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ORIGINAL ARTICLE

Subclinical hyperthyroidism in patients with type 2 diabetes

Juan J. Díez · Pedro Iglesias

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Abstract Both subclinical hyperthyroidism and type 2 diabetes (T2D) have been associated with an increase in cardiovascular disease risk and mortality. We aimed to assess the prevalence of newly diagnosed subclinical hyperthyroidism in a cohort of patients with T2D, and also to analyse the relationships between diabetes-related characteristics and the presence of subclinical hyperthyroidism. 933 diabetic patients without previous history of thyroid disease (45.4% females, mean age 66.3 years, median duration of diabetes 10 years) were evaluated. A sample of 911 non-diabetic subjects without known thyroid dysfunction was studied as control group. Serum concentrations of thyrotropin were measured in all subjects. Subclinical hyperthyroidism was present in 4.3% of female and 3.5% of male diabetic patients. Relative risk was significant only for the female gender (OR 3.69, 95% CI 1.56–8.71). In comparison with diabetic patients without thyroid hyperfunction, patients with subclinical hyperthyroidism were older, had longer duration of diabetes, showed lower fasting glucose levels, had greater proportion of goitre and diet therapy, and had lower proportion of treatment with oral agents. Logistic regression analysis showed that age and the presence of goitre were significantly related to subclinical hyperthyroidism in patients with T2D. The risk for subclinical hyperthyroidism is increased in women with T2D. Advanced age and the presence of goitre are significantly and independently related with the presence of subclinical hyperthyroidism in diabetic population.

J. J. Díez (✉) · P. Iglesias
Department of Endocrinology, Hospital Ramón y Cajal, Carretera de Colmenar Km 9, 28034 Madrid, Spain
e-mail: jdiez.hrc@salud.madrid.org

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Abbreviations

BMI	Body mass index
CI	Confidence interval
OR	Odds ratio
RAS	Renin-angiotensin system
T2D	Type 2 diabetes
TGAb	Thyroglobulin autoantibodies
TPOAb	Thyroid peroxidase autoantibodies

Introduction

Subclinical hyperthyroidism is characterized by subnormal serum thyroid stimulating hormone (TSH) concentration in association with normal serum free thyroxine (FT4) and free triiodothyronine (FT3) concentrations. The prevalence of endogenous subclinical hyperthyroidism, defined as TSH concentration under 0.40 mU/l, has been reported to be 4.4% in females and 1.8% in males from the general population [1]. This condition has been associated with an increase in the cardiovascular disease risk and even an increase in mortality rate in several populations [2–4].

Patients with type 2 diabetes (T2D) have not only an increased risk of cardiovascular disease but also a substantial increase in premature mortality rates from vascular disease and other conditions [5]. Recent retrospective [6, 7] and prospective [8–13] studies in different countries have demonstrated a striking high prevalence of thyroid dysfunction in patients with T2D, ranging from 5 to 13%, and it has been recently shown that thyroid hormones may be part of the pathogenetic mechanism to explain metabolic derangement

in the development of T2D [14]. Female sex, advanced age, thyroid autoantibodies and even genetic influences [15] have been advocated as risk factors for thyroid dysfunction in T2D patients. However, most studies have focused on subclinical hypothyroidism and very few studies have compared prevalences of thyroid dysfunction in diabetic patients and control subjects from the same population. Therefore, in our opinion it is not clear if diabetes is associated with an increased risk of subclinical hyperthyroidism.

On the other hand, some studies reported a relationship between subclinical hypothyroidism and diabetic microangiopathy [16] or dyslipidemia [17], but, to our knowledge, a link between diabetes-related characteristics, such as microangiopathy, macroangiopathy or modality of therapy, and subclinical hyperthyroidism has not been reported. With the intention to clarify these aspects we performed the present study with the aim of assessing the prevalence of newly diagnosed subclinical hyperthyroidism in a cohort of patients with T2D in comparison with a group of control subjects, and also to analyse the relationship between diabetes-related clinical and analytical parameters and the presence of subclinical hyperthyroidism.

Patients and methods

Study design

From 2004 to 2010, a total of 1,112 consecutive patients with T2D referred to our diabetic clinic were recruited for screening for thyroid dysfunction. We registered clinical and analytical diabetes-related information, as well as the presence of previously known thyroid dysfunction. All patients had been diagnosed with T2D according to American Diabetes Association criteria [18]. None of them had had a recent acute illness or an acute complication of a chronic disease. Patients taking amiodarone or any other drug known to affect thyroid function were excluded. Pregnant women were also excluded. The study protocol was approved by the local ethical committee, and all patients gave informed consent before blood sampling.

