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ORIGINAL ARTICLE

Undiagnosed thyroid dysfunction, thyroid antibodies, and iodine excretion in a Mediterranean population

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Abstract The prevalence of thyroid dysfunction varies in different populations. The aim of this cross-sectional study was to analyze the prevalence of undiagnosed thyroid dysfunction and thyroid antibodies and their relationship with urine iodine excretion in a representative sample of 1,124 (55.5% women; mean age: 44.8 ± 15.2 years) non-hospitalized Mediterranean adults, in Catalonia (Spain). Free thyroxine, thyroid-stimulating hormone, thyroperoxidase and thyroglobulin antibodies, and urine iodine were measured. Undiagnosed thyroid dysfunction was 5.3% (hypothyroidism 3.8%; 56.66% of these subjects were women). The total (diagnosed + undiagnosed) thyroid dysfunction was 8.9% (71.15% women). Thyroperoxidase antibodies were positive in 2.4% of men and 9.4% of women and thyroglobulin antibodies, in 1.3% of men and 3.8% of women. No differences were observed in urine iodine between groups with thyroid dysfunction and euthyroidism, or between subjects with positive or negative antibodies. In subjects over 60, undiagnosed thyroid dysfunction was 9.8% (hypothyroidism 6.9%, hyperthyroidism 3.3%; 36.36% women) and total thyroid dysfunction 13.61% (53.12% women). Women and men over 60 had similar thyroid dysfunction prevalence. Thus, aggressive case-finding should be recommended in both, over 60.

Keywords Undiagnosed thyroid dysfunction · Urine iodine excretion · Subclinical thyroid dysfunction · Thyroid autoimmunity

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Introduction

Golden et al. [1] in a comprehensive review on the epidemiology of all endocrine and metabolic disorders in the United States, supported by The Endocrine Society, emphasized the need for epidemiological population-based studies incorporating accurate hormone measurements determined in different geographic areas.

Thyroid dysfunction has major health implications, including increased risk of heart disease and hypercholesterolemia, although the significance of subclinical thyroid

diseases and indication for treatment continue to be debated [2–8]. The reported prevalence of abnormal thyroid function associated or not with thyroid antibodies varies in different studies. Among other factors, it should depend on the variable definitions of dysfunction states, the poorly defined and diverse populations studied including, in some cases, subjects with diagnosed and undiagnosed thyroid disease or those non-hospitalized or hospitalized, and the inaccurate measurement of thyroid function since sensitive thyroid-stimulating hormone (TSH) immunometric assays became available. In the USA, the prevalence of hypothyroidism was 4.6% in NHANES-III individuals (0.3% overt) [9], with differences in relation to ethnicities. The overall prevalence of hyperthyroidism was 1.3% (0.5% overt), also with inter-ethnicities differences. In the same study, serum thyroglobulin antibody concentrations were positive in 10% and serum thyroid peroxidase antibody concentrations were positive in 11%.

The epidemiology of hypothyroidism is better diagnosed than that of hyperthyroidism. Tunbridge et al. [10] found that 7.5% of women and 2.8% of men of all ages in Whickham, England, an iodine-sufficient area, had serum TSH concentrations above 6 mIU/l. The prevalence of subclinical hypothyroidism was approximately 5% of adults and overt hypothyroidism varied from 0.1 to 2%. Virtually all the studies report higher prevalence rates for hypothyroidism and thyroid antibody-positivity in women and the elderly [2–4, 8–15]. A high iodine intake could be associated with a higher prevalence of hypothyroidism, whereas a low iodine intake was associated with a higher prevalence of hyperthyroidism in some [16, 17], but not all [18], studies. It has also been suggested that both low and high iodine intake levels may correlate with a high tendency forwards thyroid autoimmune abnormalities [19–21].

All these data taken together illustrate the need for more information on thyroid dysfunction epidemiology in general and particularly specific data for each country or region of the world.

