determined by ultrasonography according to the method by Brunn et al. [15], and tests were performed by the same experienced radiologist (G.A.) with the same equipment, a 7.5 MHz linear phased-array transducer (Toshiba Sonolayer SA 250). The subjects were examined in the supine position with hyperextended neck and skin covered by acoustical gel. Longitudinal and transverse scans were performed; the volume of each lobe was calculated by multiplying the maximum thickness by maximum length by maximum width by 0.479. Thyroid volume was the sum of both lobes, and the isthmus was not included. Nodules smaller than 5 mm were included in volume determination.

Table **1** Population characteristics

	Whole group	*Men*	*Women*
Age (years)	41.06 (15.73)	41.38 (15.88)	40.73 (15.62)
Height (cm)	163 (10)	169 (7)	156 (7)
Weight (kg)	71.86 (14.83)	78.33 (13.01)	65.38 (13.71)
BMI (kg/m^2)	27.15 (5.04)	27.30 (4.14)	26.99 (5.82)
WHR	0.86 (0.10)	0.93 (0.08)	0.79 (0.07)
TSH (mU/l)	1.59 (0.82)	1.49 (0.80)	1.68 (0.83)
TPO Ab (%)	7.08	5.97	8.20
UIE (µg/l)	154.2 (114.8)	156.0 (107.0)	152.4 (122.3)
Smoker (%)	25	29.85	20.14
Drunker (%)	11.66	21.64	1.49

Dates are expressed as the mean (±SD) and percentage.

Results are expressed as a mean, median, and 95 % confidence interval (CI). Relationships among variables were examined by Pearson's correlation coefficient. The thyroid volume values distributed into decades were not normally distributed according to the Kolmogorov-Smirnov test. The Kruskall-Wallis non-parametric test was used to evaluate differences among decades, and the Mann-Whitney non-parametric U-test was used to compare gender. Values of $p < 0.05$ were considered significant. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS/Windows v 6.0, SPSS inc., Chicago IL, USA).

Results

The characteristics of the population studied are summarized in Table **1**. The mean age in men was 41.4 years (15 – 70 year limits), and 40.7 years (17 – 70 year limits) in women. All subjects were classified as having goiter grade 0.

The TSH value was 1.59 ± 0.82 mU/l. TPO Abs were positive in 19 subjects (7.08 %), 8 men (5.97 %) and 11 women (8.20 %). The UIE was 154.22 ± 114.8 µg/l. Table **1** shows the cigarette-smoking frequency (10 or more cigarettes at day) and alcohol consumption (20 or more grams at day) of the individuals concerned.

Table **2** Reference values of thyroid volume distributed by gender

AGE (years)	MEN n	Mean (ml)	Median (ml)	C.I. (ml)	WOMEN n	Mean (ml)	Median (ml)	C.I. (ml)
15 – 20	17	6.61	6.25	5.90 – 7.32*	16	6.03	5.41	5.12 – 6.94
21 – 30	28	10.75	9.84	9.09 – 12.41	27	8.42	6.29	5.63 – 7.21
31 – 40	17	10.32	9.71	8.72 – 11.91	23	7.10	6.64	5.95 – 8.25
41 – 50	25	10.49	9.62	7.73 – 13.25	25	7.01	6.14	6.19 – 7.84
51 – 60	29	10.35	10.17	8.86 – 11.83	24	6.53	6.78	5.92 – 7.15
61 – 70	18	9.53	8.51	7.96 – 11.09	19	6.07	5.91	5.41 – 6.72
Whole group	134	9.87	9.19	9.09 – 10.65	134	6.57	6.19	6.22 – 6.92

* $p = 0.0034$.

Table **3** Thyroid volume epidemiological studies

Study	Men	Women	Study	Men	Women
Gutekunst et al. [1]	9.1 (3.3 – 27.4)	6.9 (2.5 – 34)	Gutekunst et al. [1]	23.1 (3.8 – 105.0)	13.3 (2.6 – 124.1)
Berghout et al. [17]	13.2 (6.7 – 20.4)	8.2 (2.7 – 20.3)	Nyagaard et al. [3]		12 – 18*
Wesche et al. [27]	10.3 (± 3.4)	6.9 (± 2.9)	Hegedüs et al. [20]	19.6 (± 4.7)	17.5 (± 4.2)
Barrère et al. [28]	12.8 – 13.3*	8.3 – 9.3*	Olbricht et al. [24]	16.7 (9 – 38)	13.5 (6 – 25)
			Hintze et al. [29]	19.2 (3.2 – 187.3)	16.6 (5.4 – 98.1)
			Knudsen et al. [30]		
			Mild ID	15'8	9'6 – 12'4*
			Moderate ID	19'5	10'3 – 14'8*

Mean (± standard deviation), median (limit values). *Medians concerning to age groups.

The reference thyroid volume in our population was 7.31 ml median, 8.22 ml mean (CI: 7.75 – 8.69 ml). Differences among decades were not found ($p = 0.91$). The reference thyroid volume was 9.19 ml median and 9.87 ml mean (CI: 9.09 – 10.65 ml) in men and 6.19 ml median and 6.57 ml mean (CI: 6.22 – 9.92 ml) in women. Thyroid volume was significantly higher in men ($p < 0.0001$).

We grouped the subjects by gender into decades; the values are summarized in Table **2**, and they showed significant statistical differences in men ($p = 0.0034$) due to the effect that the youngest group showed differences compared to every other group. Significant statistical differences among age groups in women were not found ($p = 0.42$).

A negative correlation was found between thyroid volume and TSH ($r = -0.23$, $p = 0.001$). No correlations were found among thyroid volume and iodine excretion positive TPO Ab, cigarette smoking, or alcohol consumption in women, but a negative correlation was found between alcohol consumption and thyroid volume in men ($r = -0.40$, $p = 0.02$)

Discussion

Ultrasonography is now considered the most reliable method in determining thyroid volume and goiter prevalence, especially in homogeneous glands without excessive size [4,15,20].

The population participating was considered representative for this study, as the subjects randomly selected from the census had to go to the hospital on working days and undergo several tests on a subject unknown to the majority of the population; also, subjects with first-degree relatives having thyroid disease were rejected. After excluding 24 subjects with hormonal and/or ultrasonography thyroid disorders, the 268 remaining subjects distributed by age and gender were representative of the L'Hospitalet de Llobregat population.

This study presents the reference thyroid volume by ultrasonography in adults for the iodine-replete individuals of this town as a whole group and distributed according to sex and age. The mean UIE reflects a daily intake within the range recommended by WHO [22].

Local data are not only very useful when pathological volumes in clinical medicine are to be established, but also in evaluating the prevalence of disorders related to iodine deficiency and the effectiveness of preventing measures.

Thyroid volume is significantly correlated with age in children [4,23]; in our adult population, only younger men, unlike women, showed significant differences among the other decade groups. This might be because women conclude puberty development earlier, and thyroid volume does not vary in size after puberty [3,17] in subjects without pathology, in contrast to other results by different authors [20,24]. Wiersinga et al. [25] showed that most thyroid growth during puberty coincides with the accelerated growth phase, which occurs earlier in women. Ashiza-

wa et al. [26] studied 120,000 children and reported thyroid volume increase to be related to age in both sexes, but this increase stopped in girls between 14 and 16 years old.

In previous studies on healthy populations, normal values varied depending on the presence of iodine deficiency, and this leads to a great variation in the thyroid volume to be considered as normal. The results of different studies are showed in Table **3**.

Our results agree with other population studies in non-iodine deficiency areas, and are very similar to the results found by Gutekunst et al. [1] in a Swedish population that showed a median thyroid volume of 9.1 ml in men and 6.9 ml in women. Berghout et al. [17] showed median values of 13.2 ml in men and 8.2 ml in women in a Dutch population. Wesche et al. [27] showed mean values of 10.3 ± 3.4 ml in men and 6.9 ± 2.9 ml in women in Amsterdam. Barrère et al. [28] found volumes in an adult French population whose medians range between 12.8 and 13.3 ml in men and 8.3 and 9.3 ml in women.

On the other hand, higher thyroid volumes are found in iodine deficiency areas; Heguedüs et al. [20] found thyroid values of 18.6 ± 4.5 ml in a Danish population; Nyagaard et al. [3] obtained thyroid volumes between 12 and 18 ml in women. Gutekunst et al. [1] showed median values of 23.1 ml in men and 13.3 in women in a German population. Likewise, Olbricht et al. [24] obtained median values of 16.7 ml in men and 13.5 ml in women in a healthy German population without goiter. Hintze et al. [29] found median values of 19.2 ml in men and 16.6 ml in women in a German population over 60 years of age. Knudsen et al. [30] studied a Danish population from two areas with slightly different iodine status (mild and moderate iodine deficiency) in men aged 60 – 65 years and women aged 18 – 65 years, finding median values similar to other iodine-deficient areas.

Population studies performed on children in non-iodine-deficient areas showed similar volumes in 14-year-olds to those found in the first decade of our population; Vitti et al. [4] and Aghini-Lombardi et al. [31] found values of 6.3 ± 1.5 ml. However, Wiersinga et al. [25] reported medians of 12.1 ml in men and 8.9 ml in women at 18 years old in a study on schoolchildren in a Dutch population. These volumes are clearly lower than those obtained by Delange et al. [32] in a great population study performed as part of the Thyro-Mobil project that established the highest limit of normality for 15-year-old subjects in non-iodine-deficient areas at 16 ml for boys and 16.1 ml for girls.

A negative correlation between thyrotropin and thyroid volume was obtained according to Barrère [28], but contrasted with other studies [1,17,20]; there is no clear hypothesis to explain thyrotropin's influence on thyroid volume in normal glands without nodular disease in non-iodine-deficient areas. No correlation could be found between iodine excretion and thyroid volume as in other iodine-sufficient areas [1,17] in contrast to iodine-deficient areas [33]. Likewise, no correlation could be found between positive TPO Ab and thyroid volume; this is probably due to the exclusion of subjects with autoimmune thyroid disease. No influence of cigarette smoking on thyroid volume could be confirmed; however, a negative correlation could be measured between alcohol consumption and thyroid volume in men; in previous studies, this influence was related to alcohol's direct toxic effects on the thyroid gland [14] or to alcohol's protective effect against developing thyroid gland disease [34]. The lack of evidence for a correlation in women is probably due to the lack of female drinkers tested.

Obviously, larger population studies are required to achieve normal values for thyroid volume in healthy subjects, whereby standardizing the ultrasonography technique to assess thyroid volume would be necessary to minimize variation between and among observers [35]. The data obtained according to other studies in non-iodine-deficient areas as well as the random nature of the test population in this study validate the results as reference values for thyroid volume in an adult healthy population.

Acknowledgments

We wish to thank the Ajuntament de L'Hospitalet de Llobregat, Barcelona, for making the data of the town census available, Dr. Francisco Escobar del Rey for his urinary iodine excretion determinations, and Dr. Rosa Ramón and Dr. Miguel Ángel Navarro for their assistance.

References

[1] Gutekunst R, Smolarek H, Hasenpusch U, Stubbe P, Friedrich HJ, Wood WG, Scriba PC. Goitre epidemiology: thyroid volume, iodine excretion, thyroglobulin and thyrotropin in Germany and Sweden. Acta Endocrinol (Cophen) 1986; 112: 494 – 501

[2] Berghout A, Wiersinga WM, Smits NJ, Touber JL. The value of thyroid volume measured by ultrasonography in the diagnosis of goiter. Clin Endocrinol (Oxf) 1988; 28: 409 – 414

[3] Nygaard B, Gideon P, Dige-Petersen H, Jespersen N, Sølling K, Veje A. Thyroid volume and morphology and urinary iodine excretion in a Danish municipality. Acta Endocrinol (Cophen) 1993; 129: 505 – 510

[4] Vitti P, Martino E, Aghini-Lombardi F, Rago T, Antonangeli L, Maccherini D, Nanni P, Loviselli A, Balestrieri A, Araneo G. Thyroid volume measurement by ultrasound in children as a tool for the assessment of mild iodine deficiency. J Clin Endocrinol Metab 1994; 79: 600 – 603

[5] Zimmermann M, Saad A, Hess S, Torresani T, Chaouki N. Thyroid ultrasound compared with World Health Organization 1960 and 1994 palpation criteria for determination of goiter prevalence in regions of mild and severe iodine deficiency. Eur J Endocrinol 2000; 143: 727 – 731

[6] Perez C, Scrimshaw NS, Muñoz JA. Technique of endemic goiter surveys. In: Endemic goiter, Geneva. Geneva World Health Organization 1960; monogr ser 44: 369 – 383

[7] McLennar R, Gaitan E, Miller MC. Observer variation in grading and measuring the thyroid in epidemiological surveys. In: Stanbury JB (ed). Endemic goiter. Pan American Health Organization; scientific publication. New York: Wiley, 1959; 193: 66 – 77

[8] Tannahill AJ, Hooper MJ, England M, Ferris JB, Wilson GM. Measurement of thyroid size by ultrasound, palpation and scintiscan. Clin Endocrinol (Oxf) 1978; 8: 483 – 486

[9] Chen JJS, LaFrance MD, Allo MS, Cooper DS, Landerson PW. Single photon emission computer tomography of the thyroid. J Clin Endocrinol Metab 1988; 66: 1240 – 1246

[10] Crawford DC, Flower MA, Pratt BE, Hill C, Zweit J, McCready VR, Harmer CL. Thyroid volume measurement in thyrotoxic patients: comparison between ultrasonography and iodine-124 positron emission tomography. Eur J Nucl Med Mol Imaging 1997; 24: 1470 – 1478

[11] Frey P, Townsend D, Flattet A, de Gautard R, Widgren S, Jeavons A, Christin A, Smith A, Long A, Donath A. Tomographic imaging of the thyroid using I^{124}. J Clin Endocrinol Metab 1986; 63: 918 – 927

[12] Nygaard B, Nygaard T, Court-Payen M, Jensen LI, Soe-Jensen P, Gerhard NielsenK, Fugl M, Hegedus L. Thyroid volume measured by ultrasonography and CT. Acta Radiol 2002; 43: 269 – 274
[13] Huysmans DA, de Haas MM, van den Broek WJ, Hermus AR, Barentsz JO, Corstens FH, Ruijs SH. Magnetic resonance imaging for volume estimation of large multinodular goitres: a comparison with scintigraphy. Br J Radiol 1994; 67: 519 – 523
[14] Hegedüs L. Thyroid size determined by ultrasound. Dan Med Bull 1990; 37: 249 – 263
[15] Brunn J, Block U, Ruf G, Bos L, Kunze W, Seriba PC. Volumetrie der Schilddrüssenlappen mittels Real Time Sonographie. Dtsch Med Wochenschr 1981; 106: 1338 – 1340
[16] Jarlov AE, Hegedüs L, Gjorup T, Hansen JM. Accuracy of the clinical assessment of the thyroid size. Dan Med Bull 1991; 38: 87 – 89
[17] Berghout A, Wiersinga WM, Smits NJ, Touber JL. Determinants of thyroid volume as measured by ultrasonography in healthy adults in a non-iodine deficient area. Clin Endocrinol (Oxf) 1987; 26: 273 – 280
[18] Gómez JM, Maravall FJ, Gómez N, Gumà A, Soler J. Determinants of thyroid volume as measured by ultrasonography in healthy adults randomly selected. Clin Endocrinol (Oxf) 2000; 53: 629 – 634
[19] Wesche MF, Wiersinga WM. Relation between lean body mass and thyroid volume in competition rowers before and during intensive physical training. Horm Metab Res 2001; 33: 423 – 427
[20] Hegedüs L, Perrild H, Poulsen RL, Andersen JR, Holm B, Schnohr P, Jensen G, Hansen JM. The determination of thyroid volume by ultrasound and its relationship to body weight, age and sex in normal subjects. J Clin Endocrinol Metab 1983; 56: 260 – 263
[21] Benotti J, Benotti M, Pino S, Gardyna H. Determination of total iodine in urine, stool, diets, and tissue. Clin Chem 1965; 2: 932 – 936
[22] WHO, UNICEF, ICCIDD. Assessment of the iodine deficiency disorders and monitoring their elimination. A guide for programme managers. 2nd ed. Geneva: World Health Organization 2001; WHO Document WHO/NHD/01.1
[23] Semiz S, Senol U, Bircan , Gumuslu S, Bilmen S, Bircan I. Correlation between age, body size and thyroid volume in an endemic area. J Endocrinol Invest 2001; 24: 559 – 563
[24] Olbricht T, Schmitka T, Mellinghoff U, Benker G, Reinwein D. Sonographic determination of thyroid volume in subjects with healthy thyroids. Dtsch Med Wochenschr 1983; 108: 1355 – 1358
[25] Wiersinga WM, Podoba J, Srbecky M, van Vessem M, van Beeren HC, Platvoet-ter MC. A survey of iodine intake and thyroid volume in Dutch schoolchildren: reference values in an iodine-sufficient area and the effect of puberty. Eur J Endocrinol 2001; 144: 595 – 603
[26] Ashizawa K, Shibata Y, Yamashita S, Namba H, Hoshi M, Yokoyama N, Izumi M, Nagataki S. Prevalence of goiter and urinary iodine excretion levels in children around Chernobyl. J Clin Endocrinol Metab 1997; 82: 3430 – 3433
[27] Wesche MFT, Wiersinga WM, Smits NJ. Lean body mass as a determinant of thyroid size. Clin Endocrinol (Oxf) 1998; 48: 701 – 706
[28] Barrère X, Valeix P, Preziosi P, Bensimon M, Pelletier B, Galan P, Hercberg S. Determinants of thyroid volume in healthy french adults participating in the SU.VI.MAX cohort. Clin Endocrinol (Oxf) 2000; 52: 273 – 278
[29] Hintze G, Winderler J, Baumert J, Stein H, Köbberling J. Thyroid volume and goiter prevalence in elderly as determined by ultrasound and their relationship to laboratory indices. Acta Endocrinol (Cophen) 1991; 124: 12 – 18
[30] Knudsen N, Bülow I, Jorgensen T, Laurberg P, Ovesens L, Perrild H. Goitre prevalence and thyroid abnormalities at ultrasonography: a comparative epidemiological study in two regions with slightly different iodine status. Clin Endocrinol (Oxf) 2000; 53: 479 – 485
[31] Aghini-Lombardi F, Antonangeli L, Pinchera A, Leoli F, Rago T, Bartolomei AM, Vitti P. Effect of iodized salt on thyroid volume of children living in an area previously characterized by moderate iodine deficiency. J Clin Endocrinol Metab 1997; 82: 1136 – 1139
[32] Delange F, Benker G, Caron P, Eber O, Ott W, Peter F, Podoba J, Simescu M, Szybinsky Z, Vertongen F, Vitti P, Wiersinga W, Zamrazil V. Thyroid volume and urinary iodine in European schoolchildren: standardization of values for assessment of iodine deficiency. Eur J Endocrinol 1997; 136: 180 – 187
[33] Rasmussen LB, Ovesen L, Bulow I, Jorgensen T, Knudsen N, Laurberg P, Perrild H. Relations between various measures of iodine intake and thyroid volume, thyroid nodularity, and serum thyroglobulin. Am J Clin Nutr 2002; 76: 1069 – 1076
[34] Knudsen N, Bulow I, Laurberg P, Perrild H, Oversend L, Jorgensent T. Alcohol consumption is associated with reduced prevalence of goiter and solitary thyroid nodules. Clin Endocrinol (Oxf) 2001; 55: 41 – 46
[35] Zimmermann MB, Molinari L, Spelh M, Weidinger-Toth J, Podoba J, Hess S, Delange F. Toward a consensus on reference values for thyroid volume in iodine-replete schoolchildren: results of a workshop on inter-observer and inter-equipment variation in sonographic measurement of thyroid volume. Eur J Endocrinol 2001; 144: 213 – 220

Clinical Endocrinology (2000) 53, 629–634

Determinants of thyroid volume as measured by ultrasonography in healthy adults randomly selected

José Manuel Gómez*, Francisco Javier Maravall*, Núria Gómez*, Anna Gumà† and Juan Soler*
*Endocrinology and †Radiology Services, Ciudad Sanitaria y Universitaria de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain

(Received 24 February 2000; returned for revision 23 March 2000; finally revised 27 June 2000; accepted 4 August 2000)

Summary

OBJECTIVES The relationship between thyroid volume and anthropometric characteristics is a matter of controversy. The aim of this study was to investigate thyroid volume and its determinants in healthy adult subjects from a noniodine-deficient area.

DESIGN AND PATIENTS Of the 280 000 inhabitants of the city, served by L'Hospitalet de Llobregat, we randomly selected 880 subjects from the census of the city. The participation rate in the study was 44%; after application of several exclusion criteria, a further 28 subjects were excluded because of previously diagnosed thyroid disease. We finally studied 268 subjects representative of the census of the city: 134 male and 134 female, without thyroid disease. We determined the anthropometric characteristics, body mass index, waist-hip ratio, body surface area; body composition by bioelectrical impedance analyser; thyroid volume by ultrasonography; basal TSH, antithyroid antibodies and urinary iodine excretion.

