Extrapancreatic Autoimmune Manifestations in Type 1 Diabetes Patients and Their First-Degree Relatives

A multicenter study

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OBJECTIVE — To investigate the prevalence of autoimmune diseases in young patients (probands) with type 1 diabetes and their first-degree relatives, and to determine the spectrum of extrapancreatic manifestations in these subjects.

RESEARCH DESIGN AND METHODS — The study population included 109 probands age 13 ± 4.9 years and 412 first-degree relatives age 28.7 ± 16.2 years. The prevalence rates of autoimmune thyroiditis and celiac disease were determined in all probands and in 100 of the 412 first-degree relatives. Control groups included 78 subjects age 14.9 ± 10.4 years for the prevalence of autoimmune thyroiditis and 120,000 youth ages 16–17 years for the prevalence of celiac disease. Thyroiditis and celiac disease were diagnosed by abnormally high thyroid peroxidase (TPO), thyroglobulin (TG), antigliadin, and antiendomysial antibody titers. Celiac was confirmed by biopsy. A questionnaire was used to interview probands and relatives to determine the spectrum of autoimmune manifestations.

RESULTS — The prevalence of autoimmune thyroiditis determined by high TPO and/or TG titers was 27 and 25% for probands and relatives, respectively. These rates were higher than those for control subjects ($P < 000.1$). The prevalence of celiac disease among probands and screened relatives was 8.3 and 6%, respectively. These rates were higher than those for control subjects and the 312 family members interviewed only (0.1 and 0.3%, respectively; $P < 0.0001$). Interviews of participants revealed a wide range of associated autoimmune diseases. The risk of developing an autoimmune disease was higher ($P < 0.001$) in families with a proband who had an additional autoimmune manifestation.

CONCLUSIONS — Screening for autoimmune thyroiditis and celiac disease should be performed in patients with type 1 diabetes and their first-degree relatives, especially when the probands have an additional autoimmune manifestation.

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T ype 1 diabetes, a common autoimmune endocrine disease in children and adolescents, is frequently associated with other autoimmune diseases and autoantibodies (1). The most prevalent autoimmune disease associated with type 1 diabetes is Hashimoto thyroiditis. Its prevalence varies from 8 to 50% depending on the age, sex, and ethnic origin of the subjects (2–10). Because of this high prevalence, most investigators recommend screening children and adolescents with type 1 diabetes for autoimmune thyroid disease (2,3,6,7).

Celiac disease coexists with type 1 diabetes less frequently than does Hashimoto thyroiditis. Its prevalence in children and adolescents with type 1 diabetes ranges from ~3 to 8% (11–16), a much higher prevalence than that found in the general population. Thus routine screening of type 1 diabetes patients for celiac disease is also recommended (12,16,17).

In a study based solely on serological data, thyroid antibodies were found more frequently in both type 1 diabetic patients and their first-degree relatives (18). Thus, family members of type 1 diabetic patients may also be at high risk for developing type 1 diabetes and associated autoimmune diseases. The prevalence of autoimmune disorders, especially thyroid and celiac diseases in first-degree relatives, remains mostly unknown. Except for this study (18), no previous study has evaluated the prevalence of thyroid (4,6,19–22) and celiac diseases (23,24) in the same cohort. Moreover, previous studies have not examined the full extent of associated autoimmune diseases beyond a few conditions.

The present multicenter study was carried out in a cohort of type 1 diabetes patients and first-degree relatives with the following objectives: 1) to determine the prevalence of both autoimmune thyroid and biopsy-proven celiac diseases, and 2) to investigate the range of associated au-

toimmune manifestations by obtaining a detailed family history.

RESEARCH DESIGN AND METHODS

Study population
Pediatric endocrinology clinics from four medical centers participated in this multicenter study, carried out from 1997 to 2000. The study population included 109 type 1 diabetic patients who were diagnosed before age 18 years and 412 first-degree relatives. All patients and 100 of the 412 first-degree relatives were screened to determine the prevalence of autoimmune thyroid and celiac diseases. (Screening was offered to all relatives, but only 100 gave their consent.) In addition, the patients and their first-degree relatives were interviewed by the one investigator (A.M.) to detect autoimmune diseases, using a detailed questionnaire that included all signs and symptoms suggestive of autoimmune diseases. Medical history and data regarding autoimmune diseases in young children were obtained from their parents. The diagnosis of an autoimmune disease was confirmed by physical examination and/or review of the subject's medical charts.