To our knowledge, this is the first study conducted to analyze the prevalence of undiagnosed thyroid dysfunction and thyroid antibody positivity in a representative sample of non-hospitalized Mediterranean adults and to study the possible relationship between this prevalence and urine iodine concentrations as a reflection of iodine intake.

Subjects and methods

The Health Survey of Catalonia (*Encuesta de Salud de Catalunya*, ESCA 2002) in 2001 studied a representative sample of the non-hospitalized adult population of Catalonia, the northeastern region of Spain [22]. The *random sort method* was used to select a representative sample population [23]. The Health Examination Study of Catalonia was conducted in a randomly selected subsample of the participants in the ESCA 2002. The data obtained were weighted to ensure the representativeness of the sex and age groups [22, 23].

The Health Survey of Catalonia (based on interviewer-directed questionnaires with 165 items) aimed to collect information on different markers of health status in the Catalonia population (total population 6,343,110 inhabitants). A total of 8,000 subjects aged from 18 to 74 participated in the ESCA 2002. Of these, 1,173 subjects participated in a second-phase study, the Health Examination Study of Catalonia, in which additional health information and blood samples were obtained by the research team of the Health Plan Evaluation for Catalonia [24]. In the Health Survey, a specific question on the current or previous existence of thyroid disorders was posed. Forty-four subjects aged from 26 to 74; mean: 49 $\pm$ 12, answered affirmatively (diagnosed thyroid dysfunction). Ten of these subjects (22.7%) were over the age of 60 and 40 (90%) were women. Five pregnant women were excluded.

Finally, this cross-sectional study was conducted in 1,124 non-hospitalized adults (500 men, 44.5% and 624 women, 55.5% aged from 18 to 74; mean age: 44.8 $\pm$ 15.2) participating in the Health Examination Study of Catalonia. Serum TSH and free T_4 (FT_4) concentrations, the presence of thyroid antibodies (thyroid peroxidase antibodies and thyroglobulin antibodies (TPOAb and TgAb, respectively) and urine iodine excretion were analyzed.

The Health Survey and Examination Studies were approved by the Ethics Committee of the Department of Health of the Autonomous Government of Catalonia. All the subjects who participated in the study gave their informed written consent.

Blood samples obtained in fasting conditions were immediately centrifuged, and serum was stored at $-70°C$ until assayed. Samples were assayed in batches in three consecutive days by commercially available kits to measure concentrations of FT_4 (Immulite® FT_4 Chemiluminescent Enzyme Immunoassay DPC, Los Angeles, CA,) and TSH (Immulite® Third Generation TSH Chemiluminescent Enzyme Immunoassay DPC, Los Angeles, CA). Reference ranges were: FT_4 0.8–1.9 ng/dl (10.29–24.4 pmol/l) and TSH 0.3–4 mIU/l. TPOAb and TgAb were assayed with an enzyme immunoassay (Orgentec Diagnostica, Mainz, Germany). Values above 75 and 150 IU/ml, respectively, were considered positive. A single urine iodine measurement was used to assess iodine status in this population (modified Benotti method). A urine iodine concentration >100 μg/l was considered indicative of iodine sufficiency.

Data were first tested for normal distribution using the Kolmogorov–Smirnov test to apply the adequate analysis. Data were expressed as the mean (SD) and/or median

(2.5 and 97.5 percentiles). Groups were compared by Student's t test or the ANOVA test. Qualitative clinical data were compared using the chi-square test. All the statistical analyses were made with the statistical software package SPSS, version 12.0 (SPSS, Chicago, IL). All the tests were two-tailed and a P value <0.05 was considered statistically significant.

Hypothyroidism was considered if TSH was >4 μIU/ml (subclinical, if FT_4 was normal; and clinical, if FT_4 <0.8 ng/dl) and hyperthyroidism if TSH was <0.3 μIU/ml (subclinical, if FT_4 was normal; and clinical, if FT_4 >1.9 ng/dl).