RESULTS Thyroid volume in our population was higher in males (9·19 ml, CI 9·09–10·65) than in females (6·19 ml, CI 6·02–6·92), $P = 0·001$. Significant correlations were found among thyroid volume and body weight ($r = 0·39$, $P = 0·0001$), height ($r = 0·44$, $P = 0·0001$), body mass index ($r = 0·13$, $P = 0·02$), waist-hip ratio ($r = 0·38$, $P = 0·0001$), body surface area ($r = 0·48$, $P = 0·0001$), total body water ($r = 0·14$, $P = 0·02$), free fat mass ($r = 0·47$, $P = 0·0001$), fat mass ($r = 0·37$, $P = 0·001$) and body fat ($r = 0·32$, $P = 0·001$). Negative correlation was found between thyroid volume and basal TSH ($r = -0·26$, $P = 0·001$). No correlations were found among thyroid volume and iodine excretion, previous pregnacies in women, cigarette smoking and alcohol consumption. In a multiple regression analysis with thyroid volume as the dependent variable, body surface area was demonstrated to account for the 44% of variation of thyroid volume ($P = 0·0001$).

CONCLUSION It is important to know the reference values of the thyroid volume in a population free of iodine deficiency and its determinants. Body surface area accounts for much of the variation of thyroid volume. Age, gender, anthropometric variables, body composition variables and biological variables, do not significantly influence the thyroid volume when considered as possible additions to this baseline model.

Thyroid volume is usually determined clinically but recent reports define ultrasonography (US) as a more precise method of determining gland volume, and its accuracy as higher than that of clinical examination in establishing the presence of goitre. US volumetry is now considered the most reliable method of determining thyroid volume (Brunn *et al.*, 1981; Leisner, 1987; Hegedüs *et al.*, 1990; Nygaard *et al.*, 1993; Vitti *et al.*, 1994).

Several factors are known to be involved in the regulation of the volume of the thyroid gland, and the most extensively studied are the effects of iodine on the thyroid gland. The relationship among thyroid size, age, sex and anthropometric characteristics is a matter of controversy and some of these characteristics appear as determinants of thyroid volume in different studies of adults or children (Hegedüs *et al.*, 1983; Gutekunst *et al.*, 1986; Berghout *et al.*, 1988; Nygaard *et al.*, 1993; Vitti *et al.*, 1994; Lisbôa *et al.*, 1996).

In order to obtain the reference values of US thyroid volume, a group of healthy adults was studied in our noniodine-deficient area using an accurate US method. The aim of this prospective study was to investigate thyroid volume and its determinants in healthy subjects randomly selected from among 280 000 inhabitants living in the city, at L'Hospitalet de Llobregat, Barcelona.

Subjects and methods

Subjects

Subjects were recruited from L'Hospitalet de Llobregat, a

Correspondence: Dr J.M. Gómez, c/Sabino de Arana 40, 3°,2ª, Barcelona 08028. Spain. Fax: 93–2607846; E-mail: iroigsag@jet.es

working-class community adjacent to Barcelona with 280 000 inhabitants. All participants were identified by the census and self-identified as living for at least the last 4 years in the city. Eight-hundred and eighty adult subjects were randomly selected from the census of the city and were invited to participate in the study, either directly by mail or phone call and finally by verbal information. They were fully informed of the purpose of the study and gave their voluntary consent to take part in the investigation. The study was approved by the ethics committee at the hospital. The participation rate was 44% with the following exclusion criteria: subjects with goitre, subjects with family history of autoimmune disease, subjects with past or present autoimmune thyroid disease, individuals treated with thyroid hormones, antithyroid drugs or drugs containining iodine. Twenty-four subjects submitted for the study were omitted from US study because of clinical presence of previously undiagnosed nodular goitre in 10 cases and multinodular goitre in 14 cases. Thus, the final study group consisted of 296 adult subjects, representative of the whole population of the city in sex and decade distribution, and were submitted to clinical and US examination of the thyroid. Twenty-eight subjects were excluded after clinical and US examination, four because abnormal sonographic echo-patterns were observed with nodular goitre greater than 10 mm in diameter, 10 because of multinodular goitre was observed, 14 because positive antithyroid peroxidase or antithyroglobulin antibodies of which three had with coexistent low basal TSH levels and one had high basal TSH levels. Furthermore, we observed 22 subjects with nodules smaller than 10 mm, mean 4 mm, distributed in the last three decades and they were included in the study. The 268 subjects included in the study, 134 male, aged 41·4 years, range 15–70 years and 134 female, aged 40·7 years, range 15–70 years, were divided according to sex and decade. The study was performed from April 1998 until May 1999. In women we assessed the number of previous pregnancies. To determine whether subjects consumed iodized salt, an appropriate questionnaire was administered and all subjects were questioned about tobacco, expressed as number of cigarettes/day and alcohol consumption, expressed as g/day.

Body mass index (BMI) was calculated as body weight divided by height (m) squared (kg/m^2); obesity was considered if the BMI was greater than 30 kg/m^2, and we determined waist-hip ratio. The body sur face area (BSA) in m^2 was calculated by using the formula:

$$BSA = W^{0.425} \times H^{0.725} \times 71{\cdot}84 \times 10^{-4}$$

where W is the weight in kg and H the height in cm (DuBois & DuBois, 1916).

Thyroid size was estimated by palpation by one expert examiner, and was scored according to the WHO criteria (Dunn & Madeiros-Neto, 1974) (grade 0, no palpable or visible goitre; grade 1 an enlarged thyroid that is palpable but not visible when the thyroid is in a normal position; grade 2, a palpably enlarged thyroid visible when the neck is in a normal position).

Thyroid ultrasonography and echogenicity studies were performed and interpreted by the same experienced radiologist (A.G.), intraobserver variability was 10%, using the same equipment with a 7-MHz linear phased-array probe (Toshiba Sonolayer SA 250). The subjects were examined in the supine position with hyperextended neck and skin covered by acoustic gel. Thyroid volume was measured as reported previously (Brunn *et al.*, 1981). Longitudinal and transverse scans were performed, allowing the measurement of the depth, the width and the lengh of each lobe. The volume of each lobe was calculated by the ellipsoid formula (volume in ml = 1/6 pi × maximum thickness × maximum length × maximum width). Total thyroid volume was the sum of both lobes, and the isthmus was not included. Nodules smaller than 10 mm detected by ultrasonography, were included in volume determination.

Body composition was determined by a bioelectrical impedance analyser using formula provided by the manufacturers (Holtain BC Analyser, London, UK) (Lukaski *et al.*, 1986). The results are expressed as: total body water in litres, free fat mass in kg, fat mass in kg, and body fat percentage. The precision of this test in determining fat mass is within ± 3%. All examinations were done by the same investigator (F.J.M.).

Plasma TSH (normal range 0·48–4·36 mU/l) was determined by a specific two-site enzymoimmunometric assay (Eleosys 2010, Boehringer Mannheim, Germany). Serum antithyroid-peroxidase and antithyroglobulin antibodies were determined by radioimmunoassay (Bio Code, Izasa, Liège, Belgium). Values higher than 40 IU/ml were considered as positive. Urinary iodine excretion was measured in extemporary samples in all subjects and determined according to the method of Benotti (Benotti *et al.*, 1965). Urinary iodine excretion are expressed as a median.

Usual statistics (mean, SD, median and percentage) have been used to describe the data. The Kolmogorov–Smirnov test was applied separately for men and women to check normality of the thyroid volume and 95% CI were calculated for thyroid volume. Kruskal–Wallis nonparametric testing for independent samples was used to compare quantitative data of thyroid volume among decade groups. Relationships among variables were sought by Pearson's correlation coefficient and by multiple regression analysis with forward selection. The regression coefficient generated by this analysis indicates the slope of the association among the dependent variable and the specified independent variables, after adjusting for other independent variables in the model (Rossner, 1990). *P*-values of $<0{\cdot}05$ were considered statistically significant. All statistical analysis was performed using the Statistical Package for Social Sciences (SPSS for Windows, SPSS Inc., Chicago, IL, USA).

Table 1 Characteristics of the population studied. Data are expressed as median ± SD

	Whole group	Males	Females
Age (years)	41·06 ± 15·73	41·38 ± 15·88	40·73 ± 15·62
Height (cm)	162 ± 9·5	169 ± 6·8	155 ± 6·7
Weight (kg)	71·8 ± 14·83	78·33 ± 13	65·38 ± 13·7
Body mass index (kg/m^2)	27·14 ± 5·04	27·3 ± 4·14	26·99 ± 5·81
Waist-hip ratio	0·86 ± 0·1	0·93 ± 0·1	0·79 ± 0·11
Body surface area (m^2)	1·76 ± 0·19	1·88 ± 0·16	1·64 ± 0·15
Thyroid volume (ml)	8·22 ± 3·92	9·87 ± 4·61	6·57 ± 2·05
Basal TSH (mU/l)	1·58 ± 0·82	1·49 ± 0·8	1·67 ± 0·83
Urinary iodine excretion (μ/l)	154·22 ± 114·8	156 ± 107	152·43 ± 122·38
Total body water (l)	38·94 ± 7·53	44·42 ± 5·79	33·45 ± 4·44
Free fat mass (kg)	53·33 ± 10·32	60·85 ± 7·9	45·82 ± 6·09
Fat mass (kg)	18·51 ± 9·81	17·47 ± 9·29	19·56 ± 10·23
Body fat (%)	24·94 ± 10	21·42 ± 9·09	28·46 ± 9·67

Results

The characteristics of the population studied are summarized in Table 1. BMI in the whole group was 27·1 ± 5 kg/m^2 and the prevalence of obesity was 18·9% in male and 24·6% in female. All subjects were classified as having goitre grade 0. Seventy percent of women had had one or more pregnancies. The answers to the questionnaire documented that 49·3% of the subjects had regularly used iodized salt, 30·22% of subjects were smokers (more than 10 cigarettes/day) and 18·65% usually drank alcohol (more than 20 g/day). All subjects had negative antithyroid-peroxidase or antithyroglobulin antibodies. The mean iodine excretion was 154·2 μg/l, without any significant variation depending on the season in which it was performed and was higher in the subjects of the last decade (160·58 μg/l, $P = 0·002$). Thyroid volume in our control population was higher in males (median 9·19 ml, CI 9·09–10·65) than in females (6·19 ml, CI 6·02–6·92), $P = 0·001$, and similar in the different decades for each sex (Fig. 1), except in patients younger than 20 years (median 6·25 ml, CI 5·9–7·32) in males, $P = 0·001$ and 5·41 ml, CI 5·12–6·94) in females, $P = 0·01$. We therefore grouped them together with a median value for men and for women (Table 1). Significant correlations were found among thyroid volume and body weight ($r = 0·39$, $P = 0·0001$) (Fig. 2), height ($r = 0·44$, $P = 0·0001$) (Fig. 2), BMI ($r = 0·13$, $P = 0·02$), waist-hip ratio ($r = 0·38$, $P = 0·001$), BSA ($r = 0·48$, $P = 0·0001$) (Fig. 2), total body water ($r = 0·14$, $P = 0·02$), free fat mass ($r = 0·47$, $P = 0·0001$) (Fig. 2), fat mass ($r = 0·37$, $P = 0·001$) and body fat ($r = 0·32$, $P = 0·001$). Negative correlation was found between thyroid volume and basal TSH ($r = -0·26$, $P = 0·001$) (Fig. 3).

No correlations were found among thyroid volume and iodine excretion, number of previous pregnancies, cigarette smoking and alcohol consumption.

A multiple regression analysis was performed to determine the independent variables that significantly predict the thyroid volume. The baseline characteristics used were: age, gender, weight, height, BMI, waist-hip ratio, BSA, total body water, free fat mass, fat mass, body fat, basal TSH, iodine excretion, number of previous preganancies, cigarette smoking and alcohol consumption. In this model BSA had a significant association with thyroid volume and accounted for 44% of the variation in thyroid volume ($P = 0·0001$). The other variables did not attain significance when considered as possible additions to the baseline model.

Discussion

This article presents the reference thyroid volume in adults, for the iodine-replete individuals of this city with a mean iodine

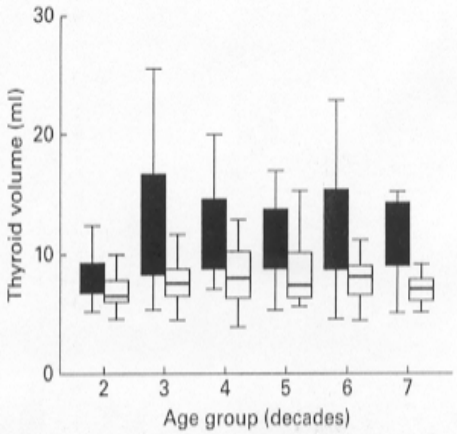


Fig. 1 Thyroid volume in the different decades. Data are expressed as median and percentile 25th and 75th in boxes and percentile 3rd and 97th as whiskers. From the second decade onwards, the difference was significant in both sexes, $P = 0·001$ in males (■) and $P = 0·01$ in females (□).

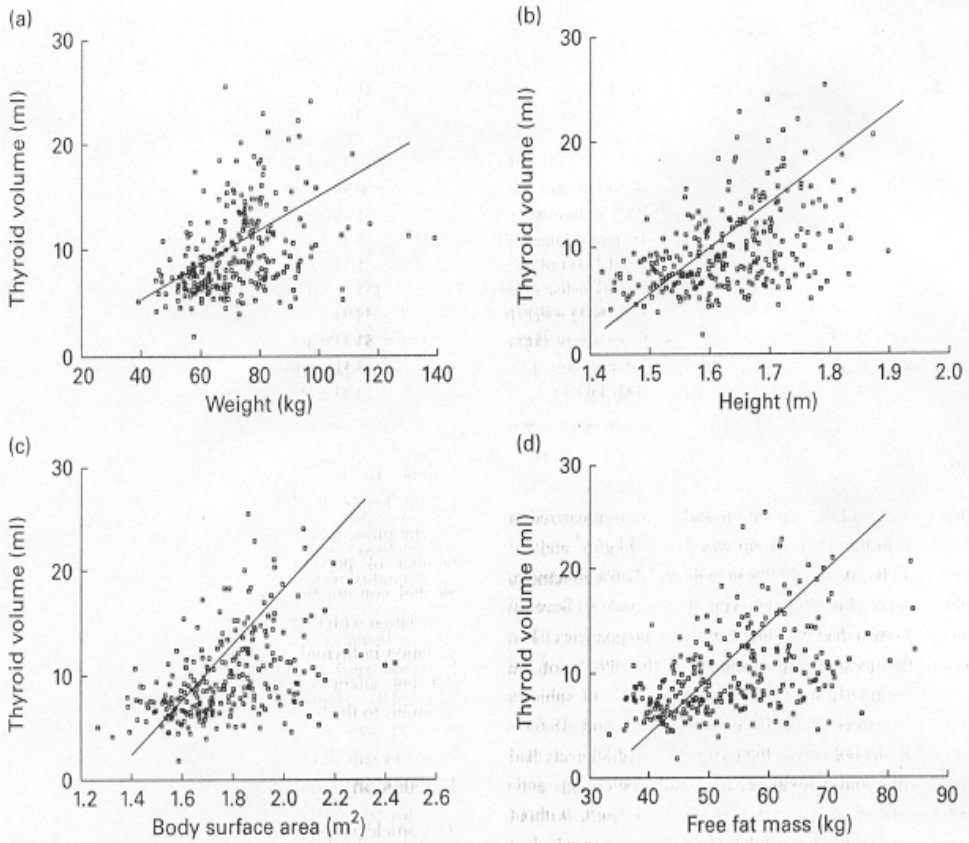


Fig. 2 Correlation among thyroid volume and anthropometric characteristics. (a) with weight, $r = 0{\cdot}39$, $P = 0{\cdot}0001$. (b) with height ($r = 0{\cdot}44$, $P = 0{\cdot}0001$). (c) with body surface area ($r = 0{\cdot}48$, $P = 0{\cdot}0001$). (d) with free fat mass ($r = 0{\cdot}47$, $P = 0{\cdot}0001$). Lines represent linear regression line.

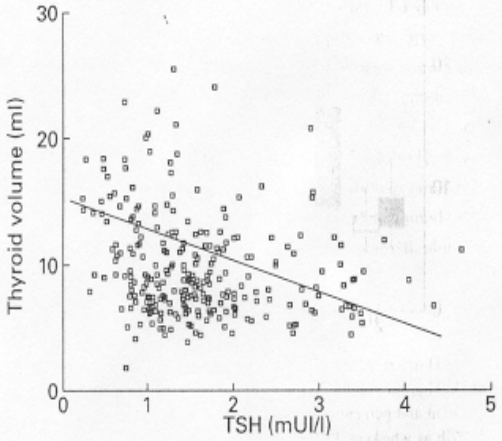


Fig. 3 Correlation between thyroid volume and basal TSH levels. ($r = -0{\cdot}26$, $P = 0{\cdot}001$). Line represents linear regression line.

excretion of 154·2 μg/l reflecting a daily intake into the optimal intake recommended by the WHO (Dunn & Madeiros-Neto, 1974; Delange *et al.*, 1997). We were unable to demonstrate a relationship between thyroid volume and iodine excretion and studies conducted in countries free of iodine deficiency do not support the view of an association between iodine intake and thyroid volume (Berghout *et al.*, 1987). In studies conducted in countries with mild iodine deficiency, thyroid volume differs significantly from volumes observed by us, with volumes of 19·6 ml and 17·5 ml found in males and females, respectively, in Copenhagen (Hegedüs *et al.*, 1983). Similarly, in countries with borderline iodine deficiency, such as France, volumes of 13·3 ml and 8·9 ml were found in males and females, respectively. These data underline the fact that other factors are also operating, such as increased thiocyanate urinary concentrations (Barrère *et al.*, 2000). Thiocyanate is an important by-product of smoking exposure and its influence over thyroid growth has been documented (Bartalena *et al.*,

1995). Some other studies have demonstrated a goitrogenic effect of smoking (Borup Christensen *et al.*, 1984; Nygaard *et al.*, 1993). We did not find any correlation between thyroid volume and smoking habits, in agreement with a recent study which has demonstrated that ,smoking habits present a goitrogenic tendency only in subjects with a family history of goitre (Georgiadis *et al.*, 1997), or when borderline iodine deficiency is observed (Barrère *et al.* 2000).

Thyroid volume correlated negatively with basal TSH without the presence of autoimmunity. The inverse correlation between thyroid volume and basal TSH has been observed in the study of Barrère *et al.* (2000), while results from Hegedüs *et al.* (1983), Gutekunst *et al.* (1986) and Berghout *et al.* (1987) concluded that there is a lack of significant correlation between TSH levels and thyroid volume, suggesting that a wide variety of environmental agents may stimulate thyroid growth.

We observed larger thyroid volumes in males than in females, data that is also supported by other studies: previous autopsy studies and studies employing US have demonstrated a significantly higher thyroid volume in males as compared to females (Hegedüs *et al.*, 1983; Berghout *et al.*, 1987; Barrère *et al.* 2000). We did not observe a correlation between thyroid volume and increasing age, except in the case of younger people, in contrast to others (Hegedüs *et al.*, 1983; Olbricht *et al.*, 1983; Berghout *et al.*, 1988) or a negative relationship between thyroid volume and age for the female group (Barrère *et al.* 2000). Some suggest that an explanation for an increase in thyroid weight with increasing age could be a lower iodine intake in the higher age groups (Hegedüs *et al.*, 1990). We have demonstrated higher urinary excretion of iodine in the subjects of the last decade.

Different studies emphasized the potential risk of goitrogenic stimulation in both mother and newborn during pregnancy, in the presence of mild iodine deficiency (Glinoer *et al.*, 1995). The question of reversibility during the postpartum period remains open for futher investigation. In our study the number of previous pregnancies was not associated with a significant increase in thyroid volume.

In our study, elevated BMI and the prevalence of obesity is higher than the general prevalence in Spain, this being 11·5% among men and 15·2% among women (Aranceta *et al.*, 1998). A positive correlation between thyroid volume and body weight in males as well as in females was found. At present it is not clear whether thyroid volume relates best to muscle mass or to total body weight (Hegedüs *et al.*, 1990); and for some authors lean body mass is the most important physiological determinant of thyroid mass in subjects living in a noniodine-deficient area (Berghout *et al.*, 1987). Moreover, Wesche *et al.* (1998), demonstrated that lean body mass as estimated by bioelectical impedance, was found to be the best determinant of thyroid volume. In our study free fat mass is also an important determinant of thyroid volume. Significant correlations have been demonstrated between thyroid volume and body height and BSA in adults in our study and in previous ones in adults (Gutekunst *et al.*, 1985; Berghout *et al.*, 1987; Barrère *et al.* 2000) or in children (Lisbôa *et al.*, 1996). Consequently, thyroid volume correlates with variables relating to body size, and these variables should be considered when the normal range of thyroid volume is assessed. In our study, age, gender, anthropometric variables, body composition variables and biological variables had no independent effect on thyroid volume. The observed effect of these variables on the thyroid volume are accounted for their relationship with BSA.

We did not find a correlation between alcohol consumption and thyroid volume as has been previously suggested (Hegedüs, 1984).

The clinical estimate of thyroid volume is prone to error, generally to an overestimation of the presence of goitre (Lisbôa *et al.*, 1996). It is, therefore , important to know the reference values of thyroid volume in a population free of iodine deficiency and its determinants, especially BSA. The effect of age, gender, anthropometric variables, body composition variables and biological variables over thyroid volume do not significantly influence thyroid volume when considered as additions to the baseline model.

Acknowledgements

The authors wish to thank the Ayuntamiento de L'Hospitalet de Llobregat, Barcelona, for making available the data of the census of the city and Dr Rosa Ramon, Francisco Escobar, Miguel Angel Navarro and Rafael Abós, for their assistance.