Serum concentrations of TSH were measured in all patients without previous thyroid dysfunction. When TSH values were lower than 0.40 mU/l serum concentrations of FT4 and FT3 were also quantified. Subclinical hyperthyroidism was defined by TSH levels under 0.40 mU/l with normal concentrations of FT4 and FT3. Overt hyperthyroidism was diagnosed when patients showed simultaneously low serum concentrations of TSH and high concentrations of FT4 or FT3. Thyroid autoimmune status was evaluated in patients with hyperthyroidism by means of the measurement of serum levels of thyroid peroxidase autoantibodies (TPOAb) and thyroglobulin autoantibodies (TGAb). Thyroid autoimmunity was considered negative when both autoantibodies were negative, and positive when any of them were positive.

Patients

From the group of 1,112 diabetic patients there were 179 patients who had previous history of thyroid dysfunction (136 hypothyroidism and 43 hyperthyroidism). Prevalence of newly diagnosed subclinical hyperthyroidism was evaluated in a group of 933 diabetic patients without previous history of thyroid dysfunction. There were 509 men (54.6%) and 424 women (45.4%) aged 22–91 years (mean ± SD 66.3 ± 12.2 years). Median duration of diabetes was 10 (5–16) years and the percentages of patients with diabetic microangiopathy, macroangiopathy, hypertension and hyperlipidemia were, respectively, 36.9, 26.4, 66.1 and 58.5%. Diet was used as the only therapy for diabetes in 146 patients (15.6%), 276 patients (29.6%) were treated with oral agents, and 511 (54.8%) with insulin (with or without oral antidiabetics). Mean fasting blood levels of glucose and hemoglobin A1c were, respectively, 9.26 ± 3.30 mg/dl and 7.80 ± 1.57%.

A group of 911 non-diabetic subjects (579 females, 63.6%, $P < 0.001$ vs. diabetic patients) who attended our clinic for overweight or nutritional counseling, and who do not have previous history of thyroid dysfunction was studied as control group. Control subjects were younger than diabetic patients (57.4 ± 16.1 years, $P < 0.001$) and showed a BMI value slightly higher that that found in diabetic patients (30.2 ± 6.0 vs. 29.6 ± 5.3 kg/m^2).

Hormone assay

Fasting samples of venous blood were obtained from an antecubital vein between 08:00 and 09:00 h for estimation of hormonal and analytical data. Serum TSH, FT4 and FT3 concentrations were determined by using commercially available immunochemiluminescent assay (Immulite, Diagnostic Products Corporation, Los Angeles, CA). For TSH assays, the sensitivity was 0.004 mU/l. The mean intra- and interassay coefficients of variation for theses assays were less than 10%. Until 2004, normal values (mean ± SD) for FT4 were 17.37 ± 3.60 pmol/l, and for FT3 were 4.61 ± 0.92 pmol/l. Since 2005, the normal values were 14.03 ± 2.57 pmol/l for FT4 and 4.80 ± 1.09 pmol/l for FT3 concentrations. Normal values for TSH were 0.4–5.0 mU/l. TPOAb and TGAb were measured using a chemiluminescent immunoassay system (Immulite Thyroid Autoantibody, Siemens Medical Solutions Diagnostic Ltd., Llanberis, Gwynedd, United Kingdom). Positivity for TPOAb and TGAb was considered when the titre of these autoantibodies was at least 100 U/ml, and at least 350 U/ml, respectively.

Statistical analysis

For quantitative variables, results are expressed as mean ± SD for normally distributed data, and as median (interquartile range) for non-parametric data. Adjustment to normal distribution was tested by the Kolmogorov test. Categorical variables are described as percentages (%). To estimate the relative risk of subclinical hyperthyroidism we used the Mantel–Haenszel test to estimate the value, 95% confidence interval, and significance of the odds ratios (OR) of subclinical hyperthyroidism in diabetic patients in relation to control subjects. For comparisons of means between two groups of subjects the Student *t* test was used for normally distributed data, and the Mann–Whitney test was employed for nonparametric data. For ratio comparisons the Chi-square test or Fisher exact test was used. Several models of logistic regression analysis were used to assess the presence of subclinical hyperthyroidism as a function of several quantitative and qualitative variables. Differences were considered significant when $P < 0.05$.

