Every Fifth Individual With Type 1 Diabetes Suffers From an Additional Autoimmune Disease: A Finnish Nationwide Study

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OBJECTIVE

The aim of this study was to quantify the excess risk of autoimmune hypothyroidism and hyperthyroidism, Addison disease, celiac disease, and atrophic gastritis in adults with type 1 diabetes (T1D) compared with nondiabetic individuals in Finland.

RESEARCH DESIGN AND METHODS

The study included 4,758 individuals with T1D from the Finnish Diabetic Nephropathy (FinnDiane) Study and 12,710 nondiabetic control individuals. The autoimmune diseases (ADs) were identified by linking the data with the Finnish nationwide health registries from 1970 to 2015.

RESULTS

The median age of the FinnDiane individuals at the end of follow-up in 2015 was 51.4 (interquartile range 42.6–60.1) years, and the median duration of diabetes was 35.5 (26.5–44.0) years. Of individuals with T1D, 22.8% had at least one additional AD, which included 31.6% of women and 14.9% of men. The odds ratios for hypothyroidism, hyperthyroidism, celiac disease, Addison disease, and atrophic gastritis were 3.43 (95% CI 3.09–3.81), 2.98 (2.27–3.90), 4.64 (3.71–5.81), 24.13 (5.60–104.03), and 5.08 (3.15–8.18), respectively, in the individuals with T1D compared with the control individuals. The corresponding ORs for women compared with men were 2.96 (2.53–3.47), 2.83 (1.87–4.28), 1.52 (1.15–2.02), 2.22 (0.83–5.91), and 1.36 (0.77–2.39), respectively, in individuals with T1D. Late onset of T1D and aging increased the risk of hypothyroidism, whereas young age at onset of T1D increased the risk of celiac disease.

CONCLUSIONS

This is one of the largest studies quantifying the risk of coexisting AD in adult individuals with T1D in the country with the highest incidence of T1D in the world. The results highlight the importance of continuous screening for other ADs in individuals with T1D.

Autoimmune diseases (ADs) comprise a range of chronic diseases in which the immune response to self-antigens results in damage or dysfunction of the target organs. As the pathogenesis of various ADs share common genetic factors and immunologic processes, these diseases often coexist within the same individual and families (1). Among the over 80 different ADs, celiac disease and hypothyroidism are the most frequently observed additional ADs in type 1 diabetes (T1D), followed by

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**A complete list of the FinnDiane Study Group can be found in the Supplementary Data.*

gastric autoimmunity (including pernicious anemia), vitiligo, hyperthyroidism, autoimmune adrenalitis, gonadal insufficiency, autoimmune hepatitis, dermatomyositis, and myasthenia gravis (2,3). In general, female sex, older age, and longer duration of diabetes confer a greater risk of multiple ADs (4).

Available evidence suggests that a common genetic background is the main factor determining the high prevalence of additional ADs in individuals with T1D. Therefore, it is not unexpected that there is a strong association between the HLA region and the ADs because this locus encodes several molecules that play key roles in the immune system (5). There is also genetic overlap between T1D and other ADs outside the HLA region (6). Clustering of ADs in the same individuals and in the same families, however, indicates that shared environmental or other pathophysiological mechanisms cannot be ruled out (7).

Finland has the highest incidence of T1D in children (62.5 per 100,000) (8) and is among the countries with the highest incidence of celiac disease in young adults (31.0 per 100,000) (9) in the world. Until now, a complete survey of the coexistence of various ADs in individuals with T1D in the Finnish adult population has not been done. In addition, the coexistence of ADs with T1D across age groups have not been fully assessed either. Studies have, in general, been conducted in relatively young individuals, but studies in individuals with long-term T1D are few. The age at onset and the peak incidence varies widely depending on the AD. The incidence of T1D is the highest in childhood and adolescence, and it often precedes celiac and thyroid autoimmunity (10). However, many other ADs become apparent between the third and the sixth decade of life. Therefore, ascertainment of the coexistence in the older ages of individuals with long-term T1D enables us to estimate the comprehensive burden of ADs across the life span as individuals have had enough time to develop other ADs.