References

Aranceta, J., Pérez Rodrigo, C., Serra Majem, L., Ribas, L., Quiles Izquierdo, J., Vioque, J. & Foz, M. (1998) Prevalencia de la obesidad en España: estudio SEEDO'97. Grupo Colaborativo Español para el Estudio de la Obesidad. *Medicina Clinica*, **111,** 441–445.

Barrère, X., Valeix, P., Preziosi, P., Bensimon, M., Pelletier, B., Galan, P. & Herceberg, S. (2000) Determinants of thyroid Volume in healthy French adults participating in the SU. VI. MAX Cohort. *Clinical Endocrinology*, **52,** 273–278.

Bartalena, L., Bogazzi, F., Tanda, M.L., Manetti, L., Dell'Unto, E. & Martino, E. (1995) Cigarette smoking and the thyroid. *European Journal of Endocrinology*, **133,** 507–512.

Benotti, J., Benotti, M., Pino, S. & Gardyna, H. (1965) Determination of total iodine in urine, stools, diets and tissues. *Clinical Chemistry*, **2,** 932–936.

Berghout, A., Wiersinga, W.M., Smits, N.J. & Touber, J.L. (1987) Determinants of thyroid Volume as measured by ultrasonography in healthy adults in a non-iodine area. *Clinical Endocrinology*, **26,** 273–280.

Berghout, A., Wiersinga, W.M., Smits, N.J. & Touber, J.L. (1988) The value of thyroid volume measured by ultrasonography in the diagnosis of goitre. *Clinical Endocrinology*, **28,** 409–414.

Borup Christensen, S., Ericsson, U.B., Janzon, L., Tibblin, S. & Mealander, A. (1984) Influence of cigarette smoking on goiter formation, thyroglobulin, and thyroid hormone levels in women. *Journal of Clinical Endocrinology and Metabolism*, **58,** 615–618.

Brunn, J., Block, U., Ruf, G., Bos, L., Kunze, W. & Seriba, P.C. (1981) Volume trie der schilddrüssenlappen mittels realtime sonographie. *Deutsche Medizinische Wochenschrift*, **106,** 1338–1340.

Delange, F., Benker, G., Caron, Ph., Eber, O., Ott, W., Peter, F., Podoba, J., Simescu, M., Syxbinsky, Z., Vertongen, F., Vitti, P., Wiersinga, W. & Zamrazil, V. (1997) Thyroid volume and urinary iodine in European schoolchildren: standardization of values for assessment of iodine deficiency. *European Journal of Endocrinology*, **136,** 180–187.

DuBois, D. & DuBois, E.F. (1916) Clinical calorimetry. X. A formula to estimate the approximate surface area in height and weight be known. *Archives of Internal Medicine*, **17,** 863.

Dunn, J. & Madeiros-Neto, G. (1974) Endemic goitre and cretinism: continuing threats to world. *Washington DC: Pan America Health Organization, WHO*, **292,** 1–195.

Georgiadis, E., Papapostolou, C., Korakis, T., Evangelopoulou, K., Mantzoros, C. & Batrinos, M. (1997) The influence of smoking habits on thyroid gland volume: an ultrasonographic approach. *Journal of the Royal Society of Health*, **117,** 355–358.

Glinoer, D., De Nayer, P., Delange, F., Lemone, M., Toppet, V., Spehl, M., Grün, J.-P., Kinthaert, J. & Lejeune, B. (1995) A randomized trial for the treatment of mild iodine deficiency during pregnancy: maternal and neonatal effects. *Journal of Clinical Endocrinology and Metabolism*, **80,** 258–269.

Gutekunst, R., Smolarek, H., Hasenpusch, U., Stube, P., Fiedrich, H.-J., Wood, W.J. & Scriba, P.C. (1986) Goitre epidemiology: thyroid volume, iodine excretion, thyroglobulin and thyrotropin in Germany and Sweden. *Acta Endocrinologica*, **112,** 494–501.

Gutekunst, R., Smolarek, H., Wächter, W. & Sciba, P.C. (1985) Strumaepidemiologie. IV. Schilddüsenvolumina bei deutschen und schwedishen shulkkindren. *Deutsche Mediziniche Wochenschrift*, **2,** 50–54.

Hegedüs, L. (1984) Decreased thyroid gland Volume in alcoholic cirrhosis of the liver. *Journal of Clinical Endocrinology and Metabolism*, **58,** 930–933.

Hegedüs, L., Perrild, H., Poulsen, L.R., Andersen, J.R. & Hegedüs, L. (1990) Thyroid size determined by ultrasound. *Danish Medical Bulletin*, **37,** 249–263.

Hegedüs, L., Perrild, H., Poulsen, L.R., Andersen, J.R., Holm, B., Schohr, P., Jensen, G. & Hansen, J.M. (1983) The determination of thyroid volume by ultrasound and its relationship to body weight, age, and sex in normal subjects. *Journal of Clinical Endocrinology and Metabolism*, **56,** 260–263.

Leisner, B. (1987) Ultrasound evaluation of thyroid diseases. *Hormone Research*, **26,** 33–41.

Lisbôa, H.K., Gross, J.L., Orsolin, A. & Fuchs, S. (1996) Clinical examination is not an accurate method of defining the presence of goiter in schoolchildren. *Clinical Endocrinology*, **45,** 471–475.

Lukaski, H.C., Bolonchuk, W.W., Hall, C.B. & Siders, W.A. (1986) Validation of tetrapolar bioelectrical impedance method to assess human body composition. *Journal of Applied Physiology*, **69,** 1327–1332.

Nygaard, B., Gideon, P., Dige-Petersen, H., Jespersen, N., Solling, K. & Veje, A. (1993) Thyroid Volume and morphology and urinary iodine excretion in a Danish municipality. *Acta Endocrinologica*, **129,** 505–510.

Olbricht, T., Schmitka, T., Mellinhoff, U., Benker, G. & Reinwein, D. (1983) Sonographishe bestimmung von schilddrüsenvolumina bei schilddrüsengesuden. *Deutsche Medizinische Wochenschrift*, **108,** 1355–1358.

Rossner, B. (1990) *Fundamentals of Biostatistics*. 3rd edn. PWS-Kent Publishing, Boston.

Vitti, P., Martino, E., Aghini-Lombardi, F., Rago, T., Antonangeli, L., Maccherini, D., Nanni, P., Loviselli, A., Balestrieri, A., Araneo, G. & Pinchera, A. (1994) Thyroid Volume measurement by ultrasound in children as a tool for the assessment of mild iodine deficiency. *Journal of Clinical Endocrinology and Metabolism*, **79,** 600–603.

Wesche, M.F.T., Wiersinga, W.M. & Smits, N.J. (1998) Lean body mass as a determinant of thyroid size. *Clinical Endocrinology*, **48,** 701–706.

Thyroid Volume As Measured By Ultrasonography in Patients With Type 1 Diabetes Mellitus without Thyroid Dysfunction

J. M. Gómez[1]
F. J. Maravall[1]
A. Gumà[2]
R. Abós[3]
J. Soler[1]
M. Fernández-Castañer[1]

Abstract

The aim of this cross-sectional study was to assess and compare thyroid volume and its derminants in a cohort of type 1 diabetes mellitus (DM1) and compare the results to a healthy control group. We studied 65 DM1 patients treated with an intensive insulin regimen and 65 matched controls. In all participants we evaluated weight, height, BMI, waist-hip ratio, body surface area and body composition variables determined by using a bioelectrical impedance analyser. Thyroid size was estimated by ultrasonography. We determined basal TSH, anti-thyroid antibodies and urinary iodine excretion. Body weight, height, BMI and body surface area were similar in DM1 patients and in controls. Fat-free mass was higher in both male and female DM1 patients than in controls (64.4 ± 6.9 *vs.* 60.4 ± 8.2 kg, p = 0.03 and 48.3 ± 5.7 *vs.* 45.4 ± 6, p = 0.04, respectively), and fat mass was lower in male DM1 patients than in controls (9.7 ± 7 *vs.* 14.2 ± 8.1 kg, p = 0.01). Thyroid volume was greater in both male and female DM1 patients than in controls (11.12 ± 2.87 *vs.* 9.63 ± 2.27 ml, p = 0.0001 and 9.5 ± 2.3 *vs.* 7.7 ± 2 ml, p = 0.002, respectively). Urinary iodine excretion was similar in the two groups. In both DM1 patients and controls, thyroid volume correlated with weight, height, BMI, waist-hip ratio, body surface area, fat-free mass and the multivariate linear regression analysis with thyroid volume as the dependent variable showed that fat-free mass in either group was the only significant determinant of thyroid volume. We conclude that DM1 patients had larger thyroid volume compared with healthy controls with similar anthropometry; body composition is different in DM1 patients and that the anthropometric and body composition variables, especially fat-free mass and body surface area, predict thyroid volume either in DM1 patients or in healthy controls.

Key words
Anti-thyroid Antibodies · Cross-sectional Study · Type 1 Diabetes Mellitus · Thyroid Volume · Thyrotropin · Ultrasonography

Introduction

Ultrasonography (US) is an accurate and precise method for measuring thyroid size *in vivo* [1,2] and that has allowed the analysis of the determinants of thyroid volume in different populations. However, interpretation of thyroid US requires valid reference criteria from the iodine-sufficient population. Several physiological and pathological factors can influence thyroid volume, including iodine supply [3], age, sex, weight, height, body mass index (BMI), body surface area (BSA), lean body mass [4], pregnancy [5], smoking [6], alcohol ingestion, natural goitrogens and thyroid autoimmunity [7], but their relative importance is a matter of controversy. In healthy adults living in non-iodine or borderline deficient areas, anthropometric and body composition variables as BSA and fat-free mass have been described as the best determinants of thyroid volume [4,8,9].

There are few studies on thyroid volume in type 1 diabetes mellitus (DM1) patients, and reports on thyroid volume and urinary iodide excretion in patients with DM1 are not available in adults;

Affiliation
[1] Endocrine Unit
[2] Radiology Service, Ciudad Sanitaria y Universitaria de Bellvitge, L'Hospitalet de Llobregat
[3] EAP Ripollet, Catalan Health Service, Barcelona, Spain

Correspondence
Dr. J. M. Gómez · Ciudad Sanitaria y Universitaria de Bellvitge · c/ Sabino de Arana 40, 3°, 2ª · 08028 Barcelona · Spain · Phone: +34 (93)3306522 · E-Mail: jmgs@csub.scs.es

Received 10 April 2002 · **Accepted after second revision** 4 March 2003

Bibliography
Horm Metab Res 2003; 35: 486–491 © Georg Thieme Verlag Stuttgart · New York · ISSN 0018-5043

Table **1** Anthropometric, body composition, clinical, biochemical characteristics and thyroid volume in men with the type 1 diabetes mellitus (DP) and controls (C)

	DP	*C*	*Lower bound 95% CI of the difference*	*Upper bound 95% CI of the difference*	*p*
N	36	36			
Age (years)	26.8 ± 5.1	25.7 ± 5.2	– 4.6	0.47	0.1
Anthropometric variables					
Weight (Kg)	74.1 ± 8.3	74.6 ± 13.2	– 5	6.1	0.85
Height (m)	1.73 ± 0.06	1.7 ± 0.07	– 0.06	0.04	0.08
BMI (Kg/m^2)	24.6 ± 2.8	25.5 ± 3.6	– 0.742	2.49	0.28
Waist/hip ratio	0.84 ± 0.05	0.86 ± 0.06	– 0.01	0.04	0.31
Body surface area (m^2)	1.88 ± 0.11	1.86 ± 0.18	– 0.09	0.05	0.62
Body composition variables					
Fat-free mass (Kg)	64.4 ± 6.9	60.4 ± 8.2	– 7.7	– 0.37	0.03
Fat mass (Kg)	9.7 ± 7	14.2 ± 8.1	0.84	8.13	0.01
Other variables					
Smoking (%)	63.4	44.8	–	–	0.14
Alcohol consumption (%)	21	30	–	–	0.15
Iodized salt (%)	51.2	65.5	–	–	0.32
Basal TSH (mU/l)	1.6 ± 1.14	1.56 ± 0.78	– 0.56	0.41	0.76
UIE (µg/l)	140.3 ± 113.5	128.1 ± 77.6	–	–	0.1
Thyroid volume (ml)	12.12 ± 2.87	9.63 ± 2.27	– 3.7	– 1.21	0.0001

Data are presented as means ± standard deviation or percentage. DP, diabetic patients; C, controls; BMI, body mass index; UIE, urinary iodine excretion.

data on children showed that US determined parameters on thyroid size were correlated to anthropometric data and urinary iodide excretion [10,11], but other authors were unable to confirm these findings [12]. Bianchi et al. [13] demonstrated that a remarkable proportion of adult patients with DM1 had US detectable alterations in thyroid volume without evidence of thyroid disease. However, the selection criteria were heterogeneous in all these studies, and did not report any data on body composition and their possible interrelation with thyroid volume; it appears that there are differences in anthropometry and body composition variables between DM1 patients and controls as have recently been described [14,15].

The aim of this cross-sectional study on DM1 is to analyse thyroid volume in a cohort of DM1 patients in comparison to a population of controls randomly selected in order to assess whether we can observe differences in thyroid volume in absence of thyroid dysfunction and autoimmunity and whether the interpretation of the disagreement in normative reference values for DM1 patients is a consequence of the differences in the anthropometric and body composition variables observed in these patients.

Materials and methods

Subjects

From 1993 to 1997, all newly diagnosed DM1 patients attending the Endocrine Unit were included in a study on the prevalence and influence of thyroid autoimmunity during the first years of evolution of the disease [16]. In 1999, the initial cohort of patients (n = 111) younger than 40 years that continued the follow-up in the Endocrine Unit were invited to participate in a cross-sectional study of thyroid volume in DM1 of short evolution; 83 of 111 eligible patients participated in the study. Seven patients were excluded because of previous autoimmune thyroid dysfunction (six primary hypothyroidism, one treated Graves' disease) and 11 were excluded because of positive serum antithyroid peroxidase antibodies. The characteristics of the 65 patients, 36 men and 29 women, included in the final analysis are shown in Table **1** and 2. Diagnosis of DM1 was made according to the presence of classical clinical criteria of insulin dependence [17] to immunological data (presence of glutamic acid-decarboxylase antibodies, 75.4% of the DM1 patients, and tyrosine phosphatase antibodies, 49.2%, and one or both immunological markers, 81.5%), and to the assessment of insulin-secretory reserve (post-glucagon C-peptide levels lower than 1 nmol/l) [16]. All diabetic patients were given instructions for diet and physical activity, and were prescribed a diet of 1,500 – 2,500 Kcal/day. All patients were treated with an intensive insulin regimen to achieve near-normal glucose levels and HbA1c values; no history of use of drugs known to affect the thyroid function was present in these 65 patients.

Sixty-five healthy adults, 36 men and 29 women without any history of DM1 and thyroid disorders were used as a control group and were recruited from L'Hospitalet de Llobregat, the same area in which diabetic patients were living; this city is a working-class community adjacent to Barcelona with 280,000 inhabitants, and all participants were randomly selected from the census of the city and invited to participate in the study, directly by mail and phone call, and finally by verbal information. Every DM1 patient was matched with a control case of the same sex and age (± two years). The controls recruited were in good health with no known diseases, and were not currently following a weight-loss diet. Subjects with goitre, past or present autoimmune thyroid dysfunction, or on treatment with thyroid hor-

mones or drugs containing iodine and subjects with positive serum anti-thyroid peroxidase antibodies were not included in the sample.

All patients and controls were fully informed of the purpose of the study and gave their voluntary consent to take part in the investigation, and the study was approved by the ethics committee at the hospital.

Methods

The study was performed from April 1998 to May 1999; the participants answered appropriate questionnaires concerning previous thyroid diseases and medications to evaluate iodised salt consumption and tobacco smoking (expressed as cigarettes/day) and alcohol consumption (expressed as g/day) before attending the investigation.

Height and weight were measured using standard anthropometric techniques and BMI was calculated (kg/m^2), and we determined waist-hip ratio. BSA in m^2 was calculated by using the formula $BSA = W^{0.425} \times H^{0.725} \times 71.84 \times 10^{-4}$, where W is the weight in kg and H the height in cm [18].

Body composition was determined during peripheral application of an excitation current of 800 ηA at 50 kHz, using a bioelectrical impedance analyser and the formula provided by the manufacturers (Holtain BC Analyser, UK) [19]. The results obtained were: total body water in l, fat-free mass in Kg and fat mass in kg. The precision of this test in determining fat mass was within ± 3%. All examinations were done by the same investigator (F.J.M.), and were performed after emptying the bladder.

Thyroid size was estimated by palpation by one expert examiner, and was scored according to the WHO criteria [20]. Thyroid ultrasonography and echogenicity studies were performed and interpreted by the same experienced radiologist (A.G.) using the same equipment with a 7 MHz linear phased-array probe (Toshiba Sonolayer SA 250). The intra-observer variability was 10%. The subjects were examined in the supine position with hyperextended neck and with skin covered by acoustical gel. Thyroid volume was measured as reported previously [21]; longitudinal and transverse scans were performed, allowing the measurement of the depth, the width and the length of each lobe. The volume of each lobe was calculated by the ellipsoid formula (volume in ml = $^1/_6$ Π × maximum thickness × maximum length × maximum width). Thyroid volume was the sum of both lobes excluding the isthmus; in each subject, three measurements were performed and the mean volume was calculated.

HbA_{1c} was determined by high-performance liquid chromatography (HA 8140, Menarini Diagnostics, Florence, Italy). Plasma basal TSH was determined by a specific two-site enzymoimmunometric assay (Elecsys, Boehringer Mannheim, Germany). Serum anti-thyroid peroxidase and anti-thyroglobulin antibodies were determined by radioimmunoassay (Bio Code, Izasa, Liège, Belgium) and values higher than 40 IU/ml were considered as positive. Urinary iodine excretion was measured in extemporary samples in control subjects and in 24 h samples in diabetic patients according to the method of Benotti et al. [22].

Data are expressed as mean± standard deviation. Usual statistics (mean, standard deviation, median, confidence intervals of the differences, and percentage) have been used to describe the data. The Kolmogorov-Smirnov test was applied to check normality of the variables in the different groups. Non-Gaussian-distributed variables were $\log_{10}$ transformed to achieve normality and this was applied to TSH concentrations in women. The bivariate analysis was performed by using the independent sample *t*-test for equality of means. For the analysis of TSH concentrations in women, we applied the Mann-Whitney U-test. DM1 and control groups were compared using the non-parametric test Chi-squared and tabulation was used to compare binomial proportions. Multivariate linear regression analysis was constructed to estimate final predictor of thyroid volume with thyroid volume as the dependent variable. The regression coefficient generated by this analysis indicates the slope of the association among the dependent variable and the specified independent variables after adjusting for other independent variables in the model [23]. Values of $p < 0.05$ were considered statistically significant. All statistics analysis was performed using the Statistical Package for Social Sciences (SPSS/Windows v 8.0, SPSS inc., Chicago IL, USA).

Results

Anthropometric and body composition data of DM1 patients and healthy controls are summarised in Tables **1** and **2**. The body weight, height, BMI, waist-hip ratio and BSA were not different in either male or female groups. Fat-free mass was higher in the DM1 group (64.4 ± 6.9 *vs.* 60.4 ± 8.2 kg, p = 0.03 in men and 48.3 ± 5.7 *vs.* 45.4 ± 6 kg, p = 0.04 in women). Fat mass was lower in men DM1 patients than in controls. Forty-six percent of the patients and 45.8% of the controls were smokers (more than 10 cigarettes/day) and 15.4% of the patients and 21.5% of the controls usually drank alcohol (more than 20 g/day). The mean urinary iodine excretion was 132.2 µg/l in patients and 115.8 µg/l in controls and was similar in both groups (Tables **1** and **2**). The insulin requirements of the DM1 patients were 0.65 ± 0.25 U/kg and the HbA1c values 6.6 ± 1.4%.

All subjects were classified as having no goitre and TSH basal concentrations and were similar in both groups. Thyroid volume was greater in DM1 patients than in controls, 11.12 ± 2.87 *vs.* 9.63 ± 2.27 ml, p = 0.0001 in men (Table **1**), and 9.5 ± 2.3 *vs.* 7.7 ± 2 ml, p = 0.002, in women (Table **2**). No nodules larger than five mm were found either in DM1 patients or in controls.

In all subjects, DM1 patients and controls, thyroid volume correlated with DM1 status (r = 0.61, p = 0.0001), weight, height, BMI, waist-hip ratio, BSA, fat-free mass but not with age basal TSH concentrations and urinary iodine excretion; there was no difference between patients and controls in tobacco (p = 0.3) or alcohol (p = 0.1) consumption. HbA_{1c} was also negatively correlated with thyroid volume in DM1 patients (Table **3**).

