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Thyroid volume in type 1 diabetes patients without overt thyroid disease

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Abstract. An association between insulin-dependent diabetes mellitus (type 1) and thyroid diseases has long been reported, but the morphological evaluation of the thyroid in type 1 diabetes patients without overt thyroid disease has always been limited to physical examination. Ultrasonography of the thyroid gland was performed in 45 patients with type 1 diabetes without overt thyroid disease, to study thyroid volume and the prevalence of thyroid nodules. Data were compared with those obtained in 45 age- and sex-matched control subjects residing in the same area. In the patients, thyroid volume had increased on average by 46%; 35% of male and 32% of female patients had a thyroid volume exceeding the 95% confidence limits of the matched controls. The prevalence of thyroid nodules was only slightly raised. On average, free thyroxine was increased in the presence of normal triiodothyronine levels. Four patients were frankly hyperthyroid. The patients also showed a higher prevalence of thyroid-microsomal antibodies, but the thyroid hormone status was not different in relation to thyroid volume, nor was thyroid volume in relation to the presence of autoantibodies. Patients with type 1 diabetes without overt thyroid disorders may have morphological, ultrasonographically detectable alterations of the thyroid gland, the expression of a possible involvement of the thyroid in an autoimmune disorder not limited to the islet cells.

Key words: Thyroid disease – Insulin-dependent diabetes mellitus

Introduction

The association between insulin-dependent diabetes mellitus (type 1) and thyroid dysfunction has long been reported [1, 2]. Overt [3] or subclinical [4] hypothyroidism of autoimmune origin frequently occurs in diabetic patients, as a late effect of thyroiditis, which may sometimes be detectable on the basis of clinical and laboratory evidence of hyperthyroidism [5], or may pass undiagnosed. Thyroid involvement may be associated with the presence of anti-thyroid antibodies [6], in particular ones against thyroid microsomal antigen (TMA), which suggests an autoimmune aetiology of thyroid disease [7].

Extensive epidemiological studies are available on the clinical and laboratory evaluation of the thyroid gland in type 1 diabetes patients with and without overt thyroid disease [2–4], but the morphological evaluation of the thyroid has always been limited to physical examination. Ultrasonography is a useful tool for a non-invasive, morphological study of the thyroid parenchyma [8]. It may be used in epidemiological studies to screen patients for nodular lesions, and the total volume of the gland may also be computed on the basis of the maximum diameters of the two lobes.

The aim of this study was to evaluate thyroid morphology by means of ultrasonography in a series of consecutive type 1 diabetes patients with no history or clinical signs of thyroid disorders. Thyroid function and the prevalence of anti-thyroid antibodies were also studied.

Materials and methods

Patients

We examined a group of 45 patients with insulin-dependent diabetes mellitus (20 male, 25 female; age 16–68 years, median 40 years), and with no history of previous thyroid disorders and/or use of drugs known to affect the thyroid homeostasis. These patients had been admitted to hospital for diabetic ketosis (n=9) or for evaluation and treatment of complications of their diabetic disease. Their glycosylated haemoglobin was on average 8.9% (SD 1.8%), ranging from 5.1% to 12.0%.

The patients were matched for sex and age (±5 years) with 45 control subjects (20 male, 25 female; age 18–64 years, median 43 years), residing in the same geographical area, who had been admitted to our department for functional disorders of the gastrointestinal tract or kidney stones, and who did not have diseases known to influence thyroid function or size.

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The study project was presented to and approved by the Senior Staff Committee of our department. All patients were informed about the aim of the research and gave their consent.

Methods

All subjects were studied by two independent examiners unaware of the clinical diagnosis, using a ALOKA SD-280 ultrasound equipment (Aloka Co, Tokyo, Japan) with a 5-MHz linear multi-array probe. A gel pad was interposed between the skin of the neck and the probe to improve the quality of the ultrasonographic image [9]. This allowed a careful evaluation of thyroid morphology and measurement of the three maximum diameters of each lobe [anteroposterior (AP), laterolateral (LL), and cranio-caudal (CC)]. The inter-observer variability of the ultrasonographic measurements was within 10%. Using the mean value of two determinations, we estimated the volume of each lobe with the formula [10]

$$\text{Volume} = AP \cdot LL \cdot CC \cdot (\pi/6)$$

and total thyroid volume as the sum of the two lobes (isthmus was not considered). The presence, number and dimensions of nodules were also registered, whereas no attempt was made to consider the echogenicity of the thyroid gland (hyper- or hypo-echoic pattern) in the absence of nodules, due to lowinter observer agreement in this evaluation.

In all cases, free thyroid hormones levels were determined by means of immunometric methods (fT_3 and fT_4; LISOPHASE, Sclavo, Siena, Italy); thyroid-stimulating hormone (TSH), anti-thyroid microsome and anti-thyroglobulin antibodies were determined by an IRMA method (Biodata-Serono, Guidonia, Rome, Italy).

The intra-assay coefficient of variation for all the determinations was lower than 5% and less than 10% for antibody determinations. The coefficient of variation among different sets of the same assay was below 10% for every determination.