Results

Prevalence and risk of subclinical hyperthyroidism in diabetic patients

Subclinical hyperthyroidism was found in 22 female (4.3%) and 15 male (3.5%) diabetic patients. Overall prevalence was, therefore, 4.0% (Table 1). No case of overt hyperthyroidism was found. In comparison with control subjects, the relative risk (OR) for subclinical hyperthyroidism was 1.67 (0.98–2.85). This OR was significant in women [3.69 (1.56–8.71), $P = 0.001$], but not in men [0.78 (0.38–1.61)]. In the female gender, this OR remained significant after adjusting for age [2.98 (1.56–8.71), $P = 0.014$], and for age and BMI [3.29 (1.37–7.92), $P = 0.005$].

Median serum TSH concentrations in diabetic patients with hyperthyroidism was 0.19 (0.09–0.28) mU/l. This value did not differ than that found in control subjects with hyperthyroidism [0.24 (0.16–0.34) mU/l]. Nine diabetic patients (24.3%) and four control subjects (18.2%, N.S.) exhibited TSH concentrations under 0.1 mU/l. We found no statistical differences in TSH levels between hyperthyroid diabetic patients treated with [0.22 (0.07–0.31) mU/l] and without metformin [0.19 (0.11–0.28) mU/l].

Table 1 Prevalence of subclinical hyperthyroidism in diabetic patients and control subjects

	Diabetic patients		Control subjects			
	n	Prevalence	*n*	Prevalence	OR	95% CI
Female	22	4.3	7	1.2	3.69*	1.56–8.71
Male	15	3.5	15	4.5	0.78	0.38–1.61
Total	37	4.0	22	2.4	1.67	0.98–2.85

Prevalences are expressed in percentages

OR odds ratio, *CI* confidence interval

* $P = 0.001$

Subclinical hyperthyroidism and diabetes-related characteristics

In comparison with patients without hyperthyroidism, patients with subclinical hyperthyroidism were older, had longer duration of diabetes, had a higher percentage of goitre, a higher percentage of subjects treated with diet, and a lower percentage of subjects treated with oral antidiabetics. Furthermore, fasting glucose levels were lower in patients with subclinical hyperthyroidism (Table 2). We found no significant differences between diabetic patients with and without subclinical hyperthyroidism in the proportions of subjects with microangiopathy, macroangiopathy, hypertension, hyperlipidemia, and in the concentrations of haemoglobin A1c, cholesterol and triglyceride. The percentage of thyroid autoimmunity and the proportions of patients treated with insulin, metformin, renin-angiotensin system blockers, calcium antagonists and statins were similar between both groups of patients. The exclusion of subjects with elevated TSH ($n = 68$) in this analysis did not change any of the found significant associations, that is, comparison of subjects with subclinical hyperthyroidism ($n = 37$) vs. euthyroid subjects ($n = 828$) gave the same results.

According to these results we performed a logistic regression analysis including the above-mentioned six significant diabetes-related characteristics as co-variates. Results of this analysis showed that only age and goitre were significant variables in this analysis (model 1, Table 3). A second model including further adjustments for sex, microangiopathy, macroangiopathy, hypertension, hyperlipidemia, therapy with renin-angiotensin blockers, calcium antagonists, statins, hemoglobin A1c, and serum levels of cholesterol and triglyceride, also showed that the presence of subclinical hyperthyroidism was significantly related to the age of the patients and the presence of goitre (model 2, Table 3).

Discussion

Results of the present paper show that overall prevalence of subclinical hyperthyroidism in a sample of 933 patients with T2D was 4.0%, markedly higher than that found in a group of non-diabetic control subjects (2.4%) from the

Table 2 Main clinical and analytical characteristics of diabetic patients with and without subclinical hyperthyroidism