Results

The prevalence of undiagnosed thyroid dysfunction (evaluated as TSH <0.3 or >4 μIU/ml) was 5.3% ($n = 60$). Hypothyroidism was 3.8% ($n = 43$) and hyperthyroidism 1.5% ($n = 17$). Subclinical hypothyroidism (TSH >4 μIU/ml and normal FT_4) was found in 18 men and 22 women ($n = 40$; 3.5%) and clinical hypothyroidism (TSH >4 μIU/ml and FT_4 <0.8 ng/dl) in three women (0.2%). Overall, 56.66% of subjects with undiagnosed thyroid dysfunction were women and 43.33% men. These figures and their relationship with thyroid antibodies are shown in Table 1. Subjects with no thyroid alteration were younger than the hypothyroid group (44.48 ± 15.07 vs. 50.60 ± 16.08 years; $P = 0.008$). No differences were observed in age between the hyperthyroid and euthyroid groups or between hyperthyroid and hypothyroid groups.

Taking into account the number of subjects with diagnosed thyroid disease excluded from the present study ($n = 44$), and these results, the total prevalence (diagnosed + undiagnosed) of thyroid dysfunction was 8.9%, with 71.15% of these subjects being women and 28.84% men.

The prevalence of TPOAb- and TgAb-positive subjects was lower among men than women. TPOAb were positive in 2.4% of men ($n = 11$) and 9.4% of women ($n = 55$). TgAb were positive in 1.3% of men ($n = 6$) and 3.8% ($n = 22$) of women. The percentage of subjects with one or two positive antibodies was higher in the hypothyroid group than the other two (44.2% vs. 11.7%, in the hyperthyroid, and vs. 5.1%, in the euthyroid; $P = 0.013$ and $P < 0.0001$). The prevalence of thyroid antibodies in subjects with and without thyroid dysfunction is shown in Table 1.

Median serum TSH concentration (2.5–97.5 percentiles) was 1.43 μIU/ml (0.38–4.59) for the total population, with no significant trend towards a rise in TSH concentrations with increasing age in either sex. In the euthyroid group, differences were found in TSH concentrations between subjects with positive antibodies (TPOAb, TgAb, or both) and those without. Serum TSH concentrations (median, 2.5–97.5 percentiles) were higher in the presence of antibodies (1.82, 0.37–3.90 μIU/ml vs. 1.39, 0.47–3.26 μIU/ml; $P < 0.0001$).

Median urine iodine concentration (2.5–97.5 percentiles) for the total population was 150.0 μg/l (40.4–338.0). No differences in urine iodine concentrations were found between groups with thyroid dysfunction (hypo or hyper) and normal TSH concentrations ($P = 0.44$) or between positive and negative antibody groups ($P = 0.66$).

No differences were observed among the groups in the percentage of women on hormonal substitutive treatment (data not shown).

In subjects over 60 years of age ($n = 225$), the prevalence of undiagnosed thyroid dysfunction was 9.8%, higher than in the other groups (4.2%, $P = 0.001$). Hypothyroidism was 6.9%, vs. 3.1% ($P = 0.008$) and hyperthyroidism 3.3%, vs. 1.1% ($P = 0.022$). Fifteen subjects presented hypothyroidism: 14 of whom were subclinical (nine men and five women), and one woman overt hypothyroidism; seven presented hyperthyroidism, subclinical in six cases (four men and two women), and overt in one man. Overall, 36.36% of subjects over 60 with undiagnosed thyroid dysfunction were women and 63.63% men. These figures are shown in Table 2.