Normal values in our laboratory are as follows: TSH, 0.4–3.5 mU/l; fT_3, 4.0–8.9 pmol/l; fT_4, 9.0–23.0 pmol/l. Titres >50 U/ml were considered positive for anti-microsome antibodies at radioimmunoassay, as well as titres >100 U/ml for anti-thyroglobulin antibodies.

Statistical analysis

Differences between diabetic patients and control subjects for thyroid volume and hormonal data were assayed for significance by means of Student's *t*-test for unpaired data while the prevalence of thyroid auto-antibodies was compared by means of Fisher's exact test.

In order to avoid a mass significance, we corrected the significance limit of the statistical tests in relation to the number of simultaneous comparisons. The limit was reduced, according to Duncan's multiple range [11], to 0.025 for echographic measurements and 0.01 for laboratory data.

Results

The mean AP diameter of the two lobes was significantly larger in diabetic patients (Table 1), and their mean total thyroid volume was larger by 46%. The thyroid gland was enlarged both in men and women. The upper 95% confidence limit of thyroid volume in the control population was 28.0 ml in men and 24.4 in women; 7 male (35%) and 8 female type 1 diabetes patients (32%) exceeded these limits. In general, the thyroid was diffusely enlarged, and the prevalence of thyroid nodules (16% in diabetes) did not differ in comparison to controls (13%).

Table 1. Anteroposterior diameter of the thyroid and mean volume of the gland in normal subjects and in patients with type 1 diabetes mellitus. Data are reported as mean (SD)

	Anteroposterior diameter		Thyroid volum
	Right (mm)	Left (mm)	(ml)
All cases			
Controls (n=45)	17.7 (2.7)	18.0 (2.5)	16.3 (5.1)
Diabetes (n=45)	20.2 (3.9)*	20.2 (3.6)*	23.8 (8.8)*
Men			
Controls (n=20)	18.3 (2.2)	18.8 (1.9)	17.8 (5.2)
Diabetes (n=20)	20.9 (3.5)*	20.7 (3.7)*	24.9 (8.0)*
Women			
Controls (n=25)	17.2 (3.1)	17.4 (2.7)	15.1 (4.7)
Diabetes (n=25)	19.7 (4.2)*	19.8 (3.5)*	22.9 (9.9)*

* Significantly different from control values (P<0.025)

Table 2. Thyroid hormone values in normal subjects and in type 1 diabetes patients (whole group). Data are reported as mean (SD)

	fT_3 (pmol/l)	fT_4 (pmol/l)	TSH (mU/l)
Control subjects	5.3 (1.6)	12.4 (2.9)	1.8 (1.0)
Diabetic patients			
Total	6.0 (3.1)	21.0 (9.2)*	1.4 (0.8)
Normal thyroid volume	6.3 (3.2)	21.6 (8.3)	1.3 (0.8)
Enlarged thyroid	5.2 (0.9)	20.0 (6.1)	1.4 (0.8)

* Significantly different from control values (P< 0.01)

Patients had fT_4 levels higher than normal (Table 2), and their fT_3/fT_4 ratio was considerably reduced [diabetes, 0.30 (SD 0.11); controls, 0.44 (0.10); P< 0.01]. TSH concentrations did not differ. Thyroid hormone levels were not different in relation to thyroid volume. Among the 45 patients, 4 had higher than normal hormone values and TSH levels below the detection limit. Two of these patients were positive for anti-microsome antibodies and had a dishomogeneous thyroid parenchyma on ultrasound examination and the final diagnosis was Hashimoto's thyroiditis. A patient had an autonomous, hyperechoic, hyperfunctioning thyroid nodule (confirmed by scintiscan), and the remaining patient had asymptomatic Graves' disease. In no patient was there laboratory evidence of hypothyroidism.

Excluding patients with definite thyroid disease, the mean fT_4 level in the diabetic patients was elevated [19.4 (6.7) pmol/l], and the fT_3/fT_4 ratio was reduced [0.28 (0.08)]. There were no differences in mean TSH levels among the groups.

Patients had a higher prevalence of anti microsome and anti-thyroglobulin antibodies (Table 3). Mean thyroid volume was 14% larger in the 15 antibody-positive diabetic patients [25.8 (10.0) ml (range: 9.4–39.7) vs. 22.7 (8.1) (range: 7.2–41.5) in patients without anti-thyroid antibodies], but the difference was not statistically significant.

Table 3. Prevalence of anti-thyroid antibodies in normal subjects and in patients with insulin-dependent diabetes mellitus. The 95% confidence interval is reported in parentheses

	Antimicrosome	Antithyroglobulin
Control subjects (n=45)	0% (0–8)	2% (0–12)
Diabetic patients (n=45)	33% (20–49)*	16% (6–29)*

* Fisher's exact test (R×C) between control subjects and diabetic patients

No correlation was found between thyroid volume and/or thyroid hormone levels and short- or long-term metabolic control, as measured by urinary glucose and glycosylated haemoglobin.