Taking into account all variables in the both groups, multivariate linear regression analysis produced a final model that explained 47% of thyroid volume variability in the whole group, patients and controls; only fat-free mass and BSA brought an indepen-

Table **2** Anthropometric, body composition, clinical, biochemical characteristics and thyroid volume in women with the type 1 diabetes mellitus (DP) and controls (C)

	DP	*C*	*Lower bound 95% CI of the difference*	*Upper bound 95% CI of the difference*	*p*
N	29	29			
Age (years)	26.1 ± 5.4	26.7 ± 6.2	– 2.59	3.7	0.72
Anthropometric variables					
Weight (Kg)	63.9 ± 9.9	60.8 ± 9.7	– 8.2	2.15	0.24
Height (m)	1.59 ± 0.05	1.59 ± 0.06	– 0.03	0.03	0.9
BMI (Kg/m^2)	24.9 ± 3.48	23.7 ± 3.1	– 2.87	0.58	0.19
Waist/hip ratio	0.73 ± 0.04	0.75 ± 0.05	– 0.008	0.04	0.19
Body surface area (m^2)	1.6 ± 0.1	1.6 ± 0.1	– 0.1	0.03	0.33
Body composition variables					
Fat-free mass (Kg)	48.3 ± 5.7	45.4 ± 6	– 5.96	– 0.25	0.04
Fat mass (Kg)	15.5 ± 6.9	15.3 ± 6.2	– 3.59	3.26	0.92
Other variables					
Smoking (%)	25	47.2	–	–	0.08
Alcohol consumption (%)	8	11.6	–	–	0.2
Iodized salt (%)	70.8	52.8	–	–	0.18
Basal TSH (mU/l)	1.69 ± 1.08	1.59 ± 0.96	–	–	0.48
UIE (µg/l)	119.7 ± 49.9	110.4 ± 70.7	– 51.8	– 15.1	0.15
Thyroid volume (ml)	9.5 ± 2.3	7.7 ± 2	– 2.96	– 0.68	0.002

Data are presented as means ± standard deviation or percentage. DP, diabetic patients; C, controls; BMI, body mass index; UIE, urinary iodine excretion.

Table **3** Correlations among thyroid volume as a dependent variable and other independent variables

Groups analysed	*Age*	*Weight*	*Height*	*BMI*	*Waist-hip ratio*	*BSA*	*Fat-free mass*	*TSH*	*UIE*	*HbA1$_c$*
All subjects	r = 0.13 p = 0.142	r = 0.629 p = 0.0001	r = 0.584 p = 0.0001	r = 0.626 p = 0.0001	r = 0.348 p = 0.0001	r = 0.669 p = 0.0001	r = 0.67 p = 0.0001	r = 0.15 p = 0.3	r = 0.11 p = 0.11	–
Diabetic patients	r = 0.1 p = 0.11	r = 0.626 p = 0.0001	r = 0.566 p = 0.0001	r = 0.534 p = 0.0001	r = 0.467 p = 0.0001	r = 0.632 p = 0.0001	r = 0.672 p = 0.0001	r = 0.12 p = 0.2	r = 0.1 p = 0.11	r = – 0.561 p = 0.0001
Controls	r = 0.12 p = 0.12	r = 0.629 p = 0.0001	r = 0.584 p = 0.0001	r = 0.36 p = 0.001	r = 0.348 p = 0.001	r = 0.669 p = 0.0001	r = 0.67 p = 0.0001	r = 0.1 p = 0.1	r = 0.09 p = 0.1	–

BMI, body mass index; BSA, body surface area; UIE, urinary iodine excretion.

dent significant contribution to thyroid volume variability. Notably, only fat-free mass brought and independent significant contribution to thyroid volume variability in DM1 patients group or in the control group (Table **4**).

Discussion

The studied subjects with a mean iodine excretion of 132.2 µg/l in patients and 115.8 µg/l in controls, reflected a daily intake within the optimal iodine intake of 150 – 300 µg/day recommend by the WHO [4, 20, 24 – 26] and similar in DM1 patients as in controls in contrast to the results of Steiss et al. [11], where the DM1 patients presented an average urinary iodine excretion higher than that in controls.

An increased thyroid volume in DM1 diabetic patients has previously been described in two studies carried out on German children and DM1 Italian adult patients [11,13] and have been attributed to the higher prevalence of thyroid autoimmunity in the DM1 population and to lower iodine ingestion in German children [11]. However, these differences have not been observed in similar studies on children in Denmark and Turkey [12]. DM1 patients are prone to autoimmune thyroid diseases as has been described in a number of studies [7,16], and the presence of thyroid autoimmunity and thyroid dysfunction can influence thyroid volume and/or echogenicity; these abnormalities might be partly an expression of thyroid involvement in a silent autoimmune process not limited to the islet cells as suggested by some authors [13]. In our cohort of DM1 patients followed from diagnosis, the differences in thyroid volume observed were not related to thyroid dysfunction or autoimmunity since patients and controls with previously diagnosed thyroid dysfunction or positive anti-thyroid antibodies or with abnormal TSH at the moment of the study had been excluded from the final analysis.

Table **4** The multivariate linear regression analysis in all subjects of the study, in diabetic patients and controls

Groups analysed	*Predictors*	β	*Significance*	*Lower bound of 95% CI for* β	*Upper bound of 95% CI for* β
All subjects Adjusted $R^2 = 0.47$					
	Constant	– 0.393	0.701	– 2.416	1.630
	Fat-free mass	0.100	0.005	0.030	0.171
	Body surface area	5.709	0.007	1.610	9.809
Diabetic patients Adjusted $R^2 = 0.32$					
	Constant	1.296	0.466	– 2.233	4.826
	Fat-free mass	0.169	0.0001	0.109	0.228
Controls Adjusted $R^2 = 0.48$					
	Constant	0.303	0.781	– 1.864	2.470
	Fat-free mass	0.158	0.0001	0.118	0.199

In areas of normal iodine supply, thyroid volume in normal subjects depends mostly on anthropometry and body composition [8,9]. A correlation linking age, weight, height and thyroid volume has been observed in some of these studies in both controls and DM1 patients, but body composition has not been analysed in any of these previous studies except in children [10,26–28]. In our population, thyroid volume correlated with DM1 status, weight, height, BMI, waist-hip ratio, BSA, fat-free mass and negatively with HbA_{1c} in DM1 patients, and we can conclude that anthropometric and body composition variables predict thyroid volume either in DM1 patients or in healthy controls.

In the DM1 population, body composition is different and there was a significant increase in fat-free mass and a decrease in fat mass, as has been shown [14,15,29–31]; on average, fat-free mass was approximately 4 kg higher in male and 2.9 kg in female DM1 patients than in controls in our study; fat mass was approximately 4.5 kg lower in male DM1 patients than in controls.

Our data suggest that differences in body composition, especially fat-free mass and BSA, could be related with the differences found in thyroid volume between DM1 patients and controls in the absence of thyroid dysfunction and autoimmunity, and they also argue for the interpretation of previous studies without body composition parameters. This is an interesting finding of this study, and to our knowledge has not previously been described. Although it is generally hypothesised that the increase in body weight observed in DM1 patients is due to a increase in body fat [29], some recent studies have demonstrated that it is due to an increase in lean body mass, which has been related to hyperinsulinism [14,15,29–31] that contribute to achieve a good control as in our patients. Interestingly, thyroid volume is negatively correlated with HbA_{1c} levels.

Thyroid volume did not differ between smokers and non-smokers, and no correlation was found between thyroid volume and daily tobacco consumption. Alcohol intake was also not related to thyroid volume; recently, increasing levels of alcohol consumption were associated with a lower prevalence of thyroid enlargement [27].

In conclusion, DM1 patients had larger thyroid volume compared with healthy controls with similar anthropometry. Body composition is different in DM1 patients and the anthropometric and body composition variables predict thyroid volume either in DM1 patients or in healthy controls. Fat-free mass and BSA in both groups were the main significant determinants of thyroid volume. Our data strongly suggest that differences in anthropometry and body composition variables in different populations may contribute to the current disagreement in normative reference values for thyroid size by US in iodine-sufficient areas.

Acknowledgements

The authors wish to thank the Ayuntamiento de L'Hospitalet de Llobregat, Barcelona, for making available the data of the census of the city, and also to thank its inhabitants and Dr. Rosa Ramón, Francisco Escobar, and Miguel Angel Navarro for their assistance.

References

[1] Gutekunst R, Smolarek H, Hasenpusch U, Stube P, Fiedrich H-J, Wood WJ, Scriba PC. Goitre epidemiology: thyroid volume, iodine excretion, thyroglobulin and thyrotropin in Germany and Sweden. Acta Endocrinol (Cophen) 1986; 112: 494–501

[2] Hegedüs L, Perrild H, Poulsen LR, Andersen JR, Hegedüs L. Thyroid size determined by ultrasound. Dan Med Bull 1990; 37: 249–263

[3] Berghout A, Wiersinga WM, Smits NJ, Touber JL. The value of thyroid volume measured by ultrasonography in the diagnosis of goitre. Clin Endocrinol (Oxf) 1988; 28: 409–414

[4] Wesche MFT, Wiersinga WM, Smits NJ. Lean body mass as a determinant of thyroid size. Clin Endocrinol (Oxf) 1998; 48: 701–706.

[5] Glinoer D, de Nayer P, Delange F, Lemone M, Toppet V, Sphel M, Grün J-P, Kinthaert J, Lejeune B. A randomized trial for the treatment of mild iodine deficiency during pregnancy: maternal and neonatal effects. J Clin Endocrinol Metab 1995; 80: 258–269

[6] Bartalena L, Bogazzi F, Tanda ML, Manetti L, Dell'Unto E, Martino E. Cigarette smoking and the thyroid. Eur J Endocrinol 1995; 133: 507 – 512
[7] Hansen D, Bennedbaek FN, Hansen LK, Hoer-Madsen M, Jacobsen BB, Hegedus L. Thyroid function, morphology and autoimmunity in young patients with insulin-dependent diabetes mellitus. Eur J Endocrinol 1999; 140: 512 – 518
[8] Barrère X, Valley P, Prizes P, Bebison M, Polluter B, Gallon P, Herceberg S. Determinants of thyroid volume in healthy French adults participating in the SU.VI.MAX cohort. Clin Endocrinol (Oxf) 2000; 52: 273 – 278
[9] Gómez JM, Maravall FJ, Gómez N, Gumà A, Soler J. Determinants of thyroid volume as measured by ultrasonography in healthy adults randomly selected. Clin Endocrinol (Oxf) 2000; 53: 629 – 634
[10] Ueda D. Sonographic measurement of the volume of the thyroid gland in healthy children. Acta Paed Jap 1989; 31: 352 – 354
[11] Steiss JO, Otter A, Grief V, Klingmuller V. Schilddrüsensonographie und Harnjodidausscheidung bei Kindern und Jugendlichen mit Diabetes mellitus typ I. Klin Pad 1996; 208: 327 – 333
[12] Darendeliler FF, Kadioglu A, Bas F, Bundak R, Gunoz H, Saka N, Neyzi OR. Thyroid ultrasound in IDDM. Ped Endocrinol 1994; 7: 33 – 37
[13] Bianchi G, Montanari P, Fabbri A, Gamberini A, Zoli M, Marchesini G. Thyroid volume in type 1 diabetes without overt thyroid disease. Acta Diabetol 1995; 32: 49 – 52
[14] Sinha A, Formica C, Tsalamandris C, Paagiotopoulos S, Hendrich E, DeLuise M, Seerman E. Effects of insulin on body composition in patients with insulin-dependent and non-insulin-dependent diabetes. Diab Med 1996; 13: 40 – 46
[15] Gómez JM, Maravall FJ, Soler J, Fernández-Castañer M. Body composition assessment in type 1 diabetes mellitus over 15 years old. Horm Metab Res 2001; 33: 670 – 673
[16] Fernández-Castañer M, Molina A, López-Jiménez L, Gómez JM, Soler J. Clinical presentation and early course of type 1 diabetes mellitus in patients with and without thyroid autoimmunity. Diabetes Care 1999; 22: 377 – 381
[17] World Health Organisation. Diabetes Mellitus: Report of a WHO Study Group Geneva: World Health Org (Tech. Rep. Ser., no. 727), 1985
[18] DuBois D, DuBois EF. Clinical calorimetry. X. A formula to estimate the approximate surface area in height and weight to be known. Arch Inter Med 1916; 17: 863
[19] Lukaski HC. Requirements for clinical use of bioelectrical impedance analysis (BIA). Ann New York Acad Sci 1999; 873: 72 – 76
[20] Dunn J, Madeiros-Neto G. Endemic goitre and cretinism: continuing threats world. Washington DC: Pan American Health Organisation, WHO 1974; 292: 1 – 195
[21] Brunn J, Block U, Ruf G, Bos L, Kunze W, Seriba PC. Volumetrie der schilddrüssenlappen mittels realtime sonographie. Deut Med Woch 1981; 106: 1338 – 1340
[22] Benotti J, Benotti M, Pino S, Gardyna H. Determination of total iodine in urine, stools, diets and tissues. Clin Chem 1965; 2: 932 – 936
[23] Rossner B. Fundamentals of Bioestatistics. 3rd edition Boston: PWS-Kent Publishing, 1990
[24] Delange FM. Iodine deficiency In: Werner & Ingbar (ed). The Thyroid. A fundamental and clinical text, edn 8 Philadelphia: Lippincott Williams & Wilkins, 2000: 295 – 316
[25] Knusen N, Büllow I, Jorgensen T, Laurberg P, Ovesen L, Perrild H. Goitre prevalence and thyroid abnormalities at ultrasonography: a comparative epidemiological study in two regions with slightly different iodine status. Clin Endocrinol (Oxf) 2000; 53: 479 – 485
[26] Wiersinga WM, Podoba J, Srbecky M, van Vessem M, van Beeren HC, Platvoetter Schiphorst MC. Survey of iodine intake and thyroid volume in Dutch schoolchildren: reference values in an iodine-sufficient area and the effect of puberty. Eur J Endocrinol 2001; 144: 595 – 611
[27] Knudsen N, Bülow I, Laurberg P, Perrild H, Oversen L, Jorgensen T. Alcohol consumption is associated with reduced prevalence of goitre and solitary thyroid nodules. Clin Endocrinol (Oxf) 2001; 55: 41 – 46.
[28] Xu F, Sullivan K, Houston R, Zhao J, May W. Thyroid volume in US and Bangladeshi schoolchildren: comparison with European schoolchildren. Eur J Endocrinol 1999; 40: 498 – 504
[29] Rigalleau V, Delafaye C, Baillet L, Vergnot V, Prunou P, Gatta B, Gin H. Composition of insulin-induced body weight gain in diabetic patients: a bio-impedance study. Diab Metab 1999; 25: 321 – 328
[30] Svenson OL. Hassager C. Body composition and fat distribution measured by dual-energy x-ay absorptiometry in premenopausal and postmenopausal insulin-dependent and non-insulin-dependent diabetes mellitus patients. Metabolism 1998; 47: 212 – 216
[31] The DCCT Research Group. Weight gain associated with intensive therapy in the diabetes control and complication trial. Diabetes Care 1988; 11: 567 – 573

J. M. Gómez
F. J. Maravall
N. Gómez
A. Gumà
R. Casamitjana
J. Soler

Pituitary-Thyroid Axis, Thyroid Volume and Leptin in Healthy Adults

Abstract

Objective: Patients with thyroid diseases usually have disturbances relating to body weight and thermogenesis. On the other hand, leptin is involved in the regulation of body weight, food intake and thermogenesis. Some studies have investigated the relationship between leptin and dysthyroid states, but the complex interactions between leptin and pituitary-thyroid axis have led to controversial results. **Design**: The aims of this cross-sectional study were to investigate the relationship among basal TSH, ultrasonographic thyroid volume and leptin in a group of 268 healthy adults randomly selected from our city, L'Hospitalet de Llobregat, Barcelona, an area free of iodine deficiency. In this euthyroid group, we determined basal TSH, thyroid autoantibodies, leptin concentrations, and thyroid volume by ultrasonography, body anthropometry, and body composition. **Results**: All subjects were free of goitre and were negative for anti-thyroid antibodies. Basal TSH concentrations were 1.49 ± 0.8 mU/l in males and 1.67 ± 0.83 mU/l in females (p = 0.6). Anti-thyroid antibodies were negative in all cases; leptin concentrations were 6.1 ± 4 ng/ml in males and 16.8 ± 11.7 ng/ml in females (p = 0.0001). Thyroid volume was 9.8 ± 4.6 ml in males and 6.5 ± 2 ml in females (p = 0.001). There were significant correlations among leptin concentrations and anthropometric and body composition variables in both sexes, without correlation with TSH concentrations. There was no significant correlation between anthropometric and body composition variables and thyroid volume in males but there was a correlation in females. In females, there was a positive correlation between leptin and thyroid volume (r = 0.181, p = 0.038). In males, there was a negative correlation between TSH concentrations and thyroid volume (r = – 0.271, p = 0.002). **Conclusions**: We did not find any correlation between leptin levels and pituitary-thyroid axis in this control population. The correlation between leptin and thyroid volume in females is probably a consequence that leptin and thyroid volume are regulated in parallel by variables relating to anthropometry and body composition.

Key words
Anthropometric Variables · Body Composition · Leptin · Pituitary-Thyroid Axis · Thyroid Volume · TSH · Ultrasonography

Introduction

Patients with thyroid disease usually have disturbances relating to body weight, food intake, oxygen consumption and thermogenesis. The mechanisms involved in the regulation of energy balance by thyroid hormones are complex and not fully elucidated [1].

Several factors are known to be involved in the regulation of body weight, which include leptin, a 167-amino acid protein encoded by the *ob* gene [2]. Since leptin deficiency was found in genetically obese *ob/ob* mice, evidence has accumulated that leptin plays an important role in the regulation of food intake and thermogenesis, and that its concentrations are closely linked to body mass index (BMI) and particularly to body fat (BF) stores [2,3]. Leptin has widespread effects on a number of hypothalamic hor-

Affiliation
Endocrinology and Radiology Services, Ciudad Sanitaria y Universitaria de Bellvitge, L'Hospitalet de Llobregat, Hormonal Laboratory, Hospital Clínic, Barcelona, Spain

Correspondence
Dr. J. M. Gómez · Endocrinology Service, Ciudad Sanitaria y Universitaria de Bellvitge, L'Hospitalet de Llobregat · c/ Sabino de Arana 40, 3°, 2ª · Barcelona 08028 · Spain
Phone: + 34 (93) 330 65 22 · Fax: + 34 (93) 206 78 46 · E-Mail: jmgs@csub.scs.es

Received 5 April 2001 · **Accepted after revision** 2 August 2001

Bibliography
Horm Metab Res 2002; 34: 67–71 © Georg Thieme Verlag Stuttgart · New York · ISSN 0018-5043

mones and not only plays a role in the regulation of metabolic efficiency but also greatly contributes to the adaptation of the organism to starvation [4]. The pituitary-thyroid axis plays a central role in the regulation of adipose tissue metabolism; both thyroid hormones and leptin influence similar aspects of body homeostasis, and there is evidence of direct effect of T_3 on leptin release [5 – 7]. Therefore, it is not surprising that a number of animal and human studies have investigated the relationship between leptin and dysthyroid states [8 – 15]. Leptin levels in euthyroid subjects suggest either pituitary-thyroid axis actions on leptin secretion or reciprocal action of leptin on the axis, or a non-causal association between the two [15].

Thyroid volume determined by ultrasonography (US) is a precise method of determining gland volume [16 – 19]. The relationship between thyroid size, age, sex and anthropometric characteristics has been established in healthy subjects living in non-iodine-deficient areas [18,19]; on the other hand, all of these variables are related with leptin concentrations [3].

The aims of this cross-sectional study was to investigate the relationship among basal TSH, US thyroid volume and leptin in a group of healthy adults randomly selected from among 280,000 inhabitants living in the city, L'Hospitalet de Llobregat, Barcelona, an area free of iodine deficiency.

Subjects and Methods

Subjects were recruited from L'Hospitalet de Llobregat, a city adjacent to Barcelona with 280 000 inhabitants. All participants were identified by the census and self-identified as having lived for at least the last four years in the city. 880 adult subjects, representative of the whole population of the city in sex and decade distribution, were randomly selected from the census of the city and were invited to participate in the study, directly by mail or phone call and finally by verbal information, with the purpose of determining reference values of thyroid volume by US and their determinants. They were fully informed of the purpose of the study and gave their voluntary consent to take part in the investigation. The study was approved by the ethics committee of the hospital. The age limit ranged from 15 – 70 years; subjects younger than 15 years were not included as a consequence of the variability of thyroid volume during puberty [20]. The upper limit of 70 years was chosen as consequence of the low probability of thyroid increase after this age [17] and the high prevalence of different diseases in older subjects. To determine whether subjects presented previous diseases or were treated with thyroid hormones, antithyroid drugs or whether they really were fasting, an appropriate questionnaire was used. The participation rate was 44% and several exclusion criteria were previously applied: subjects with goitre, with a family history of autoimmune disease, with past or present autoimmune thyroid disease, individuals treated with thyroid hormones, antithyroid drugs, drugs containing iodine or steroids, were not included in the sample. No subject was pregnant or had any chronic illness, was under treatment for arterial hypertension, heart failure or chronic hepatic failure. Twenty-four subjects submitted for the study were omitted because of clinical presence of nodular goitre in 10 cases and multinodular goitre in 14 cases, previously not diagnosed. The final study group consisted of 296 adult subjects. Twenty-eight subjects were excluded after clinical and US examination; four due to abnormal sonographic echo-patterns indicating nodular goitre greater than 10 mm in diameter, 10 due to multinodular goitre, 14 due to positive anti-thyroid peroxidase or anti-thyroglobulin antibodies findings, three of these with coexistent low basal TSH levels, one with high basal TSH levels. The 268 subjects included in the study were representative of the whole population of the city in sex and decade distribution. 134 male subjects aged 41.4 years, ranging from 15 to 70 years, and 134 female subjects aged 40.7 years, ranging from 15 – 70 years were divided according to sex and decade.

