

Thyroid function, morphology and autoimmunity in young patients with insulin-dependent diabetes mellitus

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Abstract

Objective: An association between insulin-dependent diabetes mellitus (IDDM) and autoimmune thyroid disease is well recognized. We have studied the prevalence of thyroid dysfunction, autoimmunity and morphological abnormalities by ultrasonography in young diabetics.

Subjects and methods: Among young IDDM patients less than 18 years old and living in the county of Funen, Denmark, 105 of 116 eligible patients participated. They were compared with 105 healthy children matched for sex and age. Routine thyroid function parameters (thyroxine (T₄), tri-iodothyronine (T₃), T₃ resin uptake and TSH) and thyroid autoantibodies (anti-thyroid peroxidase, TPOab, and thyroglobulin antibodies, Tgab) were measured. Thyroid size and morphology were determined by ultrasonography.

Results: Two of the diabetics had previously diagnosed hypothyroidism and three new cases of subclinical hypothyroidism were found. There were no significant differences in thyroid function variables or thyroid volume between diabetics and controls. Thyroid volume correlated significantly with age and weight in both groups. Among diabetics, 17 had thyroid autoantibodies (13 with TPOab, 14 with Tgab and 10 with both) compared with 2 children in the control group ($P < 0.001$). Forty-four with IDDM as opposed to 11 of the controls ($P < 0.001$) had morphological abnormalities at ultrasonography. Most of them had various degrees of hypoechogenicity thought to be a marker of thyroid autoimmunity. Among the 17 diabetics with autoantibodies, 10 had morphological abnormalities at ultrasonography.

Conclusions: A high proportion of young IDDM patients without any clinical signs of thyroid disease have markers of thyroid autoimmunity. Many have thyroid autoantibodies, but even more have abnormalities by thyroid ultrasonography.

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Introduction

The association between insulin-dependent diabetes mellitus (IDDM) and autoimmune thyroid disease has long been recognized (1). In several studies of both children and adults with IDDM a high prevalence of thyroid autoantibodies (Tab) (8–44%) has been found as an indicator of thyroid autoimmune disease (1–7). Most of those antibody-positive diabetics were clinically and biochemically euthyroid. How many of them will later develop thyroid dysfunction is uncertain. The Tab detected in previous studies have primarily been against thyroglobulin (Tgab) and microsomal antigens (Micab). It is now possible to measure the more sensitive and antigen-specific anti-thyroid peroxidase antibodies (TPOab) (8, 9). However, Tab in serum do not always appear in autoimmune thyroid diseases (10). There is a need for alternative ways to confirm the diagnosis of autoimmune thyroid disease. During the last decade thyroid ultrasonography (US) has been increasingly

accepted as an easy, inexpensive and non-invasive method for the investigation of thyroid volume (11–13), morphology and echogenicity (14–17). However, in childhood diabetes little is known of thyroid morphology determined by US (5, 18).

In the present study we determined the prevalence of thyroid dysfunction, Tab and thyroid US abnormalities in an epidemiologically well-defined group of young diabetics compared with age- and sex-matched healthy controls. Furthermore, we wanted to evaluate the possible relationship between markers of thyroid autoimmune disease.

Material and methods

Subjects

All patients with IDDM, less than 18 years old by the first of March 1997 and living in the county of Funen

(470 000 inhabitants), Denmark, were invited to participate in the study. A total of 116 patients were identified and 105 (90.5%) accepted to participate. The patients, 50 girls and 55 boys, had a median age of 12.8 years (range 2.3–18.2) and a median duration of diabetes of 4.8 years (range 0.2–13.3). Two patients, a 17-year-old boy and a 16-year-old girl, were treated with levothyroxine due to previously diagnosed autoimmune thyroiditis and hypothyroidism. Three were treated with budesonide inhalation ($\leq 800 \mu\text{g}/\text{day}$) because of asthma, two were treated with anti-epileptics (lamotrigin), one received angiotensin converting enzyme inhibitor due to microalbuminuria, and two girls were on oral contraceptives.

