Thyroid Dysfunction in Patients With Type 1 Diabetes

A longitudinal study

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OBJECTIVE — Cross-sectional studies have reported that the risk of thyroid dysfunction in patients with type 1 diabetes is two- to threefold higher than in the general population. However, longitudinal studies to determine the natural history of thyroid dysfunction in patients with type 1 diabetes are lacking.

RESEARCH DESIGN AND METHODS — We analyzed the incidence of thyroid dysfunction over time in a cohort of 58 patients (26 men and 32 women) enrolled in the Diabetes Control and Complications Trial at the University of Tennessee Health Science Center in 1983 and prospectively followed for 18 years. Patients underwent measurement of thyroid function tests (thyroid-stimulating hormone [TSH], thyroxine, and triiodothyronine) every year and thyroid peroxidase (TPO) antibodies at 4-year intervals.

RESULTS — A total of 18 patients had hypothyroidism, and 1 patient experienced transient hyperthyroidism. Two subjects developed hypothyroidism 7 and 18 years before the development of diabetes and were excluded from the analysis. The mean age of diagnosis was 19 ± 2 years for type 1 diabetes and 29 ± 3 years for hypothyroidism. Hypothyroidism was more common in female (41%) than in male (19%) subjects and in patients with positive TPO antibodies. Patients who were TPO positive were 17.91 times as likely to develop hypothyroidism as patients who were TPO negative (95% CI 3.89–82.54). There were no differences in BMI, lipid profile, and HbA_{1c} between patients with and without thyroid dysfunction.

CONCLUSIONS — This longitudinal study confirms the association between autoimmune thyroid dysfunction and type 1 diabetes. Our results indicate that all subjects with type 1 diabetes should undergo annual screening by serum TSH measurement to detect asymptomatic thyroid dysfunction, particularly those with positive TPO antibodies.

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Thyroid disorders are highly prevalent in the general population (1). Cross-sectional studies have reported that 7.5% of women and 2.8% of men of all ages in Whickham, U.K., had abnormal serum thyroid-stimulating hormone (TSH) levels (2). Recently, the Colorado Thyroid Disease Prevalence Study reported that among 25,682 subjects attending a state-wide health fair, 11.7% of subjects had an abnormal serum TSH concentration (3). Primary hypothyroidism (TSH >5.1 mU/l) was detected in 9.5% and hyperthyroidism in 2.1% of subjects, most of whom were asymptomatic (3). The prevalence of thyroid dysfunction increases with advancing age and in subjects with thyroid antibodies (4–8). In the 20-year follow-up study of the Wickham survey cohort (2), the mean annual incidence of spontaneous hypothyroidism increased from 4 to 27% in women who had positive thyroid antibodies. Recently, the Third National Health and Nutrition Examination Survey (NHANES III), from a sample of 17,353 people aged ≥12 years representing the geographic and ethnic distribution of the U.S. population, reported a prevalence of hypothyroidism in 4.6% (0.3% clinical and 4.3% subclinical) and hyperthyroidism in 1.3% (0.5% clinical and 0.7% subclinical) (9).

Autoimmune thyroid disorders are the most prevalent immunological diseases in patients with type 1 diabetes (10–13). Cross-sectional studies have reported a prevalence of hypothyroidism in 12–24% of female and ~6% of male patients with type 1 diabetes, as well as in 3–6% of type 2 diabetic patients (11–14). Hyperthyroidism occurs in 1–2% of patients with diabetes (11,15). The prevalence of positive thyroid peroxidase (TPO) antibodies (previously referred to as thyroid antimicrosomal antibodies) has been reported in ~80% of patients with type 1 diabetes and elevated TSH levels and between 10 and 20% in those diabetic individuals having normal TSH levels (15–18). Most patients have subclinical disease, and the development of diabetes usually precedes the diagnosis of hypothyroidism (15). Due to the increased prevalence of thyroid dysfunction in subjects with type 1 diabetes, regular screening of TSH is recommended (10). However, long-term prospective trials to evaluate the incidence and natural history of thyroid disorders in patients with type 1 diabetes are lacking. Therefore, we evaluated the thyroid status and presence of TPO antibodies in 58 patients with type 1

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Abbreviations: DCCT, Diabetes Control and Complications Trial; NHANES III, Third National Health and Nutrition Examination Survey; T_3, triiodothyronine; T_4, thyroxine; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Clinical characteristics of patients with type 1 diabetes with and without hypothyroidism*

	With hypothyroidism	Without hypothyroidism
n	18	40
Sex (M/F)	5/13	21/19
BMI (kg/m^2)	24 ± 1	22 ± 0.3
TSH (mU/l)	8 ± 1	1.9 ± 0.2
TPO antibodies [*n* (%)]	13 (72)	5 (13)*
Age, diabetes onset (years)	18 ± 2	16 ± 1
Age, hypothyroidism (years)	29 ± 3	—
Time between onset of diabetes and hypothyroidism (years)	8 ± 4	—

Data are mean ± SE. *$P < 0.01$.

diabetes enrolled in the Diabetes Control and Complications Trial (DCCT) and followed them prospectively over the past 18 years.