	Absence of hyperthyroidism		Presence of hyperthyroidism	
	n	Value	*n*	Value
Clinical data				
Sex (female)	896	487 (54.4)	37	22 (59.5)
Age (year)	896	66.1 ± 12.3	37	72.3 ± 8.0***
BMI (kg/m^2)	851	29.6 ± 5.3	34	30.2 ± 4.2
Diabetes duration (year)	854	10 (5–16)	25	14 (8–25)*
Goitre	868	51 (5.9)	29	9 (31.0)***
Microangiopathy	842	330 (39.2)	27	14 (51.9)
Macroangiopathy	861	235 (27.3)	27	11 (40.7)
Hypertension	878	597 (68.0)	32	20 (62.5)
Hyperlipidemia	877	530 (60.4)	32	16 (50.0)
Analytical data				
Glucose (mmol/l)	895	9.32 ± 3.33	37	8.00 ± 1.84***
Hemoglobin A1c (%)	852	7.81 ± 1.58	27	7.51 ± 1.39
Cholesterol (mmol/l)	894	5.15 ± 1.13	37	5.18 ± 0.95
Triglyceride (mmol/l)	893	1.31 (0.96–1.87)	37	1.38 (0.94–1.79)
Thyroid autoimmunity	629	41 (6.5)	32	2 (6.3)
Treatment				
Diet	896	131 (14.3)	37	15 (40.5)***
Oral agents	896	272 (30.4)	37	4 (10.8)**
Insulin	896	493 (55.0)	37	18 (48.6)
Metformin	896	277 (30.9)	37	6 (16.2)
RAS blockers	896	454 (50.7)	37	16 (43.2)
Calcium antagonists	896	144 (16.1)	37	8 (21.6)
Statins	896	316 (35.3)	37	12 (32.4)

Data are the mean ± SD for normally distributed data, the median (interquartile range) for nonparametric data, and the number (percentage) for qualitative variables. The total number of patients used to calculate the values of means, medians and percentages in each group is indicated by *n*

BMI body mass index, *RAS* renin-angiotensin system

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

same population of an urban area of Madrid. However, our results clearly show that the relative risk of subclinical hyperthyroidism in diabetic patients is significantly increased only in the female gender. Since the prevalence of hyperthyroidism in control subjects was higher in male than in females, and the contrary was found in our sample of diabetic patients, it may be speculated that hyperglycaemia or diabetes-related derangements may influence the innate differences in the function of the female and male immune systems or the genetic predisposition to thyroid disease. Diabetes might also have some influence on the environmental exposures in females and males, and on the possible role of epigenetic mechanisms.

In comparison with our previous studies, we found a prevalence of subclinical hyperthyroidism in diabetic population from Madrid higher that that found among diabetic patients from Segovia (1.6%) [19], and healthy subjects from Segovia (1.3%) [20]. We have not measured iodine excretion in our patients but it is possible that differences in iodine intake in both locations may account for these differences [21, 22]. Thyroid autoimmunity is also different between the two locations, being present in 6.1% of diabetic subjects in the present study in Madrid, in 15.7% of diabetic subjects from Segovia [19] and in 14.2% of the healthy population from Segovia [20].

We also found a prevalence of subclinical hyperthyroidism higher than that found by other authors in diabetic subjects [8, 9, 12]. Differences in dietary iodine intake, geographical location, ethnic characteristics, autoimmune status of the population, and methods to quantify TSH may account for diverse results in different surveys. More importantly, although in the recent literature it is assumed that the prevalence of thyroid dysfunction is increased in patients with T2D in relation to non-diabetic population, this fact has not been properly demonstrated in previous reports. We have found only 4 reports comparing prevalences of hyperthyroidism in diabetic and control subjects, and none of them have found significant differences [11, 13, 23, 24].

Akbar et al. [23] found no case of hyperthyroidism in 74 patients with T2D and 1 case in 100 controls. Ishay et al. [13] found that the prevalence of subclinical hyperthyroidism was 3.8% in a group of 335 women with T2D and 7% in a group of 113 non-diabetic women. The study of Radaideh et al. [11] showed a prevalence of newly diagnosed hyperthyroidism of 1.3% in 908 patients with T2D

Table 3 Results of two models of logistic regression to study the influence of several co-variates in the presence of subclinical hyperthyroidism in diabetic patients

	Model 1			Model 2		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (year)	**1.05**	**1.01–1.10**	**0.017**	**1.06**	**1.01–1.11**	**0.014**
Diabetes duration (year)	1.02	0.98–1.07	0.308	1.01	0.96–1.07	0.608
Goitre	**7.15**	**2.53–20.21**	**0.000**	**8.97**	**2.86–28.14**	**0.000**
Glucose (mmol/l)	0.99	0.99–1.00	0.300	0.99	0.99–1.00	0.241
Diet therapy	1.16	0.27–5.04	0.846	2.28	0.45–11.65	0.321
Oral agents	0.33	0.09–1.25	0.101	0.41	0.10–1.62	0.203
Gender (female)				1.24	0.47–3.29	0.667
Microangiopathy				1.59	0.54–4.68	0.396
Macroangiopathy				1.36	0.51–3.59	0.540
Hypertension				0.32	0.08–1.31	0.113
Hyperlipidemia				0.47	0.13–1.73	0.255
Haemoglobin A1c (%)				1.10	0.75–1.60	0.625
Cholesterol (mmol/l)				1.00	0.99–1.01	0.987
Triglyceride (mmol/l)				0.99	0.99–1.01	0.658
RAS blockers				1.91	0.56–6.50	0.299
Calcium antagonists				1.98	0.70–5.63	0.198
Statins				2.06	0.54–7.80	0.287