The control group comprised 105 healthy children and adolescents (50 girls, 55 boys) primarily relatives of the hospital staff. They were also living in the county of Funen and were matched to the diabetic children according to sex and age with a median age of 12.9 years (range 1.3–18.3). None of the controls was studied in the state of acute or recent illness. None was receiving any medication influencing thyroid function or size apart from two girls having oral contraceptives.

All diabetics and controls underwent a physical examination and a US of the thyroid gland with determination of thyroid volume and morphology. Venous blood samples were taken for determination of thyroid function variables, TPOab, Tgab and glycosylated haemoglobin (HbA_{1c}). HbA_{1c} was analysed on venous blood, otherwise serum was frozen at -20°C until analysis.

All patients, controls and their parents gave informed consent, and the study was approved by the local ethical committee (case number 96/250). The study was performed in accordance with the Helsinki Declaration.

Thyroid US

The thyroid volume was calculated on the basis of a US scanning procedure using a 5.5 MHz compound scanner (Type 1846, Brüel & Kjær, Naerum, Denmark) as described previously (11). Two of the authors (FNB and LH) performed all the US investigations without knowledge of to which group the subjects belonged (IDDM or control). Intraobserver variation using this accurate cross-sectional method, i.e. coefficient of variation on double determinations, has been assessed previously (19) and was 6.6% (FNB) and 5.1% (LH), and the interobserver variation was 5.0%. The echo pattern was investigated with a real-time 7 MHz linear array transducer (Type 8534, Brüel & Kjær), dynamically focused with a focus extension of 5–50 mm (axial resolution 0.4 mm). The gain was adjusted to produce an echo-free appearance of the lumen of the internal jugular veins, carotid arteries and neck-strap muscles. In this setting a normal thyroid gland has a medium grey-scale homogeneous echo pattern and the level of echogenicity is higher than that of the surrounding

muscles. The different morphological patterns found by US were divided into five groups (Morphology Group (MG) 0–4): MG 0: normal thyroid gland, MG 1: mild to moderate diffuse hypoechogenicity, MG 2: marked, diffuse hypoechogenicity, MG 3: non-homogeneous hypoechogenicity and MG 4: uni- or multinodularity (nodules ≥ 1 cm).

Biochemical measurements

Serum thyroxine (T_4) (normal range 65–135 nmol/l) was determined by RIA (Diagnostic Products Corp., Los Angeles, CA, USA) and serum tri-iodothyronine (T_3) (normal range 1.00–2.10 nmol/l) analysed by RIA (Johnson & Johnson, Clinical Diagnostics Ltd, Amersham, Bucks, UK). Free T_4 index (FT_4I) (normal range 58–137 arbitrary units/l) and free T_3 index (FT_3I) (normal range 0.95–2.20 arbitrary units/l) were calculated by multiplying the T_4 and T_3 levels respectively with the T_3 uptake test. Serum thyrotrophin (TSH) (normal range 0.30–4.0 mU/l) was determined by DELFIA (Wallac OY, Turku, Finland). Serum TPOab (normal range <60 U/ml) and serum Tgab (normal range <60 U/ml) were determined by RIA (Brahms Diagnostica GmbH, Berlin, Germany). HbA_{1c} (normal range 4.3–6.3%) was determined by ion-exchange chromatography.

Statistical analysis

The results are presented as medians and ranges, and comparisons between groups were analysed by Mann–Whitney's unpaired rank sum test. The relationship between thyroid volume (which had an approximately normal distribution) and other variables was studied by univariate linear regression analysis followed by multiple linear regression analysis of the significant predictors. Comparisons of frequencies of Tab and US abnormalities in diabetics and controls were performed by a chi-squared test. *P* values less than 0.05 were considered significant.