RESEARCH DESIGN AND METHODS

— The DCCT was a multicenter, randomized, clinical trial designed to determine whether an intensive treatment regimen would affect the appearance or progression of microvascular complications in patients with type 1 diabetes (19). A total of 1,441 patients were recruited in 29 clinical centers and followed for 6.5 ± 1.6 years. The major criteria for eligibility included insulin dependence, as evidenced by deficient C-peptide secretion; an age range of 13–39 years; and the absence of hypertension, hypercholesterolemia, and severe diabetes complications or medical conditions. Detailed descriptions of the eligibility criteria and randomization procedures for subjects entering the DCCT have been described elsewhere (20). Subsequent to the completion of this landmark study, all patients were enrolled in the Epidemiology of Diabetes Interventions and Complications (EDIC) trial and continued to undergo yearly follow-up (21). At the University of Tennessee Health Science Center, Memphis, a total of 58 patients with type 1 diabetes were enrolled in the DCCT in 1983 and have been followed prospectively during the past 18 years. In addition to monitoring their glycemic control and diabetes complications, all patients had yearly thyroid function tests (TSH, thyroxine [T_4], and triiodothyronine [T_3]). The presence of TPO was determined at 4-year intervals in frozen serum (stored at −70°C) of 54 patients. The Institutional Review Board at the University of Tennessee Health Science Center, Memphis approved this study.

According to the result of thyroid function tests, patients were divided into four groups: *1*) normal, when total or free T_4 and TSH were in the normal range; *2*) hypothyroidism, when total T_4 was <60 nmol/l and TSH >5.0 mU/l; *3*) subclinical hypothyroidism, when total or free T_4 were within normal limits but TSH was >5.0 mU/l; and *4*) hyperthyroidism, when the serum TSH value was suppressed and <0.03 mU/l. To determine whether subjects with type 1 diabetes are at higher risk of developing thyroid dysfunction than the general population, the results were compared with the prevalence of thyroid dysfunction and presence of TPO antibodies that was recently reported in the NHANES III (9). This survey was designed to give national normative estimates of the health and nutritional status of the U.S. civilian noninstitutionalized population conducted from 1988 through 1994 using a stratified, multistage probability design. NHANES III measured serum TSH, total serum T_4, and TPO antibodies from a sample of 17,353 people aged ≥12 years that represented the geographic and ethnic population of the U.S. (9).

Assays. Quantitative levels of TPO antibodies were measured on the DPC Immulite analyzer (Diagnostic Product Corporation, Los Angeles), which uses a solid-phase, two-site sequential immunometric methodology. The TPO antibodies were previously referred to as antimicrosomal antibodies because the antibodies bind to the microsomal part of the thyroid cells. The sensitivities of the assays were 3 IU/ml for the TPO antibodies and 0.002 mU/ml for the third-generation TSH assay. Serum TSH, T_4, and T_3 concentrations were measured at the General Clinical Research Center clinical laboratories or Endocrinology Laboratories, University of Tennessee, Memphis. The normal ranges were <32 IU/ml for the TPO antibodies and 0.4–4.0 mU/ml for TSH. Serum total T_4 and T_3 assays were performed as recommended by the manufacturers and were within specifications. For quality control, three levels of controls were assayed with each run for each assay and all values.

Statistical analysis. StatView version 5.0 (SAS Institute, Cary, NC) was used to compare demographic and clinical characteristics of patients with hypothyroidism against those without. Continuous variables were compared by Student's *t* test and categorical variables by χ^2 tests of independence. Data are expressed as means ± SE.

The SAS System for Windows version 8.1 (SAS Institute) was used to conduct logistic regression and Cox proportional hazard analyses on a subset of 54 of the study's 58 patients who were identified as not having hypothyroidism at the onset of type 1 diabetes. Both analyses focused on estimating the occurrence of hypothyroidism as a function of age at onset of diabetes, sex, and the presence or absence of TPOs. In all instances, the criterion for statistical significance was established at 0.05 before testing.

RESULTS

— There were 58 patients enrolled in the DCCT study from our institution, 26 men and 32 women (Table 1). The mean age at diagnosis of diabetes was 19 ± 2 years (range 2–37). A total of 19 (33%) patients had a thyroid dysfunction. Eighteen patients, with a mean age at diagnosis of 29 ± 3 years (range 11–48), had primary hypothyroidism. Two subjects developed hypothyroidism 7 and 18 years before the development of diabetes and were excluded from statistical analysis. In the remaining subjects, the mean time between the diagnosis of diabetes and hypothyroidism was 13 ± 3 years (range 4–32). There were no differences in BMI, lipid profile, and HbA_{1c} at diagnosis or during follow-up between patients with and without hypothyroidism.

The presence of TPO antibodies was associated with an increased risk of hypo-

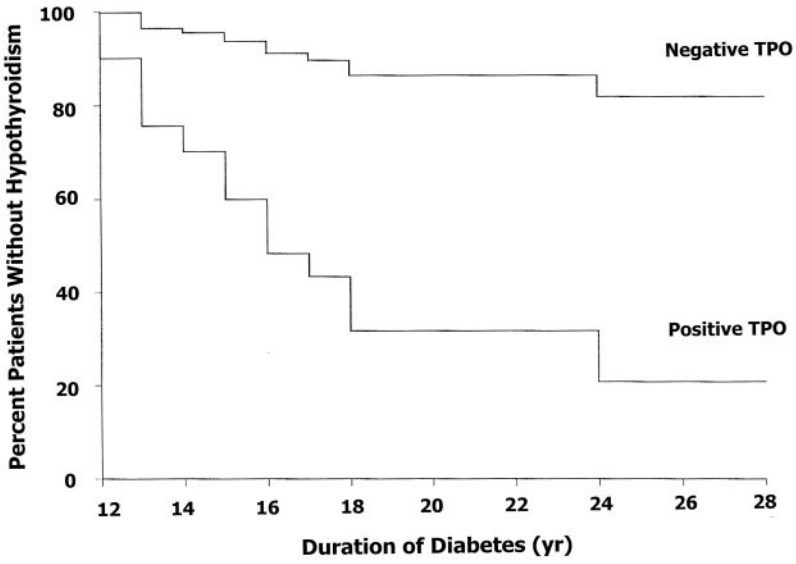

Figure 1—*Cox proportional hazard analysis for predicting development of hypothyroidism from age at onset, sex, and TPO status.*

thyroidism (Fig. 1). A total of 18 (33%) patients had positive TPO antibodies (8 men and 10 women). Hypothyroidism was most common in female subjects with positive (83%) as compared with negative (12%) TPO antibodies ($P < 0.001$). Similarly, the rate of hypothyroidism was higher in male subjects with positive (51%) than with negative (3%) TPO antibodies ($P < 0.001$). Most subjects with positive TPO antibodies (17 of 18) tested positive at the beginning of the study and remained positive throughout the study period. One patient with an initial negative TPO titer developed low-TPO titers after 12 years of follow-up. We observed no statistically significant differences in TSH values on diagnosis of hypothyroidism between patients with positive (8 ± 1 mU/l) and negative (9 ± 3 mU/l) antibodies.

The mean age for onset of hypothyroidism was 38 ± 4 years for TPO-negative subjects and 33 ± 3 years for TPO-positive subjects (P = NS), and the mean age for onset of diabetes was 17 ± 1 years for those TPO negative and 18 ± 2 years for those TPO positive (P = NS). The logistic regression of hypothyroidism (positive versus negative) on age at onset, sex, and TPO status (positive versus negative) was significant (likelihood ratio $\chi^2 = 17.33$, $P = 0.0005$). Although age at onset of diabetes ($P = 0.68$) and sex ($P = 0.45$) did not prove to be statistically significant predictors of hypothyroidism in the multivariable model, they were retained in the model to obtain odds ratios for TPO status, which was significant ($P = 0.0002$), adjusted for their effects. Patients who were TPO positive were 17.91 times as likely to develop hypothyroidism as patients who were TPO negative (95% CI 3.89–82.54), controlling for age at onset of diabetes and sex.

The Cox proportional hazard analysis for predicting development of hypothyroidism from age at onset, sex, and TPO status supported the logistic regression results (likelihood ratio $\chi^2 = 15.88$, df = 3, $P = 0.001$). Adjusted for the effects of sex and age at onset of diabetes, TPO status was a significant determinant of hypothyroidism ($P = 0.001$). The adjusted hazard ratio for TPO status of 8.99 (95% CI 2.35–34.36) indicates that patients who were TPO positive were much more likely to develop hypothyroidism in the next time interval than patients who were TPO negative with similar elapsed times since the onset of diabetes.

Most patients developed subclinical hypothyroidism. With the exception of three patients who complained of fatigue, most patients were asymptomatic at diagnosis of hypothyroidism and none developed clinically significant hypothyroidism during the study period. The mean TSH concentration at diagnosis of hypothyroidism was 8 ± 1 mU/l (range 5.3–12.2). The mean TSH level in the euthyroid group at recruitment into the study was 1.9 ± 0.2 mU/l and remained at a similar level during the study period. With the exception of one patient who remained untreated, all subjects with hypothyroidism received levothyroxine therapy at a mean daily dose of 128 mcg. The mean TSH during replacement therapy was 2.2 ± 0.2 mU/l.

One patient with positive TPO antibodies had a transient and asymptomatic period of suppressed TSH (0.03 mU/l) level at the fourth year of follow-up. His serum TSH level spontaneously reverted to a normal value in the subsequent year and remained within normal limits thereafter. Apparently, there was no associated illness or stress during the time of suppressed TSH level.

CONCLUSIONS — This long-term and prospective study provides definitive evidence of the association between autoimmune hypothyroidism and type 1 diabetes. The incidence of hypothyroidism was higher in women, especially those with positive TPO antibodies. Adjusted for the effects of sex and age at onset of diabetes, TPO status was a significant determinant of hypothyroidism ($P = 0.0013$). Controlled for age at onset of diabetes and sex, patients who were TPO positive were 17.91 times as likely to develop hypothyroidism as patients who were TPO negative (95% CI 3.89–82.54).

An association between diabetes and thyroid disease has long been recognized, although the reported prevalence of thyroid dysfunction in diabetic populations varies widely between studies (10–18). Cross-sectional studies have reported a prevalence of hypothyroidism in 12–24% of female and ~6% of male patients with type 1 diabetes, as well as in 3–6% of type 2 diabetic patients (11–13). Similarly, we observed a higher rate of thyroid dysfunction than in the general population. Recently, the NHANES III reported a prevalence of hypothyroidism in 4.6% (0.3% clinical and 4.3% subclinical) and hyperthyroidism in 1.3% (0.5% clinical and 0.7% subclinical) and a prevalence of positive TPO antibodies in 13% of the U.S. population (9). In agreement with these reports, we observed a higher prevalence of thyroid dysfunction in type 1 diabetes than in the general population, especially in patients with positive TPO antibodies. The prevalence of hypothy-

roidism was significantly associated with positive TPO antibodies (OR 8.4, 95% CI 5.8–12.1). Among subjects with positive TPO antibodies and hypothyroidism during follow-up, 95% tested positive at the beginning of the study and remained positive throughout the observation period. In this survey, the use of TPO to predict hypothyroid was found to have a 67% positive predictive value and a 90% negative predictive value. Despite the association between positive thyroid TPO antibodies and the subsequent development of hypothyroidism, annual measurement of serum TSH constitutes the preferred screening test to detect asymptomatic thyroid dysfunction. If we used TPO antibodies as the single diagnostic tool in the current study, then we would have missed 28% of cases with subclinical hypothyroidism.

Population screening for thyroid dysfunction may prevent the development of overt thyroid dysfunction and may allow early treatment of hyperlipidemia (6,22), prevention of associated cardiovascular complications (23), and metabolic bone disorders (24). The American College of Physicians recently published guidelines on screening for thyroid disease with a sensitive TSH test in the primary care setting (25). These guidelines state that screening in women <50 years of age and in men is not warranted because of the low frequency of thyroid dysfunction. Our results and previous studies (4,10–15) indicate that these recommendations do not apply to patients with type 1 diabetes, since, compared with the general population, diabetic subjects develop thyroid dysfunction at an earlier age. In addition, our results indicate that long-term follow-up is necessary because the onset of diabetes usually precedes the diagnosis of thyroid dysfunction by approximately one decade.

In the present study, we observed a lower prevalence of hyperthyroidism than previously reported (11,12). The prevalence of hyperthyroidism, including subclinical hyperthyroidism, is 1.7% in patients with type 1 diabetes and 0.3% in patients with type 2 diabetes (15). The reason for the absence of hyperthyroid cases in our study is not known but may relate to the relatively small number of subjects and/or to the more defined population of patients with type 1 diabetes included in this study.

In summary, our long-term prospective study confirms the association between autoimmune hypothyroidism and type 1 diabetes and suggests that all subjects with type 1 diabetes, particularly those with positive TPO antibodies, should undergo annual screening by serum TSH measurement to detect asymptomatic thyroid dysfunction.

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