Discussion

This work demonstrates that type 1 diabetic patients have an enlarged thyroid gland even in the absence of overt thyroid disease, and the prevalence of an enlarged thyroid is higher than 30% in the present series. The data confirm a previous study in children with type 1 diabetes, where a 20% prevalence of clinically detected goitre was reported in 371 subjects admitted to a diabetes unit [2].

There are, however, differences between thyroid enlargement detected with ultrasound and physical examination, and the sensitivity of the two techniques has never been compared. We set the upper limit of thyroid volume, in both men and women, on the basis of the 95% confidence interval calculated in a matched control population residing in the same area and with the same iodine intake. The mean volumes of our control population (17.8 in men and 15.1 in women) are similar to those reported by Hegedüs et al. [8] in a large screening in the Copenhagen area, and confirm the sex-dependence of thyroid volume. Both in male and in female diabetic patients the mean thyroid volume was increased, and the prevalence of thyroid enlargement was not gender-related.

An age-dependence of thyroid volume has also been reported [8]. We did not test the effects of age systematically, due to the limited amount of data available. In any case, the control population was age-matched (±5 years), and the small difference in mean age can hardly be blamed for the high prevalence of thyroid enlargements, as well as for the increased prevalence of thyroid abnormalities, which are also known to increase with age [12, 13].

The enlarged thyroid was not accompanied by laboratory-detectable thyroid abnormalities in the vast majority of subjects. Our patients had no clinical manifestations of thyroid disorder and were grossly euthyroid. Mean values of fT_3 and fT_4 were within normal limits, and the differences in comparison with the control population were only found on a statistical basis. This reflects the selection criteria, since patients with a history and/or overt thyroid disease were excluded. Only four patients had higher than normal hormone values and were frankly hyperthyroid on a laboratory basis. Despite normal total hormone levels (not reported in detail), the mean fT_4 was increased and the fT_3/fT_4 ratio reduced, as an expression of reduced conversion of thyroxine into triiodothyronine due to the 'catabolic' state of decompensated diabetes, an 'euthyroid sick syndrome' [14], which agrees with several previous reports [15–18]. However, the lack of correlation between thyroid volume and/or function and metabolic control suggests that the extent of metabolic imbalance is not the sole determinant of thyroid alterations.

The enlarged thyroid volume of diabetic patients was accompanied by an increased prevalence of anti-thyroid antibodies, which was of the same order of magnitude as reported in other studies of type 1 diabetic patients, in which only functional and immunological investigations were performed [7, 19].

The pathogenic significance of anti-thyroid antibodies has been debated [20–23]. Anti-microsome antibodies are a possible marker of chronic damage to thyroid follicular cells mediated by an auto-immune mechanism. Their presence, in the absence of clinical signs, can be related to a 'symptomless' chronic thyroiditis. Recently, a chronic thyroiditis was documented by means of thyroid ultrasonography and fine needle biopsy in the absence of thyroid auto-antibodies. However, the presence of thyroid antibodies does not completely explain thyroid enlargement, and in patients with anti-thyroid antibodies the thyroid volume was not significantly larger than in patients with a normal thyroid. An 'in situ' production of auto-antibodies against thyroid follicular cells has been demonstrated in thyroid diseases [24, 25], in the absence of circulating auto-antibodies. This might explain thyroid enlargement and dysfunction in type 1 diabetic patients, reflecting thyroid disease even in the absence of anti-thyroid antibodies.

In conclusion, a remarkable proportion of patients with IDDM has ultrosonographically detectable alterations in thyroid volume, without any clinical evidence of thyroid disease. These abnormalities are likely to be multifactorial, but in part expression of thyroid involvement in a silent autoimmune process [23], which might progress towards autoimmune thyroiditis, and finally clinically detectable hypothyroidism. These patients should undergo a regular clinical, laboratory and ultrasonographic follow-up.

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Book review

The Foot in Diabetes, 2nd edn. Boulton A. J. M., Connor H., Cavanagh P. R. (eds). New York Chichester: Wiley 1994, pp IX + 256

In their preface to the second edition of this book, the authors remind us that diabetic foot problems and amputation represent the most important of all long-term problems of diabetes medically, socially, and economically, and that the risk of developing foot ulceration, which can be regarded as the end-stage complication of neuropathy and vascular disease, is much greater than that of reaching the end-stage sequelae of retinopathy and nephropathy. For these reasons, the interest in diabetic foot, once the cinderella of diabetic complications, is steadily increasing.

In the line with its premises, this book is the most comprehensive and critical update of the several aspects of the diabetic foot. Epidemiology of the problem and its economic impact are the opening chapters, followed by a short historical background; then, pathophysiology of the diabetic foot is discussed in relation to established risk factors such neuropathy, ischemia and infection, and with other, usually neglected factors, such as the role of biomechanics. Several figures and diagrams are of help to the reader in order to reach a full comprehension of the text, which is well and clearly written. In the chapters dealing with the various opportunities of treatment, the authors emphasize the value of team work (diabetologist, chiropodist, radiologist, vascular surgeon, orthopedic surgeon) in the detection and management of all problems. Finally, there are two interesting sections dealing with the role of patient education in the prevention of foot problems, and the rehabilitation of the diabetic amputee.

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