Results

Clinical characteristics and biochemical measurements

No significant differences between the groups in age, height, weight and body mass index (BMI) were found (Table 1). Only one patient in the study population, a 17-year-old diabetic girl, had a small goitre. Three diabetic girls aged 7, 13 and 16 years were subclinically hypothyroid, i.e. had slightly elevated TSH (4.52, 6.18 and 4.71 mU/l respectively), but normal FT_4I . All other diabetics and controls were clinically and chemically euthyroid. No significant differences between diabetics and controls could be demonstrated in serum thyroid hormones and TSH values (Table 1). Among the

Table 1 Clinical characteristics, biochemical measurements and thyroid volume in diabetics and controls. Results are presented as median (range).

| | Diabetics (n = 105) | Controls (n = 105) | Mann-Whitney P value |
|---------------------------------------|------------------------|-----------------------|----------------------|
| Age (years) | 12.8 (2.3–18.2) | 12.9 (1.3–18.3) | 0.974 |
| Height (cm) | 155 (85–193) | 156 (76–194) | 0.514 |
| Weight (kg) | 47 (11–86) | 47 (10–83) | 0.648 |
| BMI (kg/m ²) | 19.2 (14.5–29.8) | 18.5 (14.0–25.6) | 0.063 |
| Duration of IDDM (years) | 4.8 (0.2–13.3) | – | – |
| Insulin (IU/kg per day) | 0.9 (0.2–1.8) | – | – |
| HbA _{1c} (%) | 8.0 (5.6–15.1) | 5.1 (4.4–5.6)* | <0.001 |
| TSH (U/l) | 1.51 (0.59–6.18) | 1.48 (0.47–3.46) | 0.353 |
| T ₄ (nmol/l) | 94 (66–189) | 92 (54–140) | 0.467 |
| T ₃ (nmol/l) | 1.97 (0.96–3.14) | 2.00 (1.15–2.86) | 0.421 |
| FT ₄ I (arbitrary units/l) | 86 (61–130) | 86 (55–121) | 0.965 |
| FT ₃ I (arbitrary units/l) | 1.80 (0.96–2.77) | 1.83 (1.08–2.89) | 0.244 |
| Thyroid volume (ml) | 8.7 (1.5–23.2) | 8.6 (1.3–18.3) | 0.421 |

*n = 103.

diabetics, 17 patients (16.2%) had Tab (13 TPOab, 14 Tgab and 10 both), 11 girls and 6 boys ($P=0.123$). Clinical characteristics and the level of Tab are presented in Table 2. Only one of the two patients with previously known autoimmune thyroid disease had elevated Tab (case number 15). Of the three girls with elevated TSH only two had Tab, one of them in high concentrations (Table 2). The girl with goitre had no autoantibodies. There were no significant differences between diabetics with and without autoantibodies in age, duration of diabetes, HbA_{1c}, TSH or thyroid hormones. In the control group only two (1.9%) had Tab, significantly different from the diabetics ($P<0.001$).

Thyroid volume

US revealed a median thyroid volume of 8.7 ml (range 1.5–23.2) in the diabetic group compared with 8.6 ml (range 1.3–18.3) in the control group ($P=0.421$) (Table 1). Neither was there any difference in thyroid volume between diabetics and controls when comparing females ($P=0.376$) and males ($P=0.806$) separately. In both diabetics and controls thyroid volume correlated significantly with several variables (age, weight, height, duration of IDDM and serum T₃). However, following multiple regression analysis, thyroid volume was in both groups only significantly correlated with age and

Table 2 Clinical characteristics of children with elevated thyroid antibodies.