A group of 78 healthy subjects with no family history of autoimmune disease served as a control group to assess the prevalence of autoimmune thyroid disease. This group consisted of medical staff and their children and subjects from pediatric outpatient clinics with no underlying medical pathology.

Data on the prevalence of celiac disease in Israel were based on two sources: Israel Defense Forces (IDF) draft board data and a recently published screening study in blood donors (25). The IDF data, gleaned from 120,000 consecutive candidates for army service ages 16–17 years (collected by A.L. in cooperation with the IDF), served as an additional control group to assess the prevalence of celiac disease in Israel. In this group, the diagnosis of celiac disease was based on clinical symptoms suggestive of celiac disease and positive serology (antigliadin and antiendomysial antibodies). The diagnosis was further confirmed by intestinal biopsy. The prevalence rate of celiac disease among the blood donor group was determined by serological screening of 1,570 healthy subjects (median age 38 years) with no known celiac disease. The blood samples were screened for celiac disease by antigliadin IgG, human tissue transglutaminase, and antiendomysial antibodies. The final diagnosis was based on intestinal biopsy (25).

Immunological and biochemical assays
Thyroid antibodies directed to thyroglobulin (TG) and to microsomal antigens (TG and TPO) were determined by enzyme-linked immunosorbent assay (Enzymun-Test, Boehringer Mannheim). TG and TPO titers >1/180 and 1/80, respectively, were considered diagnostic for autoimmune thyroid disease. In all patients screened for thyroid antibodies, free T4 and thyrotropin concentrations were also determined.

IgA antiendomysial antibodies (AEAs) were detected on the smooth muscle of monkey esophagus by an indirect immunofluorescence test (ImmuGlo; IMMCO Diagnostics, Buffalo, NY). All sera with fluorescence (titer ≥1/5) were considered to be positive. Antigliadin antibodies (AGAs) of IgA and IgG were determined by an indirect solid-phase enzyme immunometric assay. IgA and IgG antibody levels ≥12 units/ml were considered positive.

The diagnosis of celiac disease was based on the presence of positive AEA and AGA titers. The final diagnosis was confirmed by performing jejunal biopsy in all probands and family members tested positive for AEA and/or AGA.

GAD antibodies were determined by a commercial radioimmunoassay (CIS Bio International, Gif-Sur-Yvette Cedex, France). Levels of >1 unit/ml were considered positive. Islet cell antibodies (ICAs) were detected on monkey pancreas sections by an indirect immunofluorescence antibody test (BioSystems, Barcelona, Spain). Fluorescence at a dilution ≥25% was considered positive. Sera for these antibodies were obtained usually within days after the diagnosis, but not later than 3 months.

The E. Wolfson Hospital local ethics committee approved the study protocol. Informed consent for withdrawal of blood was obtained from all participants.

Statistical analysis
Data were stored on Excel 97 program (Microsoft). Data were analyzed using SPSS 9.0 statistical analysis software (SPSS, Chicago, IL). Frequencies of autoimmune diseases were simultaneously compared across groups (patients, first-degree relatives, and healthy subjects) using a χ^2 test. Tests were considered significant at $P < 0.05$.

RESULTS — The characteristics of the study population are shown in Table 1. The mean ages of type 1 diabetic patients and healthy subjects screened for the presence of thyroid antibodies were not significantly different. Similarly, the mean age and ethnic origins of the 100 first-degree screened relatives did not differ significantly from the mean age and ethnicity of the whole group.

Prevalence of ICAs and GAD antibodies
Positive ICAs and GAD antibodies were found in 32 of 55 (58%) and 36 of 52 (69%) probands, respectively; positive ICAs and/or GAD antibodies were found in 45 of 55 probands (81%). In first-degree relatives, positive ICAs and GAD antibodies were found in 4 of 63 subjects (6.3%) and 3 of 63 subjects (4.7%), respectively. None of the first-degree relatives were positive for both antibodies.

Prevalence of autoimmune thyroiditis in patients with type 1 diabetes and first-degree relatives
The prevalence of different thyroid antibodies in probands, first-degree relatives, and control subjects is shown in Fig. 1.