Table 1 Prevalence of undiagnosed thyroid dysfunction in 500 men and 624 women non-hospitalized participating in the Health Examination Study of Catalonia and its relationship with thyroid antibodies and prevalence of thyroid antibodies in euthyroid subjects

Thyroid function	Prevalence n (%)	Men/women (n/n)	TPOAb+ n (%)	TgAb+ n (%)	Both+ n (%)
Subclinical hypothyroidism	40 (3.5%)	18/22	15 (37.5%)	7 (17.5%)	5 (12.5%)
Overt hypothyroidism	3 (0.2%)	0/3	2 (66.7%)	0	0
Subclinical hyperthyroidism	15 (1.3%)	7/8	1 (6.7%)	0	0
Overt hyperthyroidism	2 (0.17%)	1/1	1 (50%)	1 (50%)	1 (50%)
Any dysfunction	60 (5.3%)	26 (43.33%)/34 (56.66%)	19 (31.7%)	8 (13%)	6 (10%)
Euthyroidism	1.064 (94.6%)	474 (44.54%)/590 (55.45%)	4.8%	2%	1.2%

TPOAb thyroperoxidase antibodies, *TgAb* thyroglobulin antibodies

Table 2 Prevalence of undiagnosed thyroid dysfunction in 225 non-hospitalized subjects over the age of 60 years participating in the Health Examination Study of Catalonia

Dysfunction	Prevalence *n* (%)	Men/women (*n*/*n*)
Subclinical hypothyroidism	14 (6.2%)	9/5
Overt hypothyroidism	1 (0.44%)	0/1
Subclinical hyperthyroidism	6 (2.66%)	4/2
Overt hyperthyroidism	1 (0.44%)	1/0
Any dysfunction	22 (9.8%)	14/8

If subjects with diagnosed thyroid disease and age over 60 years ($I = 10$) are considered, the total prevalence (diagnosed + undiagnosed) of thyroid dysfunction in this group was 13.61%, with 53.12% of these subjects being women and 46.87% men.

No differences in urine iodine concentration or in prevalences of thyroid antibody positivity were found between this group and younger age groups.

Discussion

Defining the epidemiology of thyroid dysfunction (particularly undiagnosed) in each geographic region will provide clues to risk factors and identify areas for the allocation of public health and research resources.

Herein, we report a prevalence of undiagnosed thyroid dysfunction of 5.3% in a representative sample of the non-hospitalized adult population of Catalonia (Spain). Hypothyroidism was 3.8% (3.5% subclinical) and hyperthyroidism 1.5% (1.3% subclinical). Overall, 56.66% of subjects with undiagnosed thyroid dysfunction were women and 43.33% men. Subjects without thyroid dysfunction were younger than the hypothyroid group. These data are similar to those reported by other authors [5, 9, 11–14, 19, 20]. The highest prevalence was of subclinical hypothyroidism (3.5%) and the least frequent, with very few cases, overt hypothyroidism (0.2%) and hyperthyroidism (0.17%), as previously published [10, 14, 25]. We confirm the higher prevalence of thyroid dysfunction in women and older subjects also found by others [2–4, 8–15].

If we take in account the 44 subjects that answered affirmatively the question about the existence of current or previous thyroid disorders, the total prevalence (diagnosed + undiagnosed) of thyroid dysfunction was 8.9%; 71.15% of these subjects were women and 28.84% men. Although, to correctly evaluate this data, we must consider that some of this individuals could be euthyroid with goiter of thyroid cancer.

Few studies have being conducted in Spain regarding the prevalence of thyroid dysfunction and were carried out in other geographic regions or with different methodological approaches. Díez et al. [26] described a prevalence of subclinical hypothyroidism around 1.02% in healthy ambulatory subjects aged from 60 to 84 years in an urban community in Madrid (Spain) and a prevalence of subclinical hyperthyroidism of 6.12%. In another study, conducted in Terrassa (Catalonia), also in older healthy ambulatory subjects, the prevalence of total hypothyroidism (overt, subclinical, and previously diagnosed) was 10.9% and that of thyroid dysfunction in general 13% [27]. These data differ from our general results, probably due to the different ages of the subjects studied and other environmental factors.

The prevalence of antibody positivity (thyroperoxidase and thyroglobulin) was lower in euthyroid subjects versus groups with thyroid dysfunction and also lower in men than women, as in other studies [9–11]. In any event, it is noteworthy that the prevalence of antibodies in non-euthyroid subjects was only around 32%.