| Patients | Sex (F/M) | Age (years) | Duration of IDDM (years) | TPOab (IU/ml) | Tgab (IU/ml) | Thyroid volume (ml) | Morphology group (MG 0–4) | TSH (mU/l) |
|----------|--------------|----------------|--------------------------------|------------------|-----------------|---------------------------|---------------------------------|---------------|
| 1 | F | 2 | 1 | 385 | Negative | 2.3 | 1 | 3.00 |
| 2 | F | 4 | 3 | 89 | 77 | 2.9 | 0 | 3.27 |
| 3 | M | 4 | 2 | Negative | 67 | 3.4 | 0 | 1.43 |
| 4 | F | 7 | 6 | 194 | >2000 | 5.5 | 1 | 4.52 |
| 5 | M | 9 | 6 | 79 | Negative | 8.6 | 1 | 1.32 |
| 6 | F | 9 | 1 | Negative | 65 | 9.9 | 0 | 2.34 |
| 7 | F | 11 | 8 | Negative | 78 | 9.0 | 0 | 1.96 |
| 8 | F | 12 | 0.25 | 107 | 184 | 14.4 | 0 | 1.27 |
| 9 | M | 13 | 4 | 210 | 538 | 12.3 | 1 | 1.21 |
| 10 | F | 13 | 2 | Negative | 290 | 12.7 | 1 | 6.18 |
| 11 | M | 14 | 8 | 1845 | 102 | 10.0 | 1 | 1.70 |
| 12 | F | 14 | 10 | 807 | 64 | 13.0 | 3 | 1.04 |
| 13 | F | 16 | 9 | >3000 | 133 | 17.4 | 2 | 1.93 |
| 14 | M | 17 | 1 | 857 | 71 | 20.6 | 0 | 1.33 |
| 15* | M | 17 | 8 | >3000 | >2000 | 15.4 | 1 | 3.72 |
| 16 | F | 17 | 2 | 329 | Negative | 10.4 | 1 | 1.34 |
| 17 | F | 17 | 7 | 677 | 152 | 21.1 | 0 | 0.83 |
| 18** | F | 11 | – | 79 | 63 | 11.9 | 0 | 2.25 |
| 19** | M | 17 | – | 972 | 0 | 12.3 | 3 | 1.68 |

*Previously diagnosed autoimmune thyroid disease.

**Controls.

weight. The relationship between thyroid volume and age and weight is demonstrated in Fig. 1.

Thyroid morphology

The distribution of the different MGs in diabetics and controls is presented in Table 3. Morphological abnormalities (MG 1–4) were found in 42% of the diabetics compared with 11% in the control group ($P<0.001$). In the diabetic group 50% of the girls and 35% of the boys had some kind of morphological abnormality ($P=0.109$). In the control group, 8% of the girls and 13% of the boys ($P=0.430$) had such abnormalities. The two patients with previously diagnosed

autoimmune thyroiditis demonstrated non-homogeneous hypoechogenicity and moderate diffuse hypoechogenicity respectively. Of the three patients with subclinical hypothyroidism, those two with Tab also had moderate, diffuse hypoechogenicity, while the third had a normal US. In the girl with goitre, US demonstrated multinodularity; her mother also had a non-toxic multinodular goitre. The most frequent morphological abnormalities in the diabetic patients were mild to moderate diffuse hypoechogenicity (23.8% of the patients) and non-homogeneous hypoechogenicity (12.4% of the patients). The abnormalities found in the control group comprised all the different morphological types. Table 3 also shows the distribution of age,