We calculated the body-mass index (BMI) as body weight divided by height squared (kg/m^2) and determined the waist-hip ratio. The body surface area (BSA) in m^2 was calculated by using the formula: $BSA = W^{0.425} \times H^{0.725} \times 71.84 \times 10^{-4}$, where W is the weight in kg and H the height in cm [21].

Thyroid size was estimated by palpation by one expert examiner (F.J.M.), and was scored according to the WHO criteria [22] (grade 0; no palpable or visible goitre; grade 1: an enlarged thyroid that is palpable but not visible when the thyroid is in a normal position; grade 2: a palpably enlarged thyroid visible when the neck is in a normal position).

Thyroid US and echogenicity studies were performed and interpreted by the same experienced radiologist (A.G.), using the same equipment with a 7 MHz linear phased-array probe (Toshiba Sonolayer SA 250); the intra-observer variability of the method was 10% and inaccuracy was 11%. The subjects were examined in the supine position with hyperextended neck and skin covered by acoustic gel. Thyroid volume was measured as reported previously [16]. Longitudinal and transverse scans were performed, allowing the measurement of the depth, the width and the length of each lobe. The volume of each lobe was calculated by the ellipsoid formula (volume in ml = $1/6\,\pi \times$ maximum thickness × maximum length × maximum width). Thyroid volume was the sum of both lobes, and the isthmus was not included.

Body composition was determined by a bioelectrical impedance analyser using formula provided by the manufacturers (Holtain BC Analyser, UK) [23]. The results obtained were: total body water in l, free fat mass in kg, fat mass in kg, and BF in %. The precision of this test in determining fat mass is within ± 3%. All examinations were done by the same investigator (F.J.M.) and were performed fasting and after emptying the urinary bladder.

Serum samples for measurement of basal TSH, anti-thyroid antibodies and leptin were drawn between 8 : 00 and 9 : 00 a. m. with subjects fasting from 9.00 p. m. of the previous day.

Plasma TSH (normal range 0.48 – 4.36 mU/l) was determined by a specific two-site enzymoimmunometric assay (Elecsys, Boehringer Mannheim, Germany). Serum anti-thyroid peroxidase and anti-thyroglobulin antibodies were determined by radioimmunoassay (RIA) (Bio Code, Izasa, Liège, Belgium). Values higher than 40 IU/ml were considered as positive. Urinary iodine excretion was measured in extemporary samples in all subjects and determined according to the method of Benotti et al. [24].

Leptin concentrations were determined using a RIA (Linco Research, St Charles, MO, USA), which uses human recombinant (HR)-leptin for both standard and tracer, with antisera raised against HR-leptin. The limit of detection of the assay was 0.5 ng/ml. The intra- and inter-assays coefficients of variation were 7% and 8%, respectively. The RIA for leptin does not cross-react with human proinsulin, insulin or glucagon.

Usual statistics (mean, SD and median) have been used to describe the result. The Kolmogorov-Smirnov test was applied separately for men and women to check normality of the variables. Confidence intervals were calculated for thyroid volume. The Kruskal-Wallis non-parametric test for independent samples was used to compare quantitative data among decade groups. Relationships among variables were sought by Pearson's correlation coefficient. If the possibility of chance occurrence was $p < 0.05$, the result was considered statistically significant [25]. All statistical analysis was performed using the Statistical Package for Social Sciences (SPSS/Windows v 8.0, SPSS inc., Chicago IL, USA).

Results

The characteristics of the population studied are summarised in Table **1**. All subjects were classified as having goitre grade 0. Basal TSH values in males were 1.49 ± 0.8, and in females 1.67 ± 0.83 mU/l ($p = 0.6$) and similar in the age groups for decades for each sex (Table **1**, Fig. **1**). The iodine excretion was 154.2 ± 114.8 µg/l. Leptin levels were 6.1 ± 4 in males and 16.8 ± 11.7 ng/ml in females, $p = 0.0001$, and different in the age groups for decades for each sex (Table **1**, Fig. **1**). Thyroid volume was higher in males (median 9.19 ml, CI 9.09 – 10.65) than in females (6.19 ml, CI 6.02 – 6.92), $p = 0.001$ and similar in the different decades for each sex, except in patients younger than 20 years (median 6.25 ml, CI 5.9 – 7.32) in males, $p = 0.001$ and (5.41 ml, CI 5.12 – 6.94) in females, $p = 0.01$ (Table **1**, Fig. **1**).

There was no correlation between thyroid volume and height, body weight, BMI, waist/hip ratio, body surface area, total body water, free fat mass, fat mass or BF with a negative correlation

Table **1** Characteristics of the population studied. Data are expressed as mean ± SD

	Males (n = 134)	*Females (n = 134)*
Age (years)	41.4 ± 15.9	40.7 ± 15.6
Height (cm)	169 ± 6.8	155 ± 6.7
Weight (kg)	78.3 ± 13	65.4 ± 13.7
Body mass index (kg/m^2)	27.3 ± 4.1	26.9 ± 5.8
Waist-hip ratio	0.93 ± 0.1	0.79 ± 0.11
Body surface area (m^2)	1.88 ± 0.16	1.64 ± 0.15
Total body water (l)	44.4 ± 5.8	33.4 ± 4.4
Free fat mass (kg)	60.8 ± 7.9	45.8 ± 6
Fat mass (kg)	17.5 ± 9.3	19.5 ± 10.2
Body fat (%)	21.4 ± 9.1	28.5 ± 9.7
Thyroid volume (ml)	9.8 ± 4.6	6.5 ± 2
Basal TSH (mU/l)	1.49 ± 0.8	1.67 ± 0.83
Leptin ng/ml	6.1 ± 4	16.8 ± 11.7

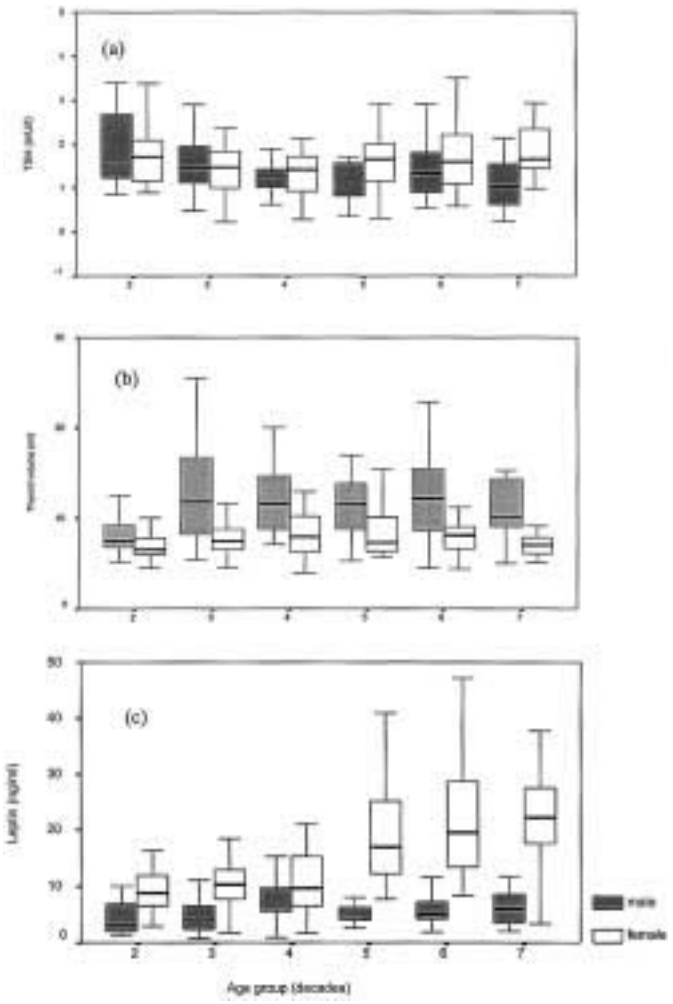


Fig. **1** Basal TSH concentrations (**a**), thyroid volume (**b**), and leptin (**c**) in decades. Data are expressed as median and percentile 25th and 75th in boxes and percentile 3rd and 97th as whiskers. From the second decade onwards the difference was significant in both sexes for thyroid volume, $p = 0.001$ in males and $p = 0.01$ in females, and for leptin $p = 0.01$ in males, 0.001 in females.

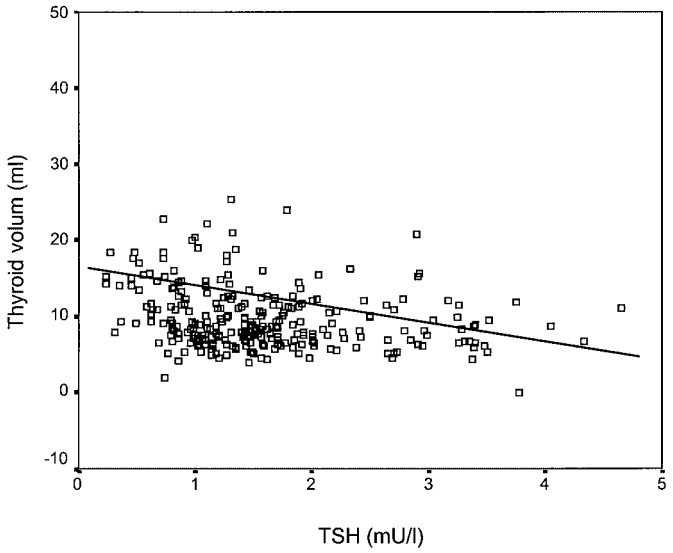


Fig. **2** Correlation between thyroid volume and basal TSH concentrations in males. ($r = -0.271$, $p = 0.002$). Line represents linear regression line.

Table **2** Correlations among leptin, anthropometric and body composition variables and thyroid volume

	Height	*Weight*	*Body mass index*	*Waist/ hip ratio*	*Body surface area*	*Total body water*	*Free fat mass*	*Fat mass*	*Body fat*	*TSH*	*Thyroid volume in male*	*Thyroid volume in female*
Leptin in male	r = 0.019 p = 0.83	r = 0.665 p = 0.0001	r = 0.697 p = 0.0001	r = 0.237 p = 0.006	r = 0.54 p = 0.0001	r = 0.224 p = 0.01	r = 0.225 p = 0.009	r = 0.74 p = 0.0001	r = 0.641 p = 0.0001	r = – 0.003 p = 0.97	r = – 0.111 p = 0.202	
Leptin in female	r = 0.14 p = 0.1	r = 0.544 p = 0.0001	r = 0.581 p = 0.0001	r = 0.307 p = 0.0001	r = 0.44 p = 0.0001	r = 0.229 p = 0.015	r = 0.211 p = 0.015	r = 0.606 p = 0.0001	r = 0.57 p = 0.0001	r = 0.37 p = 0.67		r = 0.181 p = 0.038
Thyroid volume in male	r = 0.09 p = 0.29	r = 0.06 p = 0.47	r = 0.017 p = 0.848	r = 0.118 p = 0.17	r = 0.029 p = 0.29	r = 0.09 p = 0.3	r = 0.08 p = 0.3	r = 0.01 p = 0.9	r = 0.009 p = 0.9	r = – 0.271 p = 0.002		
Thyroid volume in female	r = 0.325 p = 0.001	r = 0.379 p = 0.0001	r = 0.228 p = 0.008	r = 0.061 p = 0.48	r = 0.456 p = 0.0001	r = 0.42 p = 0.001	r = 0.421 p = 0.001	r = 0.0258 p = 0.003	r = 0.15 p = 0.08	r = – 0.112 p = 0.197		

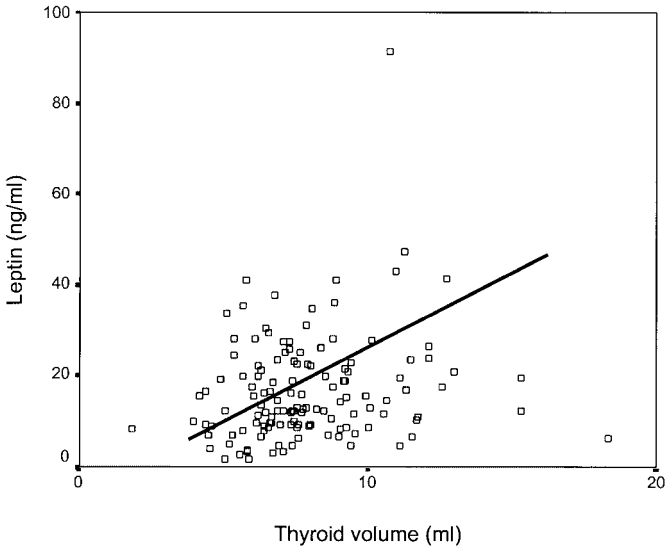


Fig. **3** Correlation between thyroid volume and leptin in females (r = 0.181, p = 0.038). Line represents linear regression line.

with TSH (r = – 0.271, p = 0.002 – see Fig. **2**) in males. Significant correlations were found between thyroid volume and height, body weight, BMI, body surface area, total body water, free fat mass, fat mass without correlation with BF, waist/hip ratio and TSH concentrations in females (Table **2**).

Significant correlations were found among leptin concentrations in males and females and body weight, BMI, waist-hip ratio, body surface area, total body water, free fat mass, fat mass, BF; and in females with thyroid volume (r = 0.181, p = 0.038) but not in males (r = 0.111, p = 0.202, see Fig. **3**) without correlation with basal TSH concentrations in either sex (Table **2**).

Discussion

To our knowledge, there are no large population-based studies of leptin status in correlation with TSH and thyroid volume. This cross-sectional study showed the lack of positive correlation between leptin and TSH levels. Leptin and the pituitary-thyroid axis play a central role in the physiological regulation of energy homeostasis. On the other hand, the presence of thyroid dysfunction in patients with leptin deficiency and leptin receptor abnormalities strongly suggests that leptin and the pituitary-thyroid axis are closely related [26]. Recent studies have shown controversial results in both humans and animals. In patients with thyroid disorders, studies have found both no correlation [9–11,14] and significant correlation between thyroid function and serum leptin levels [5,12,13,15,27,28]. Recent studies have proven the direct effect of T_3 on leptin release with an opposite effect to those of insulin on the white adipose tissue of rats with respect to leptin mRNA accumulation [5–7]. In these clinical studies, it has thus proven difficult to establish whether leptin levels are altered in hypo- and hyperthyroid patients. Control studies have been made in small groups of subjects identified from among departmental staff and from obesity clinics; they did not differentiate leptin regulation between sexes. The complex interactions of the pituitary-thyroid axis and body homeostasis regulation, either with each other or with other hormonal systems, has led to descriptive studies producing less than straight forward results.

In this well-characterised population of controls with biochemically confirmed euthyroidism, we found that TSH is similar in both sexes and that leptin levels are significantly lower in males than in females. Results also confirm significant correlations among leptin levels and anthropometric and body composition variables in both men and women. On the other hand, we found a lack of correlation between leptin and TSH levels in both sexes. Probably, leptin did not regulate TSH levels in the euthyroid state, but may regulate its dynamics as has been described [29]. Thyroid volume correlated negatively with basal TSH in males and the inverse correlation between thyroid volume and basal TSH in both sexes has been observed in the study of Barrère et al. [18], while other studies [30,31] concluded that there is a lack of significant correlation between TSH levels and thyroid volume.

We observed larger thyroid volumes in males than in females, also supported in both autopsy studies and studies using US [18,19], regulated by anthropometric and body composition variables in women. We could demonstrate that this regulation is absent in men. Leptin binding to its receptors has been demonstrated in various areas of the central nervous system, particularly the hypothalamus, but also in multiple peripheral tissues [3,4,32], but to our knowledge, there are no leptin receptors in the thyroid gland. Consequently, thyroid volume correlates with variables relating to body size in women, so thyroid volume and leptin could be regulated in parallel, under normal physiological

conditions, which may explain the leptin and thyroid volume correlation in females, absent in males.

We did not observe any correlation between thyroid volume and increasing age except in younger people, as do other studies, or any negative relationship between thyroid volume and age for the female group [18].

In conclusion, we found no correlation between leptin concentrations and pituitary-thyroid axis in this large control population study, but we did find a correlation between leptin and thyroid volume in females, probably as consequence of parallel leptin and thyroid volume regulation through variables relating to body size and composition.

Acknowledgements

The authors wish to thank the Ayuntamiento de L'Hospitalet de Llobregat, Barcelona, for making the data of the census of the city available, and to the city's inhabitants; we would also like to thank Dr. Rosa Ramón, Francisco Escobar, Miguel Angel Navarro and Rafael Abós, for their assistance.

References

[1] Freake HC, Oppenheimer JH. Thermogenesis and thyroid function. Annu Rev Nutr 1995; 15: 263 – 291
[2] Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedmann JM. Positional cloning of the mouse ob gene and its human homologue. Nature 1994; 372: 425 – 432
[3] Considine R, Sinha MK, Heiman M, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, Mckee LJ, Bauer TL, Caro JF. Serum immunoreactive leptin concentrations in normal weight and obese humans. N Engl J Med 1996; 334: 292 – 295
[4] Orban Z, Bornstein SR, Chrousos GP. The interaction between leptin and the hypothalamic-pituitary-thyroid axis. Horm Metab Res 1998; 30: 231 – 235
[5] Fain JN, Coronel EC, Beauchamp MJ, Bahouth SW. Expression of leptin and beta 3-adrenergic receptors in rat adipose tissue in altered thyroid states. Biochem J 1997; 322: 145 – 150
[6] Fain JN, Bahouth SW. Effect of tri-iodothyroinine on leptin release and leptin mRNA accumulation in rat adipose tissue. Biochem J 1998; 332: 361 – 366
[7] Leonhardt U, Gerdes E, Ritzel U, Schafer G, Becker W, Ramadori G. Immunoreactive leptin and leptin mRNA expression are increased in rat hypo- but not hyperthyroidism. J Endocrinol 1999; 163: 115 – 121
[8] Escobar-Morreale HF, Escobar del Rey F, Morreale de Escobar G. Thyroid hormones influence serum leptin concentrations in the rat. Endocrinology 1997; 138: 4485 – 4488
[9] Valcavi R, Zini M, Peino R, Casanueva FF, Diéguez C. Influence of thyroid status on serum immunoreactive leptin levels. J Clin Endocrinol Metab 1997; 82: 1632 – 1634
[10] Sreenan S, Caro JF, Refetoff S. Thyroid dysfunction is not associated with alterations in serum leptin levels. Thyroid 1997; 7: 407 – 409
[11] Corbetta S, Englaro p, Giambona S, Persani L, Blum WF, Beck-Peccoz P. Lack of effects of circulating thyroid hormone levels on serum leptin concentrations. Eur J Endocrinol 1997; 137: 659 – 663
[12] Leonhardt U, Ritzel U, Schafre G, Becker W, Ramadori G. Serum leptin levels in hypo-and hyperthyroidism. J Endocrinol 1998; 157: 75 – 79
[13] Zimmermann-Belsing T, Dreyer M, Holst JJ, Felt-Rasmussen U. The relationship between the serum leptin concentrations of thyrotoxic patients during treatment and their total fat mass is different from that of normal subjects. Clin Endocrinol (Oxf) 1998; 49: 589 – 595
[14] Sesmilo G, Casamitjana R, Halperin I, Gomis R, Vilardell E. Role of thyroid hormones on serum leptin levels. Eur J Endocrinol 1998; 139: 428 – 430
[15] Pinkney JH, Goodrick S, Katz J, Johnson AB, Lightman SL, Coppack SW, Mohamed-Ali V. Leptin and the pituitary-thyroid axis: a comparative study in lean, obese, hypothyroid and hyperthyroid subjects. Clin Endocrinol (Oxf) 1998; 49: 583 – 588
[16] Brunn J, Block U, Ruf G, Bos L, Kunze W, Seriba PC. Volumetrie der Schilddrüsenlappen mittels Realtime-Sonographie. Dtsch med Wschr 1981; 106: 1338 – 1340
[17] Hegedüs L, Perrild H, Poulsen LR, Andersen JR, Holm B, Schohr P, Jensen G, Hansen JM. The determination of thyroid volume by ultrasound and its relationship to body weight, age, and sex in normal subjects. J Clin Endocrinol Metab 1983; 56: 260 – 263
[18] Barrère X, Valeix P, Preziosi P, Bensimon M, Pelletier B, Galan P, Herceberg S. Determinants of thyroid volume in healthy French adults participating in the SU.VI.MAX cohort. Clin Endocrinol (Oxf) 2000; 52: 273 – 278
[19] Gómez JM, Maravall FJ, Gómez N, Gumà A, Soler J. Determinants of thyroid volume as measured by ultrasonography in healthy adults randomly selected. Clin Endocrinol (Oxf) 2000; 53: 629 – 634
[20] Wiersinga WM, Podoba J, Srbecky M, van Vessem M, van Beeren HC, Platvoeter-Schiphorst MC. Survey of iodine intake and thyroid volume in Dutch school children: reference values in an iodine-sufficient area and the effect of puberty. Eur J Endocrinol 2001; 144: 595 – 611
[21] DuBois D, DuBois EF. Clinical calorimetry. X. A formula to estimate the approximate surface area in height and weight be known. Arch Inter Med 1916; 17: 863
[22] Dunn J, Madeiros-Neto G. Endemic goitre and cretinism: continuing threats to world. Washington DC: Pan America Health Organization, WHO 1974; 292: 1 – 195
[23] Lukaski HC, Bolonchuk WW, Hall CB, Siders WA. Validation of tetrapolar bioelectrical impedance method to assess human body composition. J Applied Physiol 1986; 69: 1327 – 1332
[24] Benotti J, Benotti M, Pino S, Gardyna H. Determination of total iodine in urine, stools, diets and tissues. Clin Chem 1965; 2: 932 – 936
[25] Rossner B. Fundamentals of Biostatistics. 3rd edition Boston: PWS-Kent Publishing, 1990
[26] Montague CT, Farroqi IS, Whitehead JP, Soos MA, Rau H, Wareham CH, Sewter CP, Digby JE, Mohammed SN, Hurst JA, Cheetham CH, Earley AR, Barnett AH, Prins JB, O'Rahilly S. Congenital leptin deficiency is associated with severe early onset obesity in humans. Nature 1997; 387: 903 – 908
[27] Diekman MJM, Romijn JA, Endert E, Saurwein H, Wiersinga WM. Thyroid hormones modulate serum leptin levels: observations in thyrotoxic and hypothyroid women. Thyroid 1998; 8: 1081 – 1086
[28] Sera N, Yokoham N, Abe Y, Ide A, Imaizumi M, Usa T, Tominaga T, Ejima E, Ashizawa K, Ohmoto Y, Eguchi K. Thyroid hormones influence serum leptin levels in patients with Graves' disease during suppression of β-adrenergic receptors. Thyroid 2000; 10: 641 – 646
[29] Shimon I, Yan X, MaGoffin DA, Friedman TC, Melmed S. Intact leptin receptor is selectively expressed in human fetal pituitary and pituitary adenomas and signals human fetal pituitary growth hormone secretion. J Clin Endocrinol Metab 1998; 83: 4059 – 4064
[30] Berghout A, Wiersinga WM, Smits NJ, Touber JL. The value of thyroid volume measured by ultrasonography in the diagnosis of goitre. Clin Endocrinol (Oxf) 1988; 28: 409 – 414
[31] Hegedüs L, Perrild H, Poulsen LR, Andersen JR, Hegedüs L. Thyroid size determined by ultrasound. Dan Med Bull 1990; 37: 249 – 263
[32] Wauters M, Considine RV, van Gaal LF. Human leptin: from an adipocyte hormone to an endocrine mediator. Eur J Endocrinol 2000; 143: 293 – 311

DISCUSIÓN CONJUNTA DEL TEMA

3.1.- VALORES DE REFERENCIA DEL VOLUMEN TIROIDEO.