Table 1—*Characteristics of study population*

	n	M/F	Age at diagnosis (years)	Age at evaluation (years)
Probands	109	62/47	9.4 ± 4.2	13.0 ± 4.9
Relatives screened	100	42/58		29.0 ± 15.5
Relatives interviewed	312	159/153		29.0 ± 16.4
Control subjects*	78	41/37		14.9 ± 10.4

Data are n or means ± SD. *The 120,000 17-year-old youths (Israel Defense Forces draft board) served as an additional control population for celiac disease.
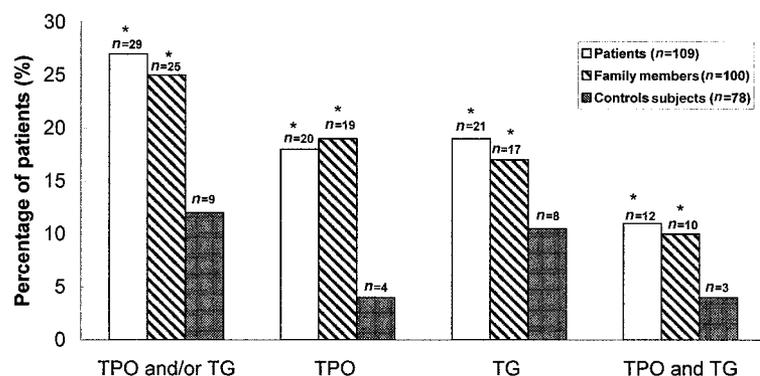
Figure 1—*Thyroid antibodies in patients with type 1 diabetes, first-degree relatives, and control subjects. *$P < 0.0001$ vs. control subjects.*

The prevalence of autoimmune thyroid disease as determined by positive TPO and/or TG antibody rates among type 1 diabetes probands was 27%, with 6% of those being hypothyroid (Fig. 1, Table 2). The corresponding rates among screened first-degree relatives (positive TPO and/or TG 25%, hypothyroid Hashimoto disease 8%) did not significantly differ from the rates found in probands (Fig. 1, Table 2), but were significantly higher than rates in control subjects.

The frequencies of positive TPO and TG antibodies alone and together were 18, 19, and 11%, respectively, in probands. The corresponding rates among first-degree relatives were quite similar (19, 17, and 10%, respectively). These rates were significantly higher ($P < 0.0001$) than the rates found in control subjects (3.8, 10, and 3.8%, respectively) (Fig. 1). The TPO titers in three control subjects were only slightly elevated (1/84, 1/118, and 1/98), whereas they were markedly elevated in most probands and family members (>5-fold in 13 probands and 12 relatives and >2.5-fold in 3 probands and 6 relatives). Among the first-

degree relatives who were screened, medical history revealed preexisting Hashimoto thyroiditis in five and Graves disease in one (Table 2). The frequency of preexisting autoimmune thyroiditis detected by interview only, was low (1%, Table 2).

Probands with Hashimoto thyroiditis did not have more relatives with positive antibodies than probands with normal antibody titers. Among 50 probands whose relatives were screened, 12 probands with thyroiditis had 8 relatives with positive antibodies and 13 relatives with normal antibody titers. Among 13 probands without thyroiditis, the corresponding numbers were 16 (positive) and 17 (normal) relatives.

Prevalence of celiac disease in patients with type 1 diabetes and first-degree relatives

The prevalence of biopsy-proven celiac disease among 109 probands was 8.3% (Fig. 2). All patients except one were diagnosed by screening. None of them had typical symptoms of Celiac disease (26). Among the 100 first-degree relatives

screened, the prevalence of biopsy-proven celiac disease was 6% (Fig. 2). The frequency of celiac disease between patients and first-degree relatives did not differ significantly.

The screening revealed celiac disease in four first-degree relatives from four unrelated families (a mother, a brother, and two sisters). These subjects were all asymptomatic. In the remaining two subjects from two unrelated families (a father and brother), biopsy-proven celiac disease was diagnosed before our study.