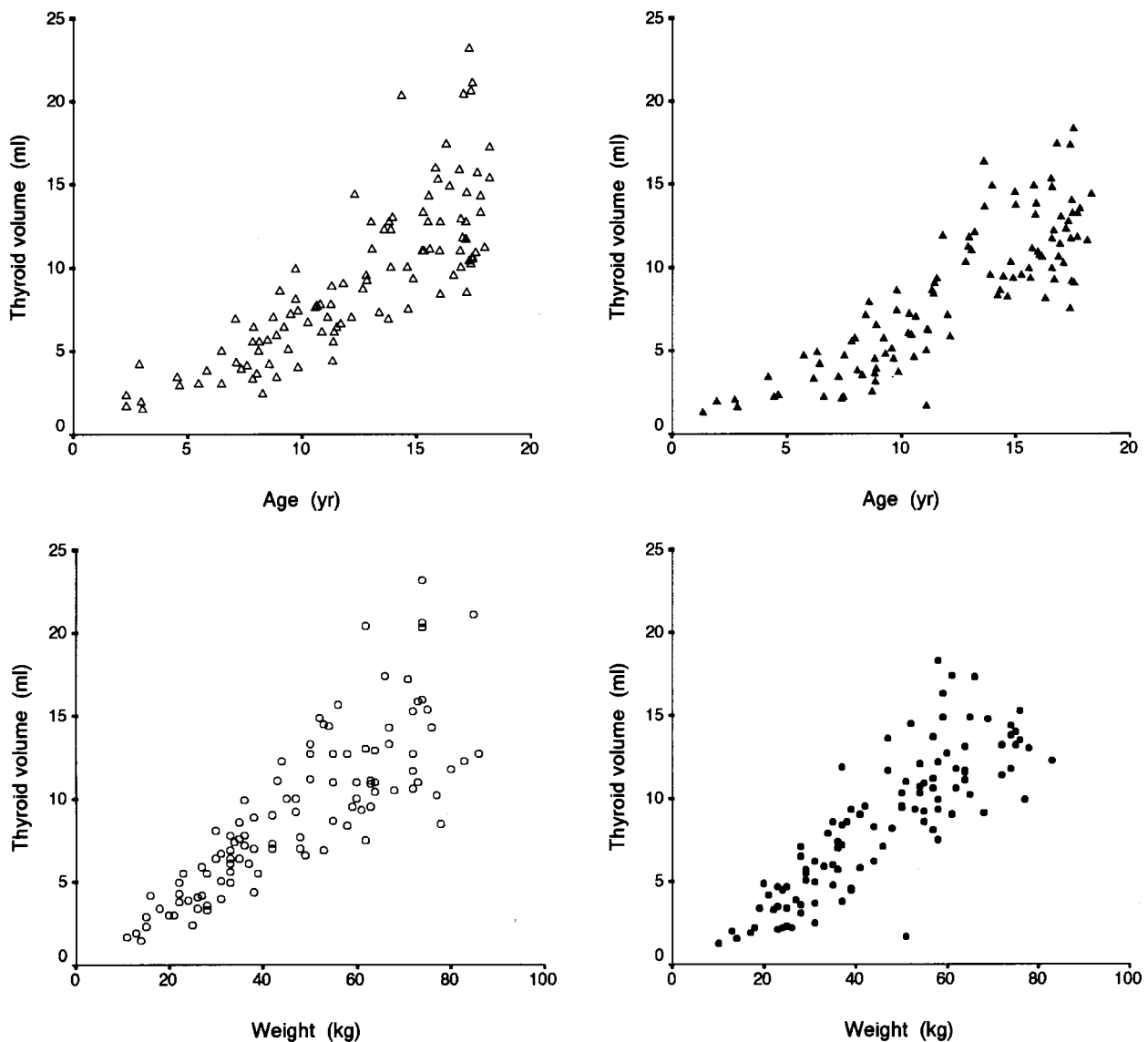


Figure 1 Thyroid volume related to age (upper panels) for (left) diabetics (Δ) and (right) controls (▲) and to weight (lower panels) for (left) diabetics (○) and (right) controls (●).

Table 3 The distribution of diabetics and controls in the different MGs and for the diabetics the relation to age, duration of diabetes, HbA_{1c}, TSH and thyroid volume (median and range).