El estudio presenta valores de referencia del volumen tiroideo por ecografía, en adultos sanos, obtenidos de una población seleccionada aleatoriamente del censo.

El examen físico es una técnica rutinaria en la valoración de los pacientes con patología tiroidea, si bien es poco fiable tanto para la determinación del volumen tiroideo[1-3], como para establecer la prevalencia de bocio[4-6], pese al uso de métodos estandarizados como la clasificación clínica de la Organización Mundial de la Salud (OMS)[7,54].

La ecografía se considera hoy día como el método de elección para la valoración del volumen tiroideo, y la prevalencia de bocio, especialmente en glándulas homogéneas, sin crecimiento endotorácico[4,16,23].

La muestra estudiada se consideró representativa de la población, ya que los sujetos, aleatoriamente seleccionados del censo, tuvieron que desplazarse al hospital en días de trabajo, para realizarse pruebas poco conocidas en la población general, puesto que además se excluyeron aquellas personas con familiares de primer grado con patología tiroidea. Sus características se reflejan en la tabla 1.

	Conjunto	*Hombres*	*Mujeres*
Edad (años)	41’06 (15’73)	41’38 (15’88)	40’73 (15’62)
Talla (cm)	163 (10)	169 (7)	156 (7)
Peso (kg)	71’86 (14’83)	78’33 (13’01)	65’38 (13’71)
IMC (kg/m^2)	27’15 (5’04)	27’30 (4’14)	26’99 (5’82)
ICC	0’86 (0’10)	0’93 (0’08)	0’79 (0’07)
TSH (mU/L)	1’59 (0’82)	1’49 (0’80)	1’68 (0’83)
Ac TPO (%)	7’08	5’97	8’20
EUI (µg/l)	154’2 (114’8)	156’0 (107’0)	152’4 (122’3)
Fumador (%)	25	29’85	20’14
Bebedor (%)	11’66	21’64	1’49
ACT (L)	38’94 (7’53)	44’42 (5’79)	33’45 (4’44)
MNG (Kg)	53’33 (10’32)	60’85 (7’9)	45’82 (6’09)
MG (Kg)	18’51 (9’81)	17’47 (9’29)	19’56 (10’23)
MG (%)	24’94 (10’00)	21’42 (9’09)	28’46 (9’67)

Datos expresados como media (± SD) y porcentajes.

TABLA 1.

CARACTERÍSTICAS DE

LA POBLACIÓN

IMC: Índice de masa corporal
ICC: Índice cintura – cadera
THS: Tirotropina
Ac TPO: Anticuerpos antiperoxidasa
EUI: Excreción urinaria de yodo
ACT: Agua corporal total
MNG: Masa no grasa
MG: Masa grasa

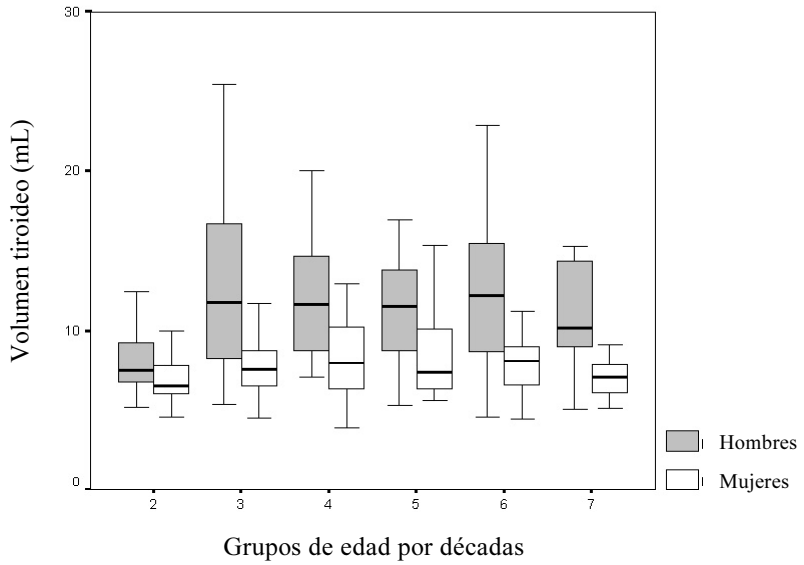
Los resultados de nuestro estudio son coincidentes con los obtenidos en otros estudios poblacionales en áreas no deficientes en yodo, y claramente inferiores a los obtenidos en zonas yodo-deficientes. Los valores de la yoduria reflejan una ingesta diaria de yodo dentro del rango recomendado por la OMS[55], por lo que nuestra población se considera como no yodo-deficiente.

TABLA 2. VALORES DE REFERENCIA DEL VOLUMEN TIROIDEO EN RELACIÓN A LOS GRUPOS DE EDAD

EDAD (años)	*n*	*Media (mL)*	*Mediana (mL)*	*I C*
15 – 20	33	6’33	5’79	5’76 – 6’90
21 – 30	55	8’61	7’29	7’54 – 9’71
31 – 40	40	8’47	7’79	7’41 – 9’53
41 – 50	50	8’75	7’54	7’24 – 10’26
51 – 60	53	8’62	6’94	7’62 – 9’61
61 – 70	37	7’75	7’31	6’75 – 8’69
GLOBAL	268	8’22	7’31	7’75 – 8’69

IC: intervalo de confianza

Figura 1. Volumen tiroideo en las diferentes décadas.



Los datos se expresan como mediana y percentil 25º – 75º en rectángulos, y percentil 3º – 97º en corchetes.

Al igual que en otros estudios[19,23,25], el volumen fue significativamente mayor en hombres que en mujeres, P = 0.001. (Tablas 3 y 4, figura 1).

TABLA 3. VALORES DE REFERENCIA DEL VOLUMEN TIROIDEO EN RELACIÓN A LOS GRUPOS DE EDAD, EN HOMBRES

EDAD (años)	*n*	*Media (mL)*	*Mediana (mL)*	*I C*
15 – 20	17	6’61	6’25	5’90 – 7’32*
21 – 30	28	10’75	9’84	9’09 – 12’41
31 – 40	17	10’32	9’71	8’72 – 11’91
41 – 50	25	10’49	9’62	7’73 – 13’25
51 – 60	29	10’35	10’17	8’86 – 11’83
61 – 70	18	9’53	8’51	7’96 – 11’09
GLOBAL	134	9’87	9’19	9’09 – 10’65

* p = 0’0034 IC: intervalo de confianza

TABLA 4. VALORES DE REFERENCIA DEL VOLUMEN TIROIDEO EN RELACIÓN A LOS GRUPOS DE EDAD, EN MUJERES

EDAD (años)	*n*	*Media (mL)*	*Mediana (mL)*	*I C*
15 – 20	16	6’03	5’41	5’12 – 6’94
21 – 30	27	8’42	6’29	5’63 – 7’21
31 – 40	23	7’10	6’64	5’95 – 8’25
41 – 50	25	7’01	6’14	6’19 – 7’84
51 – 60	24	6’53	6’78	5’92 – 7’15
61 – 70	19	6’07	5’91	5’41 – 6’72
GLOBAL	134	6’57	6’19	6’22 – 6’92

IC: intervalo de confianza

En el volumen tiroideo de nuestra población no se objetivaron diferencias significativas entre los diferentes intervalos de edad, excepto en los hombres más jóvenes, que fue más pequeño. Esto puede deberse a que finalizan el desarrollo puberal más tarde, y todavía no se ha alcanzado el volumen final.

El volumen tiroideo se correlaciona significativamente con la edad en los niños[4,56]. Durante la pubertad el incremento máximo del volumen tiroideo coincide con la fase de aceleración del crecimiento, y esto ocurre antes en las niñas[57].

Ashizawa et al.[58] estudiaron 120.000 niños, y determinaron un incremento del volumen tiroideo en relación con la edad, en ambos sexos, pero este incremento cesa en niñas, entre los 14 y los 16 años.

En etapas posteriores de la vida, en ausencia de enfermedad, el volumen tiroideo permanece invariable[3,19]. Otros autores objetivan un incremento progresivo en relación con la edad[23,59], probablemente en relación con el aumento de la prevalencia de patología nodular.

En estudios previos realizados en población sana, los valores del volumen tiroideo fueron diferentes en función de la presencia de deficiencia de yodo. Esto provoca gran variabilidad en el volumen considerado como normal.

Los resultados de diversos estudios están reflejados en la tabla 5.

TABLA 5. ESTUDIOS EPIDEMIOLÓGICOS SOBRE EL VOLUMEN TIROIDEO

Áreas yodo-suficientes			***Áreas yodo-deficientes (YD)***		
Estudio	*Volumen (ml)*		*Estudio*	*Volumen (ml)*	
	Hombres	*Mujeres*		*Hombres*	*Mujeres*
Gutekunst et al[1]	9'1 (3'3 – 27'4)	6'9 (2'5 – 34)	Gutekunst et al[1]	23'1 (3'8 – 105'0)	13'3 (2'6 –124'1)
Berghout et al[19]	13'2 (6'7 – 20'4)	8'2 (2'7 – 20'3)	Nyagaard et al[3]		12 – 18*
Wesche et al[24]	10'3 (± 3'4)	6'9 (± 2'9)	Hegedüs et al[23]	19'6 (± 4'7)	17'5 (± 4'2)
Barrère et al[25]	12'8 – 13'3*	8'3 – 9'3*	Olbricht et al[59]	16'7 (9 – 38)	13'5 (6 – 25)
			Hintze et al[61]	19'2 (3'2 –187'3)	16'6 (5'4 – 98'1)
			Knudsen et al[62]		
			Media YD	15'8	9'6 – 12'4*
			Moderada YD	19'5	10'3 – 14'8*

Datos expresados como media (± desviación estándar), mediana (valores límite), y medianas en relación a los grupos de edad*

Nuestros resultados son acordes con otros estudios poblacionales, en zonas yodosuficientes, siendo muy similares a los hallados por Gutekunst et al.[1] en población sueca, que objetivan volúmenes con una mediana de 9'1 mL en hombres, y de 6'9 mL en mujeres. Berghout et al.[19], en población holandesa obtienen valores de 13'2 mL en hombres, y de 8'2 mL en mujeres. Wesche et al.[24] objetivan valores de media 10'3 (3'4) mL en hombres y de 6'9 (2'9) mL en mujeres de la ciudad de Amsterdam. Barrère et al.[25] objetivan en población francesa adulta volúmenes cuyas medianas oscilan, según los grupos de edad, entre 12'8 y 13'3 mL en hombres, y entre 8'3 y 9'3 mL en mujeres.

Discretamente más elevados son los hallados por Rezzónico et al.[60], con valores de 14'63 (2'86) mL en hombres, y 12'09 (2'51) mL en mujeres, en población argentina, donde la yodoprofilaxis obligada data desde 1952.

Por el contrario, en zonas yododeficientes, se obtienen valores claramente más elevados, como Heguedüs et al.[23] que en población danesa objetivan valores de 18'6 (4'5) mL, Nyagaard et al.[3] obtienen, en mujeres distribuídas en cuatro grupos de edad, medianas entre 12 y 18 mL. Gutekunst et al.[1] en población alemana objetivan volúmenes de 23'1 mL en hombres, y de 13'3 mL en mujeres. Igualmente Olbricht et al.[59], en población alemana sana sin bocio, obtienen valores de 16'7 mL en hombres y 13'5 mL en mujeres. Hintze et al.[61] en población alemana de edad superior a 60 años objetivan valores de 19'2 mL en hombres, y de 16'6 mL en mujeres.

Knudsen et al.[62] estudiaron población danesa procedente de dos áreas con ligeras diferencias en los niveles de yoduria, en hombres de 60 a 65 años, y en mujeres de 18 a 65 años, y encontraron medianas similares a otras áreas yododeficientes.

Estudios poblacionales realizados en niños de zonas yodosuficientes, muestran para la edad de 14 años, volúmenes similares a los del primer intervalo de edad de nuestra población; Vitti et al.[4] y Aghini-Lombardi et al.[63] obtienen valores de 6'3 (1'5) mL, sin embargo Wiersinga et al.[57] en población escolar holandesa objetivan, a la edad de 18 años, medianas de 12'1 mL en hombres y de 8'9 mL en mujeres.

Estos volúmenes son claramente inferiores a los obtenidos por Delange et al.[64] en el gran estudio poblacional realizado con el Thyro-Movil, que establece el límite superior de la normalidad en sujetos de 15 años de zonas no yododeficientes, en 16 mL para los varones, y 16'1 mL para las mujeres.

3.2.- DETERMINANTES DEL VOLUMEN TIROIDEO.

Diversos factores están relacionados con la regulación del volumen de la glándula tiroidea. La ingesta de yodo es el más exhaustivamente estudiado, pero también otros factores ambientales y características antropométricas están implicados, y son tema de controversia en estudios poblacionales tanto de adultos, como de niños[1-5,23].

Factores como el sexo, el peso y la edad[23], la masa magra[24], la tirotropina, el consumo de tabaco[65,66] y de alcohol[67], el número de gestaciones, fase del ciclo menstrual y estación del año[60], etc. se han invocado como responsables del volumen tiroideo en diversos estudios.

En nuestro estudio, el volumen tiroideo se correlacionó significativamente con el peso, la talla, el índice de masa corporal, el índice cintura-cadera, la superficie corporal, el agua corporal total, la masa libre de grasa, la masa grasa, y el porcentaje de masa grasa (Tabla 6).

Tabla 6. Correlaciones entre el volumen tiroideo y diversas variables

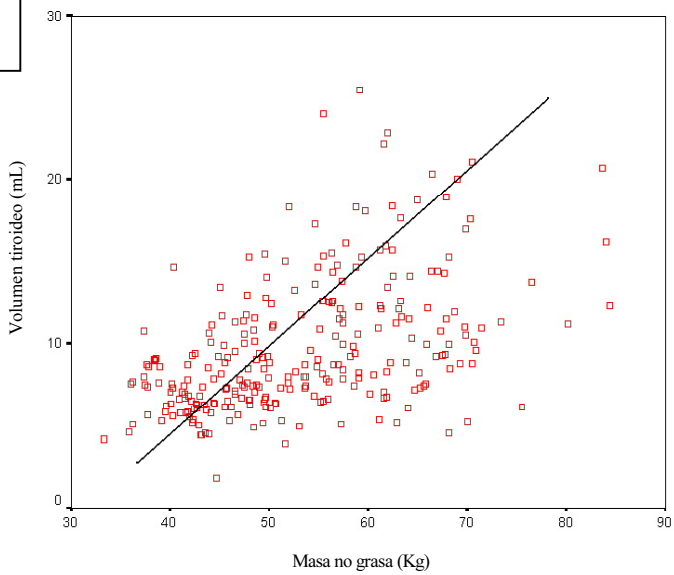
Peso	*Talla*	*IMC*	*ICC*	*ASC*
r = 0'39	r = 0'44	r = 0'13	r = 0'38	r = 0'48
P = 0'0001	P = 0'0001	P = 0'02	P = 0'001	P = 0'0001
ACT	*MNG*	*MG*	*MG %*	*TSH*
r = 0'14	r = 0'47	r = 0'37	r = 0'32	r = - 0'26
P = 0'02	P = 0'0001	P = 0'001	P = 0'001	P = 0'001

IMC: Índice de masa corporal, *ICC*: Índice cintura – cadera, *ASC*: área de la superficie corporal, *ACT*: agua corporal total, *MNG*: masa no grasa, *MG*: masa grasa, *THS*: Tirotropina.

Se encontró una correlación positiva entre el peso corporal y el volumen tiroideo, tanto en hombres como en mujeres. Es tema de controversia si el volumen tiroideo se correlaciona mejor con el peso corporal total[15], o con la masa muscular; Wesche et al.[24] demuestran que la masa magra, determinada por bioimpedanciometría, es el mejor determinante del volumen tiroideo.

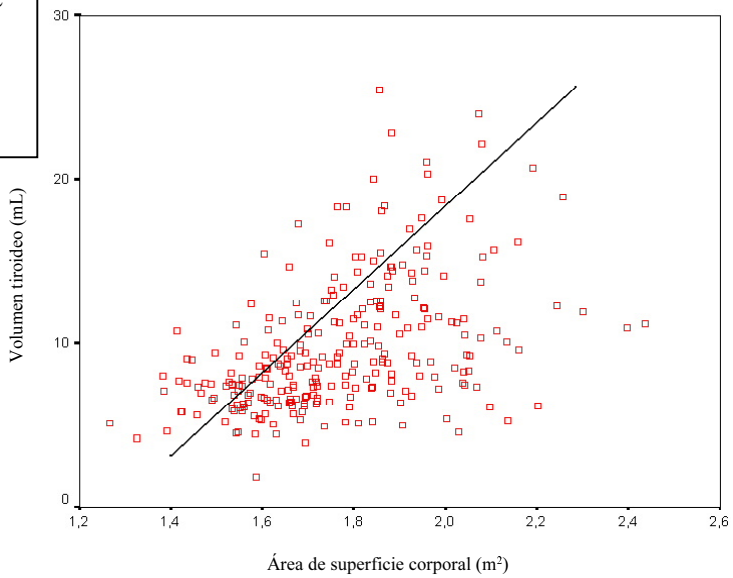
En nuestro estudio, la masa libre de grasa fue también un determinante importante del volumen tiroideo (Figura 2).

Figura 2. Correlación entre el volumen tiroideo y la masa no grasa.



Así mismo se demostró una correlación significativa entre el volumen tiroideo y la talla y el área de la superficie corporal (Figura 3), al igual que en estudios previos en adultos[1,5,19,25].

Figura 3. Correlación entre el volumen tiroideo y el área de superficie corporal.



Algunos estudios sugieren el potencial efecto bociógeno de la gestación en presencia de yododeficiencia moderada[68]. La reversibilidad de este efecto en el período posparto no está clara, y queda abierta a más estudios.

En nuestro estudio el número de gestaciones previas no se asoció con un aumento significativo del volumen tiroideo.

Tampoco se correlacionó con la excreción urinaria de yodo, al igual que en otros estudios[1,19], lo cual apoya la idea de que en países sin deficiencia de yodo no se observa una asociación entre la ingesta de yodo y el volumen tiroideo, a diferencia de las áreas yododeficientes[69].

Algunos estudios han demostrado el efecto bociógeno del consumo de tabaco. No se encontró correlación entre el volumen tiroideo y el hábito tabáquico al igual que en el estudio que describe esta tendencia bociógena sólo en sujetos con historia familiar de bocio[66], o en presencia de yododeficiencia moderada o en el límite[25].

No se objetivó correlación entre el consumo de alcohol y el volumen tiroideo en la población como conjunto, ni en las mujeres, pero sí se halló una correlación negativa en hombres ($r = - 0.40$, $P = 0.02$), que en estudios previos se ha relacionado con el efecto tóxico directo sobre la glándula[15], o con un efecto protector del alcohol frente a la aparición de patología tiroidea[70].