The prevalence rates among patients (8.3%) and the screened first-degree relatives (6%) were significantly higher than the rates among 312 family members interviewed only (0.3%; $P < 0.0001$) (Fig. 2). Among the 120,000 IDF candidates, we found a prevalence rate of celiac disease of 0.1%. In the group of 1,571 healthy blood donors, celiac disease was diagnosed in 10 subjects, establishing a prevalence of at least 1:157 in the general population. Thus the prevalence rates in type 1 diabetes patients and first-degree relatives were much higher than those observed among IDF candidates (0.1%) and a sample of healthy blood bank donors (0.6%) in Israel (25).

Of the seven probands with celiac disease, only two had a first-degree relative who was diagnosed with celiac disease. In the remaining five probands, the family history did not reveal celiac disease in other subjects from the same family.

Associated autoimmune manifestations

Among the 109 probands and 412 first-degree relatives, the most frequently found comorbid conditions were autoimmune thyroiditis and celiac disease (Table 2, Fig. 2). These conditions also frequently coexisted in the same subject or

Table 2—*The prevalence rates of autoimmune thyroiditis in type 1 diabetic patients (probands) and first-degree relatives*

	n	HT: all cases		HT: euthyroid		HT: hypothyroid		Graves disease		Newly diagnosed		Known	
		%	n (M/F)	%	n (M/F)	%	n (M/F)	%	n (M/F)	%	n (M/F)	%	n (M/F)
Probands	109	27	29 (19/10)	20	22 (15/7)	6	7 (4/3)	0	0	27	29 (19/10)	0	0
Relatives screened	100	25	25 (6/19)	17	17 (5/12)	8	8 (1/7)	1	1 (0/1)	20	20 (6/14)	6	6 (0/6)*
Relatives interviewed	312	1	3 (2/1)	NA		1	3 (2/1)	0.6	2 (1/1)	NA		1.6	5 (3/2)
Control subjects	78	11.5	9 (5/4)	11.5	9 (5/4)	0	0	0	0	11.5	9 (5/4)	0	0

Data are n or %. Hashimoto thyroiditis (HT) diagnosed by high titers of TPO and/or TG. For details see Fig. 1. *Including a mother with Graves disease. NA, not available.
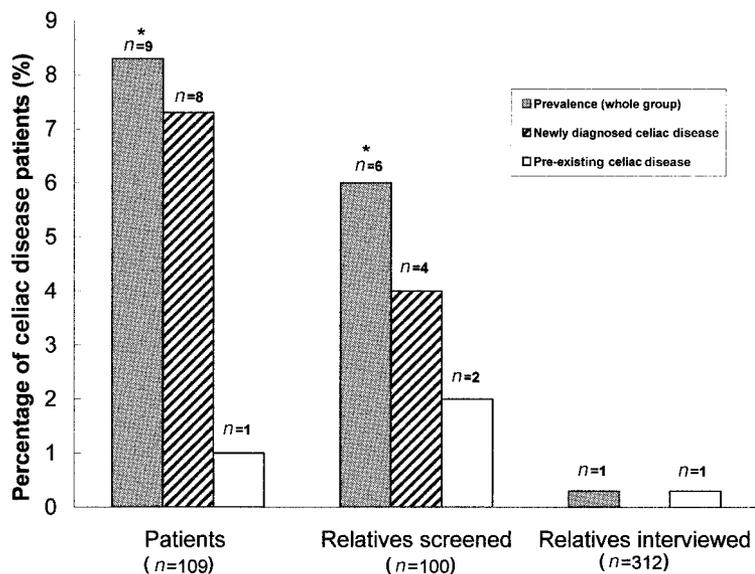
Figure 2—*Prevalence of celiac disease in patients with type 1 diabetes, first-degree relatives, and control subjects. *P < 0.0001 vs. interviewed relatives.*

family. Of the 15 subjects (9 probands and 6 relatives) with celiac disease, 4 probands and 3 relatives were diagnosed with coexisting Hashimoto thyroiditis. In the remaining 8 subjects (probands and relatives from seven families) with celiac disease but without coexisting thyroiditis, Hashimoto thyroiditis was diagnosed in

another 11 subjects within the same family of the affected individual.

We diagnosed 36 autoimmune conditions other than thyroiditis and celiac among probands and first-degree relatives. Among first-degree relatives, type 1 diabetes, psoriasis, and juvenile rheumatoid arthritis were frequently diagnosed conditions (Table 3). We also diagnosed a wide range of uncommon autoimmune diseases, including chronic urticaria, thrombotic thrombocytopenic purpura (two nondiabetic subjects, including a brother and his father), and autoimmune neuropathy (Table 3).