| Morphology group* (MG 0–4) | Diabetics | | | | | | |
|----------------------------|------------------|-------------------|------------------|--------------------------|-----------------------|------------------|---------------------|
| | Controls (n (%)) | Diabetics (n (%)) | Age (years) | Duration of IDDM (years) | HbA _{1c} (%) | TSH (U/l) | Thyroid volume (ml) |
| 0 | 94 (89) | 61 (58) | 11.4 (2.3–18.0) | 3.9 (0.2–12.2) | 8.0 (5.6–11.5) | 1.41 (0.59–4.71) | 7.8 (1.7–21.1) |
| 1 | 4 (4) | 25 (24) | 9.5 (2.4–18.2) | 4.8 (0.4–8.7) | 7.6 (6.1–11.5) | 1.90 (0.62–6.18) | 6.6 (1.5–15.7) |
| 2 | 1 (1) | 4 (4) | 15.8 (12.7–16.9) | 10.5 (3.4–12.3) | 9.4 (7.2–15.1) | 1.84 (1.21–2.17) | 13.1 (8.7–17.4) |
| 3 | 3 (3) | 13 (12) | 16.0 (12.8–18.2) | 8.1 (1.0–13.3) | 9.3 (6.5–13.4) | 1.51 (0.86–3.19) | 12.7 (7.3–20.3) |
| 4 | 3 (3) | 2 (2) | 14.4 (11.5–17.3) | 6.9 (3.3–10.4) | 7.9 (6.7–9.00) | 0.85 (0.78–0.92) | 14.8 (6.4–23.2) |

* MG 0: normal thyroid gland; MG 1: mild to moderate diffuse hypoechogenicity; MG 2: marked, diffuse hypoechogenicity; MG 3: non-homogeneous hypoechogenicity; MG 4: uni- or multinodularity.

duration of diabetes, HbA_{1c}, TSH and thyroid volume in relation to the morphological findings in diabetics. When comparing diabetic patients with a normal US (MG 0) with those having mild to moderate diffuse hypoechogenicity (MG 1) no significant differences in age, duration of diabetes, HbA_{1c} or thyroid volume were found, but serum TSH was significantly higher in MG 1 ($P=0.006$). When comparing diabetics in MG 0 with those with non-homogeneous hypoechogenicity (MG 3) there was a significantly higher age ($P=0.012$), duration of diabetes ($P=0.003$), HbA_{1c} ($P=0.001$) and thyroid volume ($P=0.002$) in MG 3, while serum TSH was almost the same in the two groups. Because of the low number of children in MG 1–4 similar comparisons between MGs were not made for the controls.

Of diabetics with any kind of US abnormality, 10 (23%) had Tab whereas 34 (77%) had no antibodies. Conversely, in diabetics without US abnormalities 7 (11%) had Tab and 54 (89%) had no antibodies, the concurrent occurrence of US abnormalities and Tab being non-significant ($P=0.123$).

Discussion

In this study thyroid dysfunction was present in five subjects (4.8%). Two patients were already receiving treatment for hypothyroidism and three patients were diagnosed for the first time with subclinical hypothyroidism, though with marginally elevated TSH. This prevalence of thyroid dysfunction is in agreement with previous studies of young diabetics (3, 5) but lower than that found in an extensive study of adult patients with IDDM demonstrating 13.4% to have clinical or subclinical thyroid dysfunction (20).

The study confirms that young diabetics have a higher prevalence of Tab (16%) than healthy controls (1.9%). Similar prevalences were found in several other studies in young (3, 5, 6) and in adult diabetics (1, 2). In contrast a recent study of newly diagnosed young diabetics showed a considerably higher prevalence with 44% having either Tgab or TPOab (7). Possible explanations for this difference could be ethnic variations,

difference in iodine intake, a more sensitive assay in the latter study or alternatively immunological abnormalities present at diagnosis of IDDM before the start of insulin treatment. In accordance with Lindberg *et al.* (7) we found antibody-positive patients in all age groups, which is in contrast to Lorini *et al.* (21), who only found Tab in children older than 10 years. In our antibody-positive patients the duration of diabetes varied between 0.25 and 10 years. Another study found a higher prevalence in patients with duration of diabetes more than 10 years, but also found an overall higher prevalence of 30% (22). Previous studies reported that Tab are more frequent among girls than boys (1, 21, 22), while we and others (3, 7) did not find such a difference.