OR odds ratio, *CI* confidence interval, *RAS* renin-angiotensin system

Values statistically significant ($P < 0.05$) are highlighted in bold

and of 0.6% in a group of 304 control subjects. In a population-based study, Gopinath et al. [24] found that the 5-year incidence of subclinical hyperthyroidism was 3.5% in a group of 113 patients with T2D and 1.8% in a group of 950 control subjects, being these differences non statistically significant. These authors did not perform sex-pooled analysis due to insufficient numbers in the gender subgroups. In comparison with these studies, our survey includes a larger number of diabetic patients and shows a significant increase in the risk of hyperthyroidism in the female gender.

In our sample of diabetic patients, subclinical hyperthyroidism was significantly related with advanced age and the presence of goitre. This is in agreement with studies in general population [1], and with some studies in diabetic patients that reported an increase in the frequency of thyroid dysfunction with increasing age [12]. However, the risk of subclinical hyperthyroidism does not seem to be increased in diabetic patients with microangiopathy or macroangiopathy, as well as in patients with hypertension or hyperlipidemia. We could not demonstrate significant relationships between hyperthyroidism and the duration of diabetes, BMI, haemoglobin A1c levels, lipid profile and the presence of thyroid autoantibodies.

Metformin has been associated with a significant reduction in serum TSH in diabetic patients with primary hypothyroidism [25]. However, in our diabetic patients with hyperthyroidism, TSH values were similar in subjects with and without metformin therapy, and we could not find any significant relationship between metformin therapy and the presence of subclinical thyroid hyperfunction. Although patients with subclinical hyperthyroidism exhibited a lower percentage of subjects treated by oral agents, and a higher proportion of subjects treated with diet only, logistic regression analysis did not show any significant relationship between subclinical hyperthyroidism and any kind of antidiabetic, antihypertensive or antihyperlipidemic treatment.

Our study has limitations. Patients with insulin therapy are overrepresented in our survey, because it is a hospital-based sample of diabetic patients. We, therefore, acknowledge that our sample is not representative of the diabetic population receiving care in the community. Control and T2D groups differ in gender and age, however we performed an analysis of OR by sex and with adjustments for age and BMI. Another limitation of our study is the absence of a second TSH measurement to confirm hyperthyroidism, since low TSH states are frequently transient. We also acknowledge that TSH measurement is not appropriate to detect hyperthyroidism of pituitary origin, although this condition is very uncommon.

Detection of hyperthyroidism in diabetic patients seems to have clinical implications. On one hand, excess thyroid hormones promote hyperglycemia by facilitating glucose

intestinal absorption, increasing insulin clearance, and enhancing hepatic glucose output [26]. On the other hand, subclinical hyperthyroidism, especially with TSH values under 0.10 mU/l has been associated with adverse cardiac end points, including atrial fibrillation [27] and cardiac dysfunction [28]. Recent surveys have also reported a significant association between low serum TSH concentrations and all-cause [2, 4, 29, 30] and cardiovascular mortality [2–4].

There is little consensus on the screening strategies for thyroid dysfunction in routine diabetes care. Although our data suggest an increased risk of subclinical hyperthyroidism in aged women with T2D that would warrant the implementation of screening programs for this condition, we have to acknowledge that the occurrence of subclinical hyperthyroidism is notably lower than that of subclinical hypothyroidism both in general population and in patients with T2D.

In summary, to the best or our knowledge this is the first survey showing that the risk of subclinical hyperthyroidism in women with T2D is significantly increased in comparison with control subjects. Age and goitre in physical examination seems to be factors related with the presence of subclinical hyperthyroidism in diabetic population. Our results suggest that screening programs for subclinical hyperthyroidism in elderly diabetic women might be warranted. Subclinical hyperthyroidism might be seriously considered as an additional risk factor in diabetic patients who are at higher risk of cardiovascular disease.

Conflict of interest The authors declare that they have no conflict of interest in relation to this article.

Ethical standards The experiments comply with the current laws of the country in which they were performed.

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