Clustering of autoimmune manifestations in families
In our cohort, we screened at least two members per family (a proband and a relative) of 50 families (of 109) and interviewed all family members. We analyzed these 50 families separately to determine

Table 3—*Coexisting autoimmune diseases and manifestations in type 1 diabetes patients and their first-degree relatives*

	Patients	Relatives
n	109	412
Type 1 diabetes	109	9
Autoimmune thyroiditis	29 (29)	28 (25)
Celiac disease	9 (8)	7 (6)
Juvenile rheumotoid arthritis	1	4
Psoriasis	1	6
Vitiligo	1	2
Chronic urticaria	1	1
Autoimmune neuropathy	1	1
Thrombotic thrombocitopenic purpura	0	2
Alopecia	0	3
Myasthenia gravis	0	1
Pernicious anemia	2	0

Data are *n*, with number of subjects diagnosed by screening shown in parenthesis. (See also Tables 2 and 3.)

the frequency of associated autoimmune diseases. Among the 50 families, the mean number of autoimmune conditions per family (including type 1 diabetes in index cases) was 1.9 (Table 4). Among 35 families (autoimmune families), the mean number of autoimmune conditions per family was 2.3 (Table 4). Clustering of autoimmune conditions were observed in 19 of the families (two or more autoimmune conditions per subject in 15 probands and seven relatives), and 4 of 19 families had four to five autoimmune conditions per family (Table 5). In the remaining 15 families (nonautoimmune families), no associated autoimmune diseases were found besides the diabetic index case (Table 4).

We also analyzed the prevalence of autoimmune conditions in relation to probands' autoimmune status. In the 15 families in which the probands exhibited an associated autoimmune disease, 18 of 24 relatives (75%) also had an autoimmune condition. In 35 families, relatives of probands with no associated autoimmune disease had a significantly lower frequency of autoimmune conditions (28 of 77 first-degree relatives [36.3%]) than the former group. Thus the risk of developing an autoimmune disease was significantly higher (*P* < 0.001) for relatives of probands who had an additional autoimmune condition.

CONCLUSIONS — Our results indicated that the prevalence rates of common autoimmune conditions and diseases, such as Hashimoto thyroiditis and celiac disease, among diabetic patients and their first-degree relatives were significantly higher than in the control groups. The high prevalence rates among relatives were revealed by our screening strategy, as the frequency of these conditions among relatives who were not screened (interviewed only) remained low.

Table 4—*Autoimmune diseases and manifestations detected by screening and interview in 50 families*

	n	Autoimmune families	Nonautoimmune families
Families	50	35	15
Probands and relatives	250 (100)	177 (71)	73 (29)
Subjects per family	5 ± 1.5	5.1 ± 1.6	4.9 ± 1.2
Autoimmune manifestations per family	1.9 ± 0.9	2.3 ± 0.8	1.0 ± 0.0

Data are *n*, *n* (%), or means ± SD.

Table 5—*Clustering of autoimmune manifestations in four diabetes type 1 families*

	Family 1	Family 2	Family 3	Family 4
Family members (*n*)	5	7	7	5
Index case	DB, VIT, HT	DB, HT	DB	DB, HT, CD
Father	None	Not screened	DB	Not screened
Mother	CD	None	HT	HT
Brother	VIT	—	Not screened	PS, CU, JRA
Brother	GAD	—	Not screened	Not screened
Sister	—	Not screened	—	HT
Sister	—	HT, CD	DB	—
Sister	—	HT	HT, MG, CD	—
Sister	—	HT	—	—

DB, type 1 diabetes; VIT, vitiligo; HT, Hashimoto thyroiditis; CD, celiac disease; PS, psoriasis; CU, chronic urticaria; JRA, juvenile rheumatoid arthritis; MG, myasthenia gravis; GAD, high glutamic acid decarboxylase Ab titer.

In our study, the prevalence of positive TPO and/or TG antibodies in type 1 diabetic patients and their first-degree relatives was 27 and 25%, respectively, suggesting that the risk of developing Hashimoto thyroiditis in relatives is as high as the risk in probands. The prevalence of thyroid autoimmunity in family members in previous studies has ranged from 13 to 55% (4,6,19–22).