It has been questioned whether Tgab provides further diagnostic information compared with the single use of TPOab (or Micab) in the diagnosis of autoimmune thyroid disease (1, 8, 23). In our study Tab were with equal frequency directed against Tg and TPO with 14 of 17 of antibody-positive patients having Tgab and 13 of 17 having TPOab. Additionally, 4 of 17 had only Tgab indicating that information is missed if only TPOab are measured.

It is difficult to compare our thyroid volume results with previous studies due to differences in age distribution and iodine intake. Our results seem in agreement with an extensive study of healthy children from 12 European countries (13) and with a smaller study of Turkish diabetic and control children (5). On the other hand, compared with studies of Italian and Swedish children, living in iodine-sufficient areas, our children had a considerably higher thyroid volume through the different age groups (24, 25). The fact that the Funen population is borderline iodine deficient (daily urinary iodine excretion 50–80 μg) (26) is the most likely explanation for this marked difference. Minor differences in thyroid volume could also be explained by differences in the method of determining thyroid volume. In the present study thyroid volume was measured by a cross-sectional method (inaccuracy 5–10%), in the others by a method with an inaccuracy

of 15–20%. Confirming previous studies we found thyroid volume primarily to be dependent on age and weight (5, 12, 13, 24, 25) and without relation to the level of thyroid hormones (5, 11, 27). In agreement with the study by Darendeliler *et al.* (5) we found no difference in thyroid volume between diabetics and controls. In contrast, a study of 45 adult IDDM patients with no history of thyroid disease showed a notably higher thyroid volume in diabetics than in age- and sex-matched controls (27). This higher thyroid volume could be an expression of an ongoing autoimmune process causing alterations in the thyroid gland in many of the diabetics.

In diabetics a high prevalence of morphological abnormalities by thyroid US was demonstrated. This finding is not supported by Darendeliler *et al.* demonstrating US abnormalities in only 2 of 83 young diabetics (5). We have no obvious explanations for this discrepancy. Our investigations were performed by two experienced examiners who were blinded according to whether the patients were diabetics or controls. The dominant US finding in our study was various degrees of hypoechogenicity. This US abnormality has previously been described in patients with autoimmune thyroid disease where the diagnosis was additionally confirmed by either fine-needle aspiration biopsy or the presence of Tab (14). However, our study showed no obvious relationship between the occurrence of US hypoechogenicity and Tab. The prevalence of US hypoechogenicity was considerably higher than the prevalence of Tab and seven patients had Tab without concomitant US abnormalities. However, there was a tendency towards patients having higher antibody concentrations also having morphological abnormalities, and conversely some patients with low antibody concentrations had a normal US (Table 2). Also the strikingly higher frequency of US hypoechogenicity in diabetics compared with controls (40% versus 8%), and a significantly higher TSH in MG 1 and 2 compared with MG 0 in diabetics, points at US hypoechogenicity being a marker of autoimmune thyroid disease.

To our knowledge there are no other studies, except for the one by Darendeliler *et al.* (5), which have evaluated the relationship between Tab and US in diabetics. Previous studies in non-diabetics with known or suspected thyroid disease are conflicting. In patients diagnosed with autoimmune thyroid disease (by Tab and/or fine-needle aspiration biopsy) prevalences of US abnormalities of 18–95% are reported (10, 15, 17). The US finding of hypoechogenicity is not specific for the diagnosis of autoimmune thyroid disease but is also seen, for example, in Graves' disease and subacute thyroiditis (10, 17). However, some studies have shown US hypoechogenicity to be a valuable prognostic marker in autoimmune thyroid disease predicting the development of hypothyroidism (10, 17).

Presently, we do not know the significance of our US results. One can speculate that US hypoechogenicity

might be an early sign of an autoimmune process in the thyroid gland and thus a prognostic marker of future autoimmune thyroiditis. Further investigations including a regular follow-up of the patients from this study are needed.

In conclusion, we demonstrated that a large proportion of diabetic children and adolescents with a relatively short duration of diabetes have markers of thyroid autoimmune disease. A few have thyroid dysfunction, many have Tab, but even more have abnormalities by thyroid US, the significance of this needing further investigation.

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