The median serum TSH concentration (2.5–97.5 percentiles) was 1.43 μIU/ml (0.38–4.59) for our total population, with no significant trend towards a rise in TSH concentrations with increasing age in women or men. These results are similar to those obtained by O'Leary et al. [15] in Australia. In contrast, some authors showed that serum TSH distribution shifted progressively towards higher concentrations with age and suggested that, as a consequence, the prevalence of subclinical hypothyroidism could be significantly overestimated if no age-specific range is used [9, 13, 28] and others observed a decrease in serum TSH with age [29]. As reported [10, 15, 28], in the euthyroid group we found TSH concentrations to be higher in subjects with thyroid antibodies.

According to current recommendations from the World Health Organization (WHO), median urinary iodine concentrations of 100–199 μg/l in samples from adults indicate adequate iodine intake [30]. Our data indicate that our population is iodine-sufficient, meet WHO guidelines for iodine sufficiency, and are quite similar to the data from the NHANES III survey, with median urine iodine of 145 μg/l [9]. In our study, no relationship was found between urine iodine concentrations and serum TSH, as previously published [31], or between urine iodine and thyroid antibody positivity. Some authors reported that a high iodine intake could be associated with a higher prevalence of hypothyroidism, whereas a low iodine intake could be associated with a higher prevalence of hyperthyroidism [16, 17]. These data are not confirmed by others [18]. Low and high iodine intake has been associated with a high tendency to thyroid autoimmune abnormalities [19–21]. The lack of a relationship found in our study among TSH and urine iodine and thyroid antibodies suggest that iodine intake does not influence the development of thyroid dysfunction or thyroid autoimmunity, in this population. Anyway, accepting the possibility that iodine could induce the

thyroid autoimmune process should be considered that only a genetically predisposed population will present the disease [32].

Thyroid dysfunction, particularly subclinical hypothyroidism, is more frequent in women over 60 years of age. The data are less consistent in men. In those over 65, the prevalence rises and approaches that of women in some but not all, studies [9, 15, 26, 33]. Probably due to this, some current consensuses [3, 9] that recommend against population-based screening consider aggressive case-finding appropriate in women over 60, among others risk groups. Díez et al. [26], in a population aged over 60, found a 2.04% prevalence of hypothyroidism and 6.46% of hyperthyroidism, with a higher prevalence in men (7.78%) than in women (4.72%). In our study, the prevalence of undiagnosed thyroid dysfunction was 9.8% in subjects older than 60 years, higher than in the other age groups. Hypothyroidism was 6.9% and hyperthyroidism 3.3%. No differences in urine iodine concentration or prevalences of thyroid antibodies were found between this group and the others. Only 36.36% of subjects over 60 with undiagnosed thyroid dysfunction were women and 63.63% men. If subjects over 60 with diagnosed thyroid disease are also considered, the total prevalence (diagnosed + undiagnosed) of thyroid dysfunction in this group was 13.61%, similar to that reported by Sender Palacios et al. [27]. Women constituted 53.12% of these subjects and 46.87% were men. Therefore, in people older than 60, the prevalence of thyroid dysfunction is similar in women and men. These data should be taken into account when proposing new diagnoses recommendations. It is not unreasonable to believe that the present recommendations permit women to be diagnosed of thyroid dysfunction earlier than men.

The strength of this study lies in the representative nature of the sample of the non-hospitalized adult Catalan population.

In summary, we report new epidemiological data on undiagnosed thyroid dysfunction and thyroid autoimmunity in a representative sample of an iodine-sufficient non-hospitalized adult Mediterranean population from Catalonia, the northeastern region of Spain. We show that iodine intake does not influence the development of thyroid dysfunction or thyroid autoimmunity in this population. Our study indicates that the prevalence of thyroid dysfunction is increased in the population over 60 (women and men), and for this reason aggressive case-finding should be considered in both sexes.

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