La ausencia de correlación en mujeres podría deberse al escaso número de mujeres bebedoras.

Se objetivó una correlación negativa entre el volumen tiroideo y los valores de tirotropina basal (Tabla 6, figura 4), en ausencia de autoinmunidad y nodularidad, al igual que Barrère et al.[25], sin embargo otros estudios[1,19,23] no hallan correlaciones significativas entre ambos parámetros, y no existe una hipótesis clara sobre la influencia de la tirotropina en el volumen tiroideo, en áreas sin yododeficiencia.

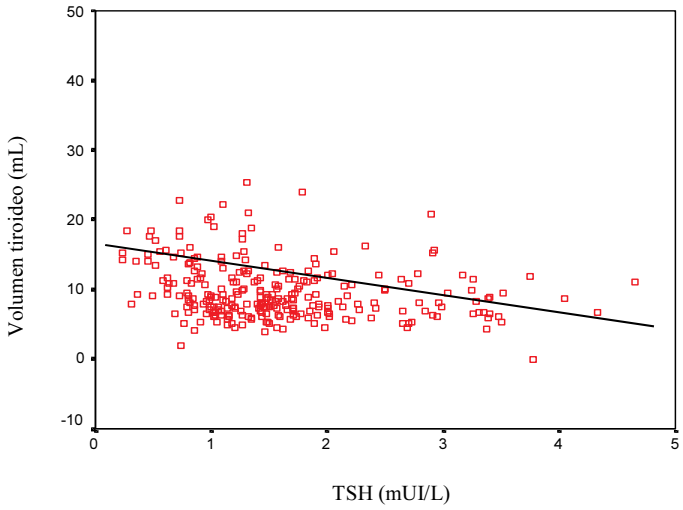


Figura 4. Correlación entre el volumen tiroideo y los valores de TSH

El análisis de regresión múltiple mostró que la superficie corporal contribuye en el 44 % de la variabilidad del volumen tiroideo (P = 0'0001).

La edad, el sexo, el resto de variables antropométricas y de composición corporal, y las variables de funcionalismo tiroideo no tuvieron un efecto independiente sobre el volumen tiroideo en este modelo, y el efecto observado de estas variables se debe a su relación con la superficie corporal.

3.3.- VOLUMEN TIROIDEO EN PACIENTES CON DIABETES MELLITUS TIPO 1.

La influencia de la composición corporal en la variabilidad del volumen tiroideo también puede ser estudiada en situaciones clínicas que cursen con cambios en la composición corporal, como es el caso de la diabetes mellitus tipo 1.

Nuestro grupo demostró que los pacientes con diabetes mellitus tienen diferente composición corporal con relación a los sujetos sanos[26], y que esto explica las diferencias halladas en el volumen tiroideo.

Los datos antropométricos y de composición corporal de los pacientes con diabetes mellitus y los controles sanos quedan reflejados en las tablas 7 y 8.

El peso, la talla, el índice de masa corporal, el índice cintura-cadera, y el área de superficie corporal no fueron diferentes ni en hombres ni en mujeres. La masa no grasa fue superior en el grupo de pacientes con diabetes mellitus, en ambos sexos. La masa grasa fue inferior en hombres con diabetes mellitus, con respecto a los controles.

La yoduria, y la proporción de fumadores y personas que consumían alcohol diariamente fueron similares en ambos grupos. Los requerimientos de insulina de los pacientes con diabetes mellitus fueron de 0'65 ± 0'25 U/Kg y la HbA1c 6'6 ± 1'4 %.

Tabla 7.
Características de los pacientes con diabetes mellitus y sujetos controles, en hombres.

	PD	**C**	Límite inferior del 95 % IC de la diferencia	Límite inferior del 95 % IC de la diferencia	**P**
N	36	36			
Edad (años)	26'8 ± 5'1	25'7 ± 5'2	- 4'6	0'47	0'1
Variables antropométricas					
Peso (Kg)	74'1 ± 8'3	74'6 ± 13'2	- 5'0	6'1	0'85
Talla (m)	1'73 ± 0'06	1'70 ±0'07	- 0'06	0'04	0'08
IMC (Kg/m^2)	24'6 ± 2'8	25'5 ± 3'6	- 0'742	2'49	0'28
ICC	0'84 ± 0'05	0'86 ± 0'06	- 0'01	0'04	0'31
ASC (m^2)	1'88 ± 0'11	1'86 ± 0'18	- 0'09	0'05	0'62
Variables de Composición corporal					
MNG (Kg)	64'4 ± 6'9	60'4 ± 8'2	- 7'7	- 0'37	**0'03**
MG (Kg)	9'7 ± 7'0	14'2 ± 8'1	0'84	8'13	**0'01**
Otras variables					
Fumadores (%)	63'4	44'8			0'14
Alcohol (%)	21	30			0'15
Sal yodada (%)	51'2	65'5			0'32
TSH (mU/L)	1'60 ± 1'14	1'56 ± 0'78	- 0'56	0'41	0'76
EUI (µg/L)	140'3 ± 113'5	128'1 ± 77'6			0'1
Volumen tiroideo (mL)	12'12 ± 2'87	9'63 ± 2'27	- 3'7	- 1'21	**0'0001**

Datos presentados como media ± desviación estándar o porcentajes, PD: pacientes con diabetes mellitus, C: controles, IC: Intervalo de confianza, IMC: índice de masa corporal, ICC: índice cintura-cadera, ASC: área de la superficie corporal, MNG: masa no grasa, MG: masa grasa, TSH: tirotropina, EUI: excreción urinaria de yodo.

Tabla 8
Características de los pacientes con diabetes mellitus y sujetos controles, en mujeres.

	PD	**C**	Límite inferior del 95 % IC de la diferencia	Límite suprior del 95 % IC de la diferencia	**P**
N	29	29			
Edad (años)	26'1 ± 5'4	26'7 ± 6'2	- 2'5	3'7	0'72
Variables antropométricas					
Peso (Kg)	63'9 ± 9'9	60'8 ± 9'7	- 8'2	2'1	0'24
Talla (m)	1'59 ± 0'05	1'59 ±0'06	- 0'03	0'03	0'9
IMC (Kg/m^2)	24'9 ± 4'4	23'7 ± 3'1	- 2'87	0'58	0'19
ICC	0'73 ± 0'04	0'75 ± 0'05	- 0'008	0'04	0'19
ASC (m^2)	1'6 ± 0'1	1'6 ± 0'1	- 0'1	0'03	0'33
Variables de Composición corporal					
MNG (Kg)	48'3 ± 5'7	45'4 ± 6'0	- 5'96	- 0'25	**0'04**
MG (Kg)	15'5 ± 6'9	15'3 ± 6'2	- 3'59	3'26	0'92
Otras variables					
Fumadores (%)	25'0	47'2			0'08
Alcohol (%)	8'0	11'6			0'2
Sal yodada (%)	70'8	52'8			0'18
TSH (mU/L)	1'69 ± 1'08	1'59 ± 0'96			0'48
EUI (µg/L)	119'7 ± 49'9	110'4 ± 70'7	- 51'8	- 15'1	0'15
Volumen tiroideo (mL)	9'5 ± 2'3	7'7 ± 2'0	- 2'96	- 0'68	**0'002**

Datos presentados como media ± desviación estándar o porcentajes, PD: pacientes con diabetes mellitus, C: controles, IC: Intervalo de confianza, IMC: índice de masa corporal, ICC: índice cintura-cadera, ASC: área de la superficie corporal, MNG: masa no grasa, MG: masa grasa, TSH: tirotropina, EUI: excreción urinaria de yodo.

Clínicamente, en ningún sujeto se objetivó bocio, y la tirotropina basal fue similar en ambos grupos. El volumen tiroideo fue superior en pacientes diabéticos frente a los sujetos controles, 12'12 ± 2'87 frente a 9'63 ± 2'27 ml, p = 0'0001 en hombres (Tabla 7), y 9'5 ± 2'3 frente a 7'7 ± 2'0 ml, p = 0'002, en mujeres (Tabla 8).

No se objetivaron nódulos mayores de 5 mm ni en pacientes con diabetes mellitus, ni en controles sanos.

En todos los sujetos, el volumen tiroideo se correlacionó con el peso, la talla, el índice de masa corporal, el índice cintura-cadera, la superficie corporal y la masa no grasa, pero no con la edad, la TSH ni con la yoduria.

No hubo diferencias entre pacientes con diabetes mellitus y controles con respecto al consumo de alcohol y tabaco. El volumen tiroideo no fue diferente entre fumadores y no fumadores, y no se halló correlación entre el volumen tiroideo y el consumo de tabaco, ni alcohol.

En los pacientes con diabetes mellitus el volumen tiroideo se correlacionó negativamente con la HbA1c (Tabla 9).

Tabla 9
Correlaciones entre el volumen tiroideo como variable dependiente y otras variables independientes

Grupo	Edad	Peso	Talla	IMC	ICC	ASC	MNG	TSH	EUI	HbA1c
Todos	r= 0'13	r= 0'629	r= 0'584	r= 0'626	r= 0'348	r= 0'669	r= 0'67	r= 0'15	r= 0'11	
	p= 0'142	p= 0'0001	p= 0'0001	p= 0'0001	p=0'0001	p=0'0001	p=0'0001	p= 0'3	p= 0'11	
PD	r= 0'1	r= 0'626	r= 0'566	r= 0'534	r= 0'467	r= 0'632	r= 0'672	r= 0'12	r= 0'1	r=-0'561
	p= 0'11	p=0'0001	p=0'0001	p=0'0001	p=0'0001	p= 0'0001	p=0'0001	p= 0'2	p= 0'11	p=0'0001
C	r= 0'12	r= 0'629	r= 0'584	r= 0'36	r= 0'348	r= 0'669	r= 0'67	r= 0'1	r= 0'09	
	p= 0'12	p= 0'0001	p=0'0001	p= 0'001	p=0'0001	p=0'0001	p= 0'0001	p= 0'1	p= 0'1	

PD: pacientes con diabetes mellitus, C: controles, IMC: índice de masa corporal, ICC: índice cintura-cadera, ASC: área de la superficie corporal, MNG: masa no grasa, TSH: tirotropina, EUI: excreción urinaria de yodo.

Tomando en conjunto todas las variables en ambos grupos, el análisis de regresión lineal multivariante obtuvo un modelo final que explicó el 47 % de la variabilidad del volumen tiroideo en el grupo entero, en pacientes y en controles. Sólo la masa no grasa y el área de la superficie corporal tuvieron una contribución significativa independiente sobre la variabilidad del volumen tiroideo.

Concretamente, sólo la masa no grasa tuvo una contribución significativa independiente sobre la variabilidad del volumen tiroideo en el grupo de diabéticos y controles por separado. (Tabla 10)

Tabla 10
Análisis de regresión lineal multivariante en todos los sujetos del estudio, pacientes con diabetes mellitus y controles.

Grupo analizado	Predictores	β	Significación	Límite inferior del 95 % IC para β	Límite superior del 95 % IC para β
Todos R^2 ajustada = 0'47					
	Constante	- 0'393	0'701	- 2'416	1'630
	MNG	0'100	0'005	0'030	0'171
	ASC	5'709	0'007	1'610	9'809
PD R^2 ajustada = 0'32					
	Constante	1'296	0'466	- 2'233	4'826
	MNG	0'169	0'0001	0'109	0'228
C R^2 ajustada = 0'48					
	Constante	0'303	0'781	- 1'864	2'470
	MNG	0'158	0'0001	0'118	0'199

PD: pacientes con diabetes mellitus, C: controles, IC: Intervalo de confianza, MNG: masa no grasa, ASC: área de la superficie corporal.

La yoduria obtenida, tanto en pacientes con diabetes mellitus, como en controles sanos refleja una ingesta óptima de yodo, dentro de los límites recomendados por la OMS[54,55,71], y similar en ambos grupos, a diferencia de los resultados obtenidos por Steiss et al.[28], que objetivaron un promedio de yoduria superior en pacientes con diabetes mellitus que en controles.

El volumen tiroideo mayor en pacientes con diabetes mellitus tipo 1 ya fue descrito en dos estudios realizados en niños alemanes[28] y adultos italianos[30], y se atribuyó a la elevada prevalencia de autoinmunidad tiroidea en los sujetos con diabetes mellitus, y a la baja ingesta de yodo en niños alemanes. Sin embargo, estas diferencias no se ha observado en estudios similares realizados en niños daneses y turcos[29].

Con relativa frecuencia los pacientes con diabetes mellitus tipo 1 presentan enfermedades tiroideas autoinmunes, como se ha descrito en estudios previos[49,72], y la presencia de autoinmunidad y disfunción tiroidea puede influir sobre el volumen tiroideo y la ecogenicidad; estas anormalidades podrían ser en parte, una expresión de la afectación tiroidea de un proceso autoinmune silente no solamente limitado al islote pancreático, como se ha sugerido por algunos autores[30].

En nuestro grupo de pacientes con diabetes mellitus seguidos desde el diagnóstico, las diferencias observadas en el volumen tiroideo no se pueden atribuir a disfunción tiroidea o presencia de autoinmunidad, ya que tanto pacientes como controles con disfunción tiroidea previa, o con anticuerpos antitiroideos positivos y/o TSH fuera de los límites de la normalidad en el momento del estudio, fueron excluidos del análisis final.

La correlación entre volumen tiroideo y la edad, el peso y la talla, ha sido observada previamente en otros estudios, pero la composición corporal no fue analizada, excepto en niños[27,57,73]. En nuestra población, el volumen tiroideo se correlacionó con el peso, la talla, el IMC, el índice cintura-cadera, la superficie corporal y la masa no grasa, y negativamente con la HbA1c en pacientes con diabetes mellitus, por lo que podemos afirmar que las variables antropométricas y de composición corporal predicen el volumen tiroideo tanto en sujetos con diabetes mellitus tipo 1, como en controles sanos.

En los pacientes con diabetes mellitus tipo 1 la composición corporal es diferente, con un incremento significativo de la masa no grasa, así como una disminución de la masa grasa, como se ha descrito previamente[26,74-77]. En promedio, la masa no grasa fue aproximadamente 4 Kg superior en hombres y 2’9 Kg en mujeres del grupo de pacientes con diabetes mellitus con respecto a los controles; la masa grasa fue aproximadamente 4’5 Kg menor en hombres con diabetes mellitus que en controles.

Nuestros datos sugieren que las diferencias en la composición corporal, especialmente la masa no grasa, y la superficie corporal, se relacionan con las diferencias encontradas en el volumen tiroideo, entre pacientes y controles, en ausencia de disfunción tiroidea ni autoinmunidad. Este interesante hallazgo, desde nuestro punto de vista, no ha sido descrito previamente.

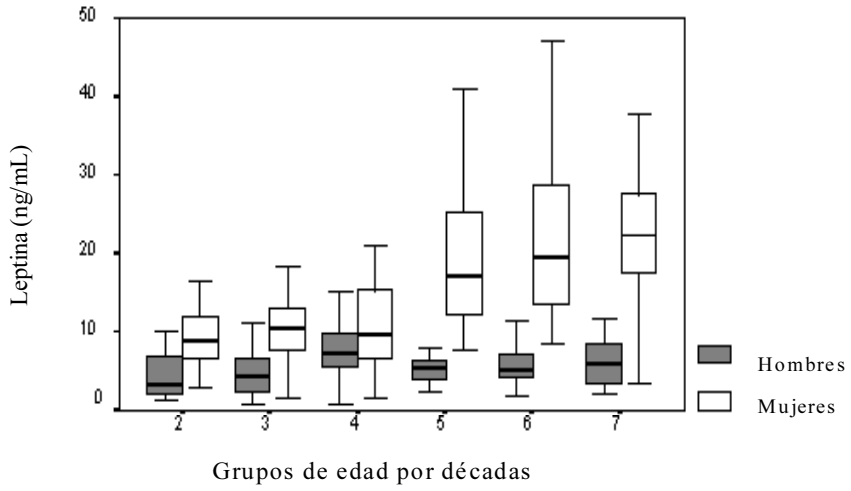
Aunque generalmente se ha hipotetizado que el aumento de peso observado en pacientes con diabetes mellitus tipo 1 se debe a un incremento de la masa grasa[75], algunos estudios recientes han demostrado que se debe a un aumento de la masa magra, en relación al hiperinsulinismo[26,74-77] que contribuye a alcanzar un buen control metabólico, como en nuestros pacientes. Además, el volumen tiroideo se correlacionó negativamente con la HbA1c.

3.4.- EJE HIPÓFISO-TIROIDEO, VOLUMEN TIROIDEO Y LEPTINA.

Leptina y hormonas tiroideas tienen influencia sobre aspectos similares de la homeostasis energética, por lo que el objetivo final de nuestro estudio fue valorar la relación entre ambos sistemas, y el posible papel de la leptina como determinante novedoso del volumen tiroideo.

En nuestra población, las concentraciones de leptina fueron 6'1 ± 4'0 en hombres, y 16'8 ± 11'7 ng/mL en mujeres, P = 0'0001, y diferentes en las diferentes décadas de cada sexo (Figura 5). La concentración de leptina fue significativamente superior en mujeres, y progresivamente creciente en cada intervalo de edad.

Figura 5. Concentraciones de leptina en las diversas décadas.



Los datos se expresan como mediana y percentil 25º – 75º en rectángulos, y percentil 3º – 97º en corchetes. A partir de la segunda década, las diferencias entre sexos fueron significativas (P = 0.01 en hombres, P = 0.001 en mujeres)

Se hallaron correlaciones significativas entre las concentraciones de leptina y las variables antropométricas y de composición corporal (peso, índice de masa corporal, índice cintura-cadera, área de superficie corporal, agua corporal total, masa libre de grasa, masa grasa y porcentaje de masa grasa) en ambos sexos, pero no con la talla ni con las concentraciones de tirotropina (Tabla 11).

Tabla 11.
Correlaciones entre leptina, variables antropométricas y de composición corporal, y volumen tiroideo.

	Leptina en hombres	Leptina en mujeres
Talla	r=0'019 P=0'83	r=0'14 P=0'1
Peso	r=0'665 P=0'0001	r=0'544 P=0'0001
IMC	r=0'697 P=0'0001	r=0'581 P=0'0001
ICC	r=0'237 P=0'006	r=0'307 P=0'0001
ASC	r=0'54 P=0'0001	r=0'44 P=0'0001
ACT	r=0'224 P=0'01	r=0'229 P=0'015
MNG	r=0'225 P=0'009	r=0'211 P=0'015
MG	r=0'74 P=0'0001	r=0'606 P=0'0001
MG %	r=0'641 P=0'0001	r=0'57 P=0'0001
TSH	r= -0'003 P=0'97	r=0'37 P=0'67
Volumen tiroideo hombres	r= -0'111 P=0'202	
Volumen tiroideo mujeres		r=0'181 P=0'038

IMC: índice de masa corporal, ICC: índice cintura-cadera, ASC: área de superficie corporal, ACT: agua corporal total, MNG: masa no grasa, MG: masa grasa, TSH: tirotropina.

En nuestro estudio no objetivamos diferencias en la tirotropina entre ambos sexos, pero los niveles de leptina fueron significativamente inferiores en hombres con respecto a las mujeres. Así mismo se encontraron correlaciones significativas entre los niveles de leptina y las variables antropométricas y de composición corporal entre ambos sexos. No obstante no se objetivó correlación entre leptina y tirotropina ni en hombres, ni en mujeres.

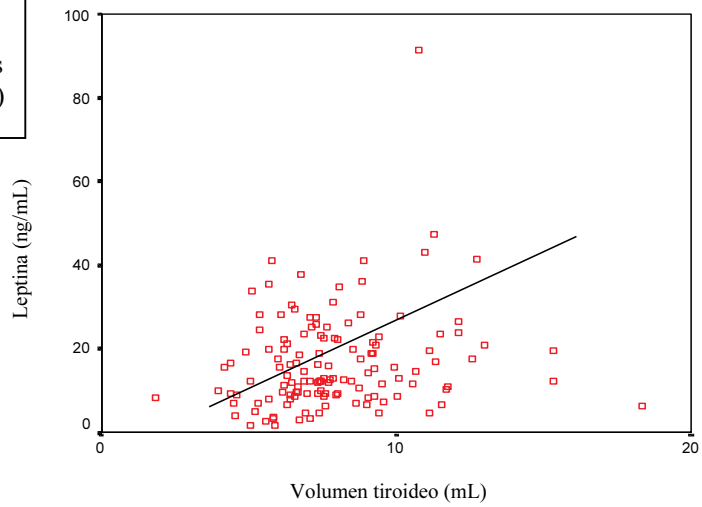
Probablemente la leptina no regule las concentraciones de TSH en sujetos eutiroideos, pero esta relación puede ser diferente en presencia de disfunción tiroidea[44,46,47].

El volumen tiroideo fue mayor en hombres que en mujeres, y en la población global y en mujeres se comprobó una correlación significativa con las variables antropométricas y de composición corporal. No obstante, en mujeres sí se objetivó una correlación positiva entre leptina y volumen tiroideo (Figura 6), pero no en hombres.

La unión de la leptina a sus receptores ha sido demostrada en varias áreas del sistema nervioso central, particularmente el hipotálamo, pero también en múltiples tejidos periféricos[33,34,78], si bien en nuestro conocimiento, no hay receptores de leptina en la glándula tiroidea

Consecuentemente, el volumen tiroideo y la leptina podrían estar regulados en paralelo, bajo condiciones fisiológicas normales, lo cual explicaría la correlación entre leptina y volumen tiroideo en mujeres, pero no en hombres.