Knowledge of the long-term burden of ADs is particularly important as the accumulation of ADs may have adverse consequences by complicating diabetes management, disturbing glycemic control, and contributing to the development of complications of diabetes (11). Hypothyroidism, celiac disease, and Addison disease can lead to hypoglycemia (12,13), and hyperthyroidism increases the risk of hyperglycemia. To avoid such complications a cost-effective screening policy of concomitant ADs should routinely be implemented even in nonsymptomatic individuals.

Finally, comparisons of ADs between individuals with and without T1D are sparse. The excess risks related to T1D have been assessed by using indirect comparisons between individuals with T1D and the general population without age and sex matching. However, the age distribution and the calendar time may show substantial differences between these two groups and may, thus, result in unreliable estimates.

Therefore, we aimed to quantify the excess risk of ADs in adult individuals with long-term T1D compared with sex- and age-matched control individuals without T1D.

RESEARCH DESIGN AND METHODS

Study Population

A total of 4,758 individuals with T1D were included from the nationwide multicenter Finnish Diabetic Nephropathy Study (FinnDiane) cohort. The FinnDiane is an ongoing, nationwide, multicenter study, initiated to identify genetic and environmental risk factors for complications of diabetes. A detailed description of the FinnDiane recruitment protocol has previously been presented (14). Briefly, adult individuals ($\geq$18 years old) with T1D across Finland were asked to participate. T1D was defined as age at onset of diabetes $<$40 years, an initiation of insulin treatment within 1 year of diagnosis, and C-peptide $\leq$0.3 nmol/L at the baseline visit. The study protocol was in accordance with the principles of the Declaration of Helsinki as revised in 2000 and was approved by the Ethical Committee of Helsinki and Uusimaa Hospital District. Written informed consent was obtained from each participant.

For each FinnDiane participant, three individuals matched for sex, age, and place of residence in the year of the diagnosis of diabetes of the FinnDiane participant were selected from the Population Register Centre. In Finland, all costs of diabetes medications are reimbursed independently of socioeconomic status, and therefore, individuals with diabetes can be identified from the Finnish National Drug Reimbursement Register. On the basis of this reimbursement information, a total of 1,357 individuals from the control group had diabetes and were excluded from the analyses. After exclusion of people with diabetes, there were 12,434 control individuals left.

Ascertainment of ADs

ADs were identified by linking the data with the Finnish nationwide health registries; the Finnish Care Register for Health Care including specialized outpatient care (data available for the years 1970–2015), the Finnish National Drug Reimbursement Register (available for the years 1965–2015), the Drug Prescription Register (available for the years 1993–2015), and the National Health Insurance Dietary Grant Register (available for the years 2002–2015).

ADs included autoimmune hypothyroidism and hyperthyroidism, Addison disease, celiac disease, and atrophic gastritis. The specific codes used for the identification of ADs are listed in Supplementary Table 1. In case of medication, continuous purchases of medication were a prerequisite for a diagnosis of the AD in question. Treatment for Addison disease usually involves corticosteroids, but this could not be taken into account because these medications are also used for other diseases.

Statistical Methods

The baseline characteristics are presented as mean ($\pm$SD) for normally distributed values, otherwise they were presented as median (interquartile range, IQR). Categorical variables are reported as percentages. Differences between groups were analyzed by ANOVA for normally distributed continuous variables, otherwise they were analyzed by the Kruskal-Wallis test. Differences between the categorical variables were analyzed using the χ^2 test.

The prevalence of each AD was calculated for all T1D and control individuals and separately for men and women. The Cochran-Mantel-Haenszel test was used to compare risks and produce odds ratios (ORs) with 95% CIs between individuals with T1D and control subjects. The effect of age at onset of diabetes, duration of diabetes, and age on the risk of ADs was studied using the generalized additive modeling (GAM) without a priori assumptions of the shape of the relation. GAM was thus conducted under binomial distribution, and the link function was logit.

GAM is an extension of the generalized linear model and allows the inclusion of nonparametric smoothing functions to identify potential nonlinearity in the relationship between the independent and the dependent variables (15,16). The generalized cross-validation function was used as a criterion for selection of the smoothing parameters to determine an appropriate level of smoothing. To graphically show these relationships, the partial residual plots are shown.

The statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R open source software (https://www.r-project.org). GAM models were fitted using the mgcv library in R.

RESULTS

Clinical Characteristics

The median age of the FinnDiane individuals at the end of the follow-up in 2015 or death was 51.4 (IQR 42.6–60.1) years; 2,523 (53%) were diagnosed with T1D under 15 years of age, and the median duration of diabetes was 35.5 (26.5–44.0) years. There were 1,245 additional ADs that were identified in 1,087 individuals with T1D. The most prevalent AD on top of T1D was hypothyroidism ($n = 859$, 18.1%) followed by celiac disease ($n = 207$, 4.4%), hyperthyroidism ($n = 112$, 2.4%), atrophic gastritis ($n = 49$, 1.0%), and Addison disease ($n = 18$, 0.4%).

Table 1 shows the baseline clinical variables of the FinnDiane participants according to each AD. There was a female preponderance for all ADs, although this was not significant for atrophic gastritis. It was most conspicuous for hyperthyroidism where the proportion of women reached 71.4%. Women were also more likely to develop multiple ADs with a prevalence of 31.6% compared with 14.9% in men ($P < 0.0001$).

Individuals with hypothyroidism were older, had a longer duration of diabetes, and had a lower body weight but higher BMI (adjusted for sex) than those without any additional AD. Alongside female predominance, the individuals with hyperthyroidism more often had a history of smoking. Individuals with Addison disease had a worse lipid profile, lower HDL cholesterol and a tendency to higher triglyceride concentrations. Individuals with celiac disease had lower age at onset and longer duration of diabetes as well as lower body weight and BMI. Atrophic gastritis was associated with older age, higher age at onset of diabetes, and longer duration of diabetes.

Clustering of ADs

Altogether 22.8% of the individuals with T1D had at least one additional AD. Table 2 shows the different combinations of ADs. Of T1D individuals, 937 (19.7%) had only one additional AD, 143 (3.0%) had two, 6 (0.13%) had three, and 1 patient (0.02%) had four ADs together with T1D. The most prevalent combination was hypothyroidism and celiac disease. Although Addison disease was not a frequent AD, 16 out of 18 (89%) clustered with another AD and mostly with hypothyroidism (78%). Similarly, 53% of the cases of atrophic gastritis clustered with hypothyroidism. Of the nondiabetic control subjects, 7.3% had one AD, and 0.7% had two ADs.

Comparison with Nondiabetic Control Subjects

As many as 18.1% of the individuals with T1D had hypothyroidism, while the percentage in the control subjects was 6.0%, giving rise to an odds ratio (OR) of 3.43 (95% CI 3.09–3.81, $P < 0.0001$). The OR for hyperthyroidism was 2.98 (2.27–3.90, $P < 0.0001$) with a prevalence of 2.4% in individuals with T1D compared with 0.8% in the control subjects. Addison disease was rare in both groups; the prevalence was 0.38% in those with T1D and 0.016% in control subjects, resulting in an OR of 24.13 (5.60–104.03). The OR for celiac disease was 4.64 (3.71–5.81) with prevalence rates of 4.4% and 0.99% in those with and without T1D, respectively. Finally, atrophic gastritis was present in 1.03% of the individuals with T1D and 0.20% of control subjects, yielding an OR of 5.08 (3.15–8.18).

In the individuals with T1D, the ORs for hypothyroidism, hyperthyroidism, Addison disease, celiac disease, and atrophic gastritis were 2.96 (95% CI 2.53–3.47), 2.83 (1.87–4.28), 2.22 (0.83–5.91), 1.52 (1.15–2.02), and 1.36 (0.77–2.39), respectively, for women compared with men. In the nondiabetic control subjects, the ORs for women compared with men were 5.54 (4.58–6.70), 6.30 (3.64–10.91), 1.95 (1.35–2.81), and 1.25 (0.58–2.71) for hypothyroidism, hyperthyroidism, celiac disease, and atrophic gastritis, respectively. The OR for women compared with men regarding the combination of hypothyroidism and hyperthyroidism was 3.02 (2.59–3.53) in those with T1D, while it was 5.56 (4.63–6.69) in those without T1D.

Modeling the Effect of Age at Onset, Duration of Diabetes and Age

A linear relationship between the age of diabetes onset and the risk of hypothyroidism was found ($P = 0.08$ for nonlinearity) (Fig. 1*A*). The risk of hypothyroidism increased 1.7% (95% CI 0.9–2.5%, $P < 0.0001$) by each increasing year of age at onset of diabetes. The risk increased 1.3% (0.7–2.0%, $P < 0.0001$) by year of age (Fig. 1*B*). In a subsample where the year of diagnosis was 1980 or later and when an accurate age at diagnosis of hypothyroidism was achievable, the age-specific incidence increased from 0.16 (0.03–0.48) per 1,000 person-years in the age group 0–9 years to 12.0 (8.4–16.5) and 11.4 (4.2–24.8) in the age groups 40–49 and 50–59 years, respectively.

Opposite to hypothyroidism, the risk of celiac disease was 1.5% (95% CI 0.1–3.0%, $P = 0.048$) higher for each decreasing year of age at onset of diabetes ($P = 0.04$ for nonlinearity) (Fig. 2*A*). The highest risk was seen in those with an age at diagnosis of diabetes under 10 years compared with all other individuals with T1D with an OR of 1.38 (1.02–1.85, $P = 0.03$), but thereafter, the risk leveled off. When both the age at onset and the duration of diabetes were in the model, the duration was not significant (Fig. 2*B*); however, without age at onset, the OR for duration was 1.01 (1.00–1.02, $P = 0.03$). There was no association with age at diagnosis of diabetes, duration of diabetes, or age regarding the risk of hyperthyroidism, Addison disease, or atrophic gastritis.

CONCLUSIONS

This study shows that ADs are more often present in individuals with T1D than in the general population and that as many as 22.8% of the individuals with T1D suffer from an additional AD. To our knowledge, this study shows for the first time in a large Finnish nationwide cohort the magnitude of the excess risk of concomitant ADs by using age- and sex-matched control subjects from the general population. In fact, the individuals with T1D had 3.4-, 4.6-, and 2.9-times-higher risk of hypothyroidism, celiac disease, and hyperthyroidism, respectively, which were the most prevalent ADs. The OR for atrophic gastritis was 5.1 and for the rare Addison disease 24.1. This study also shows that late onset of T1D and aging increases the risk of hypothyroidism,

Table 1—Baseline characteristics of adults with T1D from the FinnDiane study cohort according to each AD

	No AD (n = 3,671)	Any AD (n = 1,087)	Hypothyroidism (n = 859)	Hyperthyroidism (n = 112)	Addison disease (n = 18)	Celiac disease (n = 207)	Atrophic gastritis (n = 49)
Sex, female	42.1	65.7****	68.9****	71.4****	66.7*	57.5****	55.1
Age (years)	37.5 (28.7–46.9)	39.4 (30.0–48.2)**	39.5 (30.4–48.3)***	37.2 (28.8–46.5)	41.3 (35.6–44.9)	38.7 (28.9–47.5)	46.2 (36.6–55.3)****
Age at diabetes diagnosis (years)	14.2 (9.2–22.6)	14.0 (9.2–23.3)**	14.3 (9.5–24.1)	13.2 (8.4–21.2)	12.5 (6.0–20.1)	12.8 (7.1–20.9)*	17.7 (11.0–27.2)*
Age at diagnosis of diabetes							
0–14 years	52.8	57.3	52.4	58.0	55.6	59.9*	46.9
≥15 years	47.2	42.7	47.6	42.0	44.4	40.1	53.1
Duration of diabetes (years)	21.3 (11.6–30.9)	22.0 (13.9–31.5)	22.0 (13.5–31.3)*	22.1 (12.2–29.9)	27.6 (21.2–33.1)	22.8 (15.3–31.8)*	24.2 (18.0–37.8)**
HbA_{1c} (%)	8.4 ± 1.5	8.4 ± 1.5	8.5 ± 1.5	8.6 ± 1.6	8.4 ± 1.6	8.5 ± 1.4	8.4 ± 1.3
HbA_{1c} (mmol/mol)	68.4 ± 16.2	68.8 ± 16.0	69.0 ± 16.3	70.4 ± 17.0	68.3 ± 17.4	69.1 ± 15.4	68.0 ± 15.4
Smoking history	47.1	46.9	46.7	58.2*	33.3	43.5	62.2*
Height (cm)†	171.9 ± 1.5	168.5 ± 9.2	168.2 ± 9.1	167.7 ± 9.0	167.3 ± 7.9	168.7 ± 8.9	170.1 ± 10.1
Weight (kg)†	74.1 ± 13.4	71.9 ± 13.3	72.0 ± 13.5*	71.1 ± 12.6	68.4 ± 11.0	69.6 ± 11.7*	74.1 ± 16.1
BMI (kg/m^2)†	25.0 ± 3.6	25.2 ± 3.8*	25.4 ± 3.8**	25.2 ± 3.7	24.5 ± 4.0	24.4 ± 3.4*	25.5 ± 4.4
Waist-to-hip ratio	0.88 ± 0.09	0.85 ± 0.08	0.85 ± 0.08	0.84 ± 0.07	0.84 ± 0.06	0.85 ± 0.08	0.88 ± 0.08
Systolic blood pressure (mmHg)	135 ± 19	133.±18 NS	133 ± 18.6	130 ± 18	129 ± 19	132 ± 16	139 ± 19
Diastolic blood pressure (mmHg)	80 ± 10	79 ± 10 NS	79 ± 10	78 ± 10	77 ± 7	78 ± 10	82 ± 9
Total cholesterol (mmol/L)	4.93 ± 1.02	4.91 ± 0.90	4.93 ± 0.90	4.92 ± 0.79	5.32 ± 0.95	4.87 ± 0.94	4.86 ± 0.81
LDL cholesterol (mmol/L)	3.05 ± 0.88	3.03 ± 0.81	3.05 ± 0.81	2.98 ± 0.73	3.44 ± 0.93	3.02 ± 0.84	3.05 ± 0.83
HDL cholesterol (mmol/L)	1.33 ± 0.40	1.37 ± 0.39	1.37 ± 0.39	1.40 ± 0.38	1.17 ± 0.37*	1.31 ± 0.41	1.35 ± 0.38
Triglycerides (mmol/L)	1.05 (0.79–1.51)	1.00 (0.74–1.42)	1.00 (0.75–1.42)	1.04 (0.74–1.54)	1.28 (0.96–1.78)	0.99 (0.72–1.50)	0.98 (0.73–1.34)

Data are mean ± SD, median (IQR), or percentage. P value refers to ANOVA, Kruskal-Wallis test, or χ^2 test. NS, not significant. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$; comparison with the T1D individuals without additional AD. †Sex-adjusted.

whereas early onset of T1D increases the risk of celiac disease. There is a clear female preponderance for all ADs except for atrophic gastritis.

In this Finnish cohort of T1D, the prevalence rates for the clustering of ADs appeared to be higher compared with a recent multinational systematic meta-analysis in individuals with T1D (2). The prevalence rates in our study were approximately double that in the meta-analysis for thyroid diseases and for Addison disease. However, the prevalence rates were rather similar for celiac disease, but nearly four times higher for atrophic gastritis. The prevalence of hypothyroidism was higher also in the nondiabetic control subjects in our study compared with the other general populations, but it was lower or similar for the other ADs (2). These differences in the prevalence rates may be due to the geographical origin of our study population indicating potential differences in the genetic and environmental exposures, screening policies, and, most importantly, the age differences between the studies (17).

Table 2—Clustering of ADs in individuals with T1D

Combination of ADs	Number
Hypothyroidism + celiac disease	58
Hypothyroidism + hyperthyroidism	52
Hypothyroidism + atrophic gastritis	26
Hypothyroidism + Addison disease	14
Hypothyroidism + hyperthyroidism + celiac diasease	5
Hypothyroidism + hyperthyroidism + Addison disease	2
Hypothyroidism + hyperthyroidism + atrophic gastritis	1
Hypothyroidism + hyperthyroidism + Addison disease + celiac disease	1
Hyperthyroidism + celiac disease	10
Hyperthyroidism + Addison disease	2
Hyperthyroidism + atrophic gastritis	2
Hyperthyroidism + Addison disease + celiac disease	1
Addison disease + celiac disease	3

Sex Differences

In line with previous studies (18) but in contrast to T1D, per se (19), there was a clear preponderance of women for most ADs. When all ADs were pooled, 31.6% of the women had at least one additional AD, while the percentage was 14.9% in men in our study.

The possible explanations for the sex-specific differences included immune response and organ vulnerability, reproductive capacity, sex hormones, genetic predisposition, parental inheritance, and epigenetics relating the level of exposure to external factors and the response to them (18). In our study, women were particularly prone to develop thyroid diseases, but interestingly, the sex differences were less pronounced in the individuals with T1D (OR = 3.02) than in the control subjects (OR = 5.56). However, ORs of between 6 and 10 for women compared with men in general populations have been observed, which are even higher than we found in our study (20,21). This phenomenon has, to our knowledge, not been observed before. The reason for this finding can only be speculated about, but it may be due to

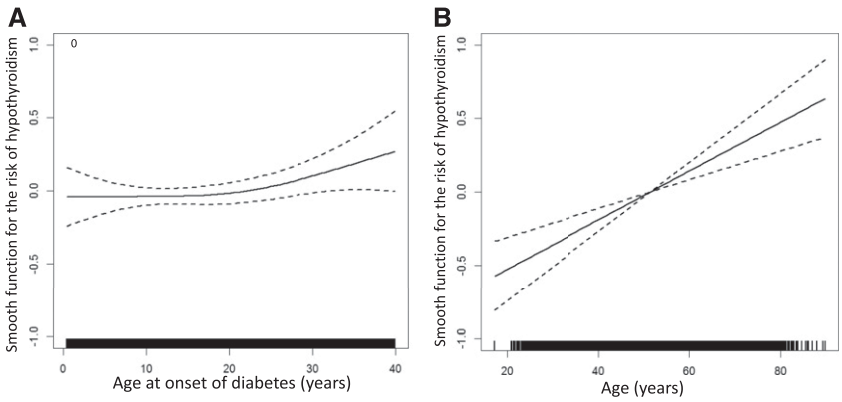

Figure 1—Plots of estimated smoothing splines of the association between the risk of hypothyroidism and the age at diagnosis of diabetes (*A*) and age (*B*). Dashed lines represent 95% CI. The area above zero represents increased risk, and the area under zero represents decreased risk.

the fact that islet autoimmunity may increase the risk of other ADs by overruling the sex-specific immune reactivity in individuals with T1D.

Hypothyroidism

This study demonstrated a twice as high prevalence of hypothyroidism in Finland compared with other cohorts. However, it also showed that the proportion of hypothyroidism increased along with increasing age. Therefore, because the median age at the end of our study was over 50 years, the high prevalence of 18.1% for hypothyroidism is not surprising when compared with the prevalence of 9.4% with a mean age of 19.2 years in a recent meta-analysis (2). Also, the meta-analysis showed a 4.6% increase of autoimmune hypothyroidism for every 10-year increase in age, and therefore, the prevalence ranged from 0.6 to 44%, depending on the age of the study population. In support of our data, the prevalence of hypothyroidism in the study