It is noteworthy that 6% of our type 1 diabetic patients already had hypothyroidism at screening, despite their young ages (mean age 13 years). We found equal rates of thyroid autoimmunity in male and female subjects. Similar findings have been previously reported in only one study (3). By contrast, in nondiabetic children and adolescents, Hashimoto thyroiditis predominantly occurs in female subjects and hypothyroidism does not usually appear in young ages (27).

Prevalence rates of biopsy-proven celiac disease in type 1 diabetic patients and their first-degree relatives were 8 and 6% respectively, indicating that the relatives of type 1 diabetic patients are at increased risk for developing celiac disease as well. In two recent reports, the prevalence rates of celiac disease in type 1 diabetic patients were found to be 7.6 and 6.2% (18,28). In earlier studies, celiac disease in type 1 diabetic patients either was not detected or was observed in low frequencies (2–3%) (10,11,29). The only study that examined the prevalence of both autoimmune thyroid and celiac diseases in the same cohort of type 1 diabetic patients and their first-degree relatives did not find a difference between first-degree relatives and control subjects (18). Because that study was based on serological markers alone (guin-

ea pig tissue transglutaminase and antigliadin antibodies) that have poor predictive values (25,30), it probably underestimated the true prevalence. Other previous studies examined only offspring or siblings of type 1 diabetic patients. This approach may also underestimate the prevalence rates of celiac disease (31,32). Our findings demonstrated that the determination of the true prevalence rate of celiac disease in families requires screening all family members (parents and siblings) and confirming positive serology by biopsy.

The possibility could be raised that the high prevalence rates of Hashimoto and celiac diseases we found in first-degree relatives could be attributable to self-selection bias (relatives with symptoms may have been more willing to be screened). However, almost all relatives identified by screening were asymptomatic and thus were not aware of their condition. Therefore, self-selection bias cannot explain the high rates we observed.

In our study, the subjects with biopsy-proven celiac disease were all asymptomatic. In adult nondiabetic subjects, untreated celiac disease may be associated with increased mortality and morbidity (33). Thus, early diagnosis of celiac disease in both type 1 diabetes patients and their first-degree relatives may improve diabetic control and result in better outcome.

An interesting finding in our study was the coexistence of celiac disease and thyroid autoimmunity in many type 1 diabetic patients and family members. This association has been previously reported in nondiabetic subjects with celiac disease and has been shown to lead to diagnostic

difficulties and treatment delay (34). Roldan et al. (10) did not find an association between these two autoimmune diseases in type 1 diabetic patients. A more recent study (18) reported celiac and thyroid autoimmune diseases coexisting in 6.6% of young diabetic patients and 0.4% of the first-degree relatives. Our findings show that these diseases may frequently coexist, not necessarily within the same individual, but also within the same family. Thus the evaluation of many relatives may reveal additional individuals with either condition.

Besides celiac disease and thyroiditis, our study detected several additional autoimmune conditions, such as thrombotic thrombocytopenic purpura, autoimmune neuropathy, and chronic urticaria. These conditions were detected by our thorough clinical evaluation of the patients and their family members. Apart from the chronic urticaria that we recently reported (35), these conditions have not been previously reported in association with type 1 diabetes.

By searching for a wide range of autoimmune conditions, we found that the risk of developing several coexisting autoimmune diseases and conditions was especially high in "autoimmune families" where the probands manifested an additional autoimmune manifestation. These "autoimmune families" may have some common susceptibility alleles leading to the expression of multiple autoimmune diseases (36,37). However, at present the genes or mechanisms responsible for this susceptibility are not known.

In summary, antibody screening for celiac and Hashimoto thyroiditis revealed a significantly higher prevalence rates of these conditions in type 1 diabetic patients and their first-degree relatives compared to nonscreened relatives or healthy individuals. A search for associated autoimmune conditions revealed many "autoimmune families" with multiple autoimmune manifestations, especially when the proband had an associated autoimmune disease. Thus, we recommend screening and evaluation of all type 1 diabetic patients for autoimmune conditions and also advise first-degree relatives to undergo similar screening.

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