Figura 6.
Correlación entre el volumen tiroideo y la leptina en mujeres (r =0.181, p = 0.038)



La correlación positiva, en mujeres, entre volumen tiroideo y leptina, podría deberse a que ambos se regulan, en condiciones fisiológicas, en paralelo a través de las variables de composición y tamaño corporal.

CONCLUSIONES FINALES

1) La población de L'Hospitalet de Llobregat es yodosuficiente, según las recomendaciones de la OMS.

2) Los valores obtenidos para el volumen tiroideo, y las tablas con la distribución por edad y sexo, se pueden considerar de referencia para poblaciones yodosuficientes.

3) El volumen tiroideo es mayor en hombres que en mujeres.

4) En hombres, el grupo de edad más joven muestra un volumen tiroideo inferior al resto de intervalos de edad, lo cual no ocurre en mujeres. Probablemente está en relación con la finalización del desarrollo puberal, que ocurre a edad más temprana en las mujeres.

5) En etapas posteriores de la vida, en ausencia de enfermedad, el volumen tiroideo se mantiene invariable.

6) Los valores de volumen tiroideo obtenidos en nuestra población son claramente inferiores a los valores obtenidos en el estudio Thyro-Mobil, ofrecidos como valores estándar de normalidad.

7) La ecografía es el método de elección para valorar el volumen tiroideo en estudios poblacionales, pero es esencial estandarizar la técnica, para minimizar los errores intra e inter-observador.

8) En ausencia de yododeficiencia, la edad, el sexo, las variables antropométricas, de composición corporal y biológicas, no tienen un efecto independiente sobre el volumen tiroideo. El efecto observado de estas variables sobre el volumen tiroideo es a través de su relación con la superficie corporal.

9) Los pacientes con diabetes mellitus tipo 1 tienen un volumen tiroideo superior con respecto a la población sana.

10) La composición corporal en pacientes con diabetes mellitus tipo 1 es diferente, y la masa no grasa y el área de la superficie corporal son los principales determinantes del volumen tiroideo tanto en sujetos con diabetes mellitus como en controles sanos.

11) Diferencias en la antropometría y la composición corporal pueden contribuir a que aparezcan divergencias en los valores de referencia del volumen tiroideo ecográfico, entre diferentes poblaciones yodosuficientes.

12) En nuestra población no se ha objetivado correlación entre los niveles de leptina, y el eje hipófiso-tiroideo.

13) Los niveles de leptina son superiores en mujeres que en hombres, y en las mujeres aumentan progresivamente con la edad.

14) En mujeres, la correlación entre leptina y volumen tiroideo, probablemente es consecuencia de que ambos son regulados en paralelo por variables antropométricas y de composición corporal.

BIBLIOGRAFÍA

1.- Gutekunst R, Smolarek H, Hasenpusch U, Stubbe P, Friedrich HJ, Wood WG, Scriba PC. Goitre epidemiology: thyroid volume, iodine excretion, thyroglobulin and thyrotropin in Germany and Sweden. Acta Endocrinol (Cophen) 1986; 112: 494 – 501.

2.- Berghout A, Wiersinga WM, Smits NJ, Touber JL. The value of thyroid volume measured by ultrasonography in the diagnosis of goiter. Clin Endocrinol (Oxf) 1988; 28: 409 – 414.

3.- Nygaard B, Gideon P, Dige-Petersen H, Jespersen N, Sølling K, Veje A. Thyroid volume and morphology and urinary iodine excretion in a Danish municipality. Acta Endocrinol (Cophen) 1993; 129: 505 – 510.

4.- Vitti P, Martino E, Aghini-Lombardi F, Rago T, Antonangeli L, Maccherini D, Nanni P, Loviselli A, Balestrieri A, Araneo G. Thyroid volume measurement by ultrasound in children as a tool for the assessment of mild iodine deficiency. J Clin Endocrinol Metab 1994; 79: 600 – 603.

5.- Lisbôa HK, Gross JL, Orsolin A, Fuchs S. Clinical examination is not an accurate method of defining the presence of goiter in schoolchildren. Clin Endocrinol (Oxf) 1996; 45: 471 – 475.

6.- Zimmermann M, Saad A, Hess S, Torresani T, Chaouki N. Thyroid ultrasound compared with World Health Organization 1960 and 1994 palpation criteria for determination of goiter prevalence in regions of mild and severe iodine deficiency. Eur J Endocrinol 2000; 143: 727 – 731.

7.- Perez C, Scrimshaw NS, Muñoz JA. Technique of endemic goiter surveys. In: Endemic goiter, Geneva. Geneva World Health Organization 1960; monogr ser 44: 369 – 383.

8.- McLennar R, Gaitan E, Miller MC. Observer variation in grading and measuring the thyroid in epidemiological surveys. In: Stanbury JB (ed). Endemic goiter. Pan American Health Organization; scientific publication. New York: Wiley, 1959; 193: 66 – 77.

9.- Tannahill AJ, Hooper MJ, England M, Ferris JB, Wilson GM. Measurement of thyroid size by ultrasound, palpation and scintiscan. Clin Endocrinol (Oxf) 1978; 8: 483 – 486.

10.- Chen JJS, LaFrance MD, Allo MS, Cooper DS, Landerson PW. Single photon emission computer tomography of the thyroid. J Clin Endocrinol Metab 1988; 66: 1240 – 1246.

11.- Crawford DC, Flower MA, Pratt BE, Hill C, Zweit J, McCready VR, Harmer CL. Thyroid volume measurement in thyrotoxic patients: comparison between ultrasonography and iodine-124 positron emission tomography. Eur J Nucl Med Mol Imaging 1997; 24: 1470 – 1478.

12.- Frey P, Townsend D, Flattet A, De Gautard R, Widgren S, Jeavons A, Christin A, Smith A, Long A, Donath A. Tomographic imaging of the thyroid using I^{124}. J Clin Endocrinol Metab 1986; 63: 918 – 927.

13.- Nygaard B, Nygaard T, Court-Payen M, Jensen LI, Soe-Jensen P, Gerhard Nielsen K, Fugl M, Hegedus L. Thyroid volume measured by ultrasonography and CT. Acta Radiol 2002; 43: 269 – 274.

14.- Huysmans DA, de Haas MM, van den Broek WJ, Hermus AR, Barentsz JO, Corstens FH, Ruijs SH. Magnetic resonance imaging for volume estimation of large multinodular goitres: a comparison with scintigraphy. Br J Radiol 1994; 67: 519 – 523.

15.- Hegedüs L. Thyroid size determined by ultrasound. Dan Med Bull 1990; 37: 249 – 263.

16.- Brunn J, Block U, Ruf G, Bos L, Kunze W, Seriba PC. Volumetrie der schilddrüssenlappen mittels real time sonographie. Dtsch Med Wochenschr 1981; 106: 1338 – 1340.

17.- Leisner B. Ultrasound evaluation of thyroid diseases. Horm Res 1987; 26: 33 – 41.

18.- Jarlov AE, Hegedüs L, Gjorup T, Hansen JM. Accuracy of the clinical assessment of the thyroid size. Dan Med Bull 1991; 38: 87 – 89.

19.- Berghout A, Wiersinga WM, Smits NJ, Touber JL. Determinants of thyroid volume as measured by ultrasonography in healthy adults in a non-iodine deficient area. Clin Endocrinol (Oxf) 1987; 26: 273 – 280.

20.- Zimmermann MB, Molinari L, Spelh M, Weidinger-Toth J, Podoba J, Hess S, Delange F. Toward a consensus on reference values for thyroid volume in iodine-replete schoolchildren: results of a workshop on inter-observer and inter-equipment variation in sonographic measurement of thyroid volume. Eur J Endocrinol 2001; 144: 213 – 220.

21.- Gómez JM, Maravall FJ, Gómez N, Gumà A, Soler J. Determinants of thyroid volume as measured by ultrasonography in healthy adults randomly selected. Clin Endocrinol (Oxf) 2000; 53: 629 – 634.

22.- Wesche MF, Wiersinga WM. Relation between lean body mass and thyroid volume in competition rowers before and during intensive physical training. Horm Metab Res 2001; 33: 423 – 427.

23.- Hegedüs L, Perrild H, Poulsen RL, Andersen JR, Holm B, Schnohr P, Jensen G, Hansen JM. The determination of thyroid volume by ultrasound and its relationship to body weight, age and sex in normal subjects. J Clin Endocrinol Metab 1983; 56: 260 – 263.

24.- Wesche MFT, Wiersinga WM, Smits NJ. Lean body mass as a determinant of thyroid size. Clin Endocrinol (Oxf) 1998; 48: 701 – 706.

25.- Barrère X, Valeix P, Preziosi P, Bensimon M, Pelletier B, Galan P, Hercberg S. Determinants of thyroid volume in healthy french adults participating in the SU.VI.MAX cohort. Clin Endocrinol (Oxf) 2000; 52: 273 – 278.

26.- Gómez JM, Maravall FJ, Soler J, Fernández-Castañer M. Body composition assessment in type 1 diabetes mellitus patients over 15 years old. Horm Metab Res 2001; 33: 670 – 673.

27.- Ueda D. Sonographic measurement of the volume of the thyroid glan in healthy children. Acta Paed Jap 1989; 31: 352 – 354.

28.- Steiss JO, Otter A, Grief V, Klingmuller V. Schilddrüsensonographie und Harnjodidausscheidung bei Kindern und Jugendlichen mit Diabetes mellitus typ I. Klin Pad 1996; 208: 327 – 333.

29.- Darendeliler FF, Kadioglu A, Bas F, Bundak R, Gunoz H, Saka N, Neyzi OR. Thyroid ultrasound in IDDM. Ped Endocrinol 1994; 7: 33 – 37.

30.- Bianchi G, Montanari P, Fabbri A, Gamberini A, Zoli M, Marchesini G. Thyroid volume in type 1 diabetes without overt thyroid disease. Acta Diabetol 1995; 32: 49 – 52.

31.- Freake HC, Oppenheimer JH. Thermogenesis and thyroid function. Annu Rev Nutr 1995; 15: 263 – 291.

32.- Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedmann JM. Positional cloning of the mouse ob gene and its human homologue. Nature 1994; 372: 425 – 432.

33.- Considine R, Sinha MK, Heiman M, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, Mckee LJ, Bauer TL, Caro JF. Serum immunoreactive leptin concentrations in normal weight and obese humans. N Engl J Med 1996; 334: 292 – 295.

34.- Orban Z, Bornstein SR, Chrousos GP. The interaction between leptin and the hypothalamic-pituitary-thyroid axis. Horm Metab Res 1998; 30: 231 – 235.

35.- Fain JN, Coronel EC, Beauchamp MJ, Bahouth SW. Expression of leptin and beta 3-adrenergic receptors in rat adipose tissue in altered thyroid states. Biochem J 1997; 322: 145 – 150.

36.- Fain JN, Bahouth SW. Effect of tri-iodothyronine on leptin release and leptin mRNA accumulation in rat adipose tissue. Biochem J 1998; 332: 361 – 366.

37.- Leonhardt U, Gerdes E, Ritzel U, Schafer G, Becker W, Ramadori G. Immunoreactive leptin and leptin expresión are increased in rat hypo- but not hyperthyroidism. J Endocrinol 1999; 163: 115 – 121.

38.- Montague CT, Farroqi IS, Whitehead JP, Soos MA, Rau H, Wareham CH, Sewter CP, Digby JE, Mohammed SN, Hurst JA, Cheetham CH, Earley AR, Barnet AH, Prins JB, O'Rahilly S. Congenital leptin deficiency is associated with severe early onset obesity in humans. Nature 1997; 387: 903 – 908.

39.- Escobar-Morreale HF, Escobar del Rey F, Morreale de Escobar G. Thyroid hormones influence serum leptin concentrations in the rat. Endocrinology 1997; 138: 4485 – 4488.

40.- Valcavi R, Zini M, Peino R, Casanueva FF, Diéguez C. Influence of thyroid status on serum immunoreactive leptin levels. J Clin Endocrinol Metab 1997; 82: 1632 – 1634.

41.- Sreenan S, Caro JF, Refetoff S. Thyroid dysfunction is not associated with alterations in serum leptin levels. Thyroid 1997; 7: 407 – 409.

42.- Corbetta S, Englaro P, Giambona S, Persani L, Blum WF, Beck-Peccoz P. Lack of effects of circulating thyroid hormone levels on serum leptin concentrations. Eur J Endocrinol 1997; 137: 659 – 663.

43.- Leonhardt U, Ritzel U, Schafre G, Becker W, Ramadori G. Serum leptin levels in hypo- and hyperthyroidism. J Endocrinol 1998; 157: 75 – 79.

44.- Zimmermann-Belsing T, Dreyer M, Holst JJ, Felt-Rasmussen U. The relationship between the serum leptin concentrations of thyrotoxic patients during treatment and their total fat mass is different from that of normal subjects. Clin Endocrinol (Oxf) 1998; 49: 589 – 595.

45.- Sesmilo G, Casamitjana R, Halperin I, Gomis R, Vilardell E. Role of thyroid hormones on serum leptin levels. Eur J Endocrinol 1998; 139: 428 – 430.

46.- Pinkney JH, Goodrick s, Katz j, Johnson AB, Lightman SL, Coppack SW, Mohamed-Ali V. Leptin and the pituitary-thyroid axis: a comparative study in lean, obese, hypothyroid and hyperthyroid subjects. Clin Endocrinol (Oxf) 1998; 49: 583 – 588.

47.- Diekman MJM, Romijn JA, Endert E, Saurwein H, Wiersinga WM. Thyroid hormones modulate serum leptinlevels: observations in thyrotoxic and hypothyroid women. Thyroid 1998; 8: 1081 – 1086.

48.- Sera N, Yokoham N, Abe Y, Ide A, Imaizumi M, Usa T, Tominaga T, Ejima E, Ashizawa K, Ohmoto Y, Eguchi K Thyroid hormones influence serum leptin levels in patients with Graves' disease during suppression of β-adrenergic receptors. Thyroid 2000; 10: 641 – 646.

49.- Fernández-Castañer M, Molina A, López-Jimenez L, Gómez JM, Soler J. Clinical presentation and early course of type 1 diabetes mellitus in patients with and without thyroid autoimmunity. Diabetes Care 1999; 22: 377 – 381.

50.- World Health Organization. Diabetes Mellitus: Report of a WHO Study Group Geneva: World Health Org (Tech. Rep. Ser., no. 727), 1985.

51.- DuBois D, DuBois EF. Clinical calorimetry, X. A formula to estimate the approximate surface area in height and weight be known. Arch Inter Med 1916; 17: 863.

52.- Benotti J, Benotti M, Pino S, Gardyna H. Determination of total iodine in urine, stool, diets, and tissue. Clin Chem 1965; 2: 932 – 936.

53.- Lukasky HC, Bolonchuck WW, Hall CB, Siders WA. Validation of tetrapolar bioelectrical impedance method to assess human body composition. J Appl Phys 1986; 69: 1327 – 1332.

54.- Dunn J, Madeiros-Neto G. Endemic goiter and cretinism: continuing threats to world. Washington DC: Pan America Health Organization. WHO 1974; 292: 1 – 195.

55.- WHO, UNICEF, ICCIDD. Assessment of the iodine deficiency disorders and monitoring their elimination. A guide for programme managers. 2nd ed. Geneva: World Health Organization 2001; WHO Document WHO/NHD/01.1.

56.- Semiz S, Senol U, Bircan, Gumuslu S, Bilmen S, Bircan I. Correlation between age, body size and thyroid volume in an endemic area. J Endocrinol Invest 2001; 24: 559 – 563.

57.- Wiersinga WM, Podoba J, Srbecky M, van Vessem M, van Beeren HC, Platvoet-ter MC. A survey of iodine intake and thyroid volume in Dutch schoolchildren: reference values in an iodine-sufficient area and the effect of puberty. Eur J Endocrinol 2001; 144: 595 – 603.

58.- Ashizawa K, Shibata Y, Yamashita S, Namba H, Hoshi M. Yokoyama N, Izumi M, Nagataki S. Prevalence of goiter and urinary iodine excretion levels in children around Chernobyl. J Clin Endocrinol Metab 1997; 82: 3430 – 3433.

59.- Olbricht T, Schmitka T, Mellinghoff U, Benker G, Reinwein D. Sonographic determination of thyroid volume in subjects with healthy thyroids. Dtsch Med Wochenschr 1983; 108: 1355 – 1358.

60.- Rezzónico JN, Bossa N, Muñoz P, Leiva RA. Volumen tiroideo ecográfico en mujeres normales: correlación con variables antropométricas y edad. Comparación con

mujeres obesas y varones. Influencia del ciclo menstrual, las estaciones del año y el ejercicio físico. Endocrinología 1997; 44: 213 – 217.

61.- Hintze G, Winderler J, Baumert J, Stein H, Köbberling J. Thyroid volume and goiter prevalence in elderly as determined by ultrasound and their relationship to laboratory indices. Acta Endocrinol (Cophen) 1991; 124: 12 – 18.

62.- Knudsen N, Bülow I, Jorgensen T, Laurberg P, Ovesens L, Perrild H. Goitre prevalence and thyroid abnormalities at ultrasonography: a comparative epidemiological study in two regions with slightly different iodine status. Clin Endocrinol (Oxf) 2000; 53: 479 – 485.

63.- Aghini-Lombardi F, Antonangeli L, Pinchera A, Leoli F, Rago T, Bartolomei AM, Vitti P. Effect of iodized salt on thyroid volume of children living in an area previously characterized by moderate iodine deficiency. J Clin Endocrinol Metab 1997; 82: 1136 – 1139.

64.- Delange F, Benker G, Caron P, Eber O, Ott W, Peter F, Podoba J, Simescu M, Szybinsky Z, Vertongen F, Vitti P, Wiersinga W, Zamrazil V. Thyroid volume and urinary iodine in European schoolchildren: standardization of values for assessment of iodine deficiency. Eur J Endocrinol 1997; 136: 180 – 187.

65.- Borup Chistensen S, Ericsson UB, Janzon L, Tibblin S, Mealander A. Influence of cigarette smoking on goiter formation, thyroglobulin, and thyroid hormone levels in women. J Clin Endocrinol Metab 1984; 58: 615 – 618.

66.- Georgiadis E, Papapostolou C, Korakis T, Evangelopoulou K, Mantzoros C, Batrinos M. The influence of smoking habits on thyroid gland volume: an ultrasonography approach. J R Soc Health 1997; 117: 355 – 358.

67.- Hegedüs L. Decreased thyroid gland volume in alcoholic cirrhosis of the liver. J Clin Endocrinol Metab 1984; 58: 930 – 933.

68.- Glinoer D, De Nayer P, Delange F, Lemone M, Toppet V, Spehl M, Grün JP, Kinthaert J, Lejeune b. A randomized trial for the treatment of mild iodine deficiency during pregnancy: maternal and neonatal effects. J Clin Endocrinol Metab 1995; 80: 258 – 269.

69.- Rasmussen LB, Ovesen L, Bulow I, Jorgensen T, Knudsen N, Laurberg P, Perrild H. Relations between various measures of iodine intake and thyroid volume, thyroid nodularity, and serum thyroglobulin. Am J Clin Nutr 2002; 76: 1069 – 1076.

70.- Knudsen N, Bulow I, Laurberg P, Perrild H, Oversend L, Jorgensent T. Alcohol consumption is associated with reduced prevalence of goiter and solitary thyroid nodules. Clin Endocrinol (Oxf) 2001; 55: 41 – 46.

71.- Delange FM. Iodine deficiency In: Werner & Ingbar (ed). The thyroid. A fundamental and clinical text, ed 8 Philadelphia: Lippincott Williams & Wilkins, 2000: 295 – 316.

72.- Hansen D, Bennedbaek FN, Hansen LK, Hoer-Madsen M, Jacobsen BB, Hegedüs L. Thyroid function, morphology and autoimmunity in young patients with insulin-dependent diabetes mellitus. Eur J Endocrinol 1999; 140: 512 – 518.

73.- Xu F, Sullivan K, Houston R, Zhao J, May W. Thyroid volume in US and Bangladeshi schoolchildren: comparison with European schoolchildren. Eur J Endocrinol 1999; 40: 498 – 504.

74.- Sinha A, Formica C, Tsalamandris C, Paagiotopoulos S, Hendrich E, De-Luise M, Seerman E. Effects of insulin on body composition in patients with insulin-dependent and non-insulin-dependent diabetes. Diab Med 1996; 13: 40 – 46.

75.- Rigalleau V, Delafaye C, Baillet L, Vergnot V, Prunou P, Gatta B, Gin H. Composition of insulin-induced body weight gain in diabetic patients : a bio-impedance study. Diab Metab 1999; 25: 321 – 328.

76.- Svenson OL, Hassager C. Body composition and fat distribution measured by dual-energy x-ray absorptiometry in premenopausal and postmenopausal insulin-dependent and non-insulin-dependent diabetes mellitus patients. Metabolism 1998; 47: 212 – 216.

77.- The DCCT Research Group. Weight gain associated with intensive therapy in the diabetes control and complication trial. Diabetes Care 1988; 11: 567 – 573.

78.- Wauters M, Considine RV, van Gaal LF. Human leptin: from an adipocyte hormone to an endocrine mediator. Eur J endocrinol 2000; 143: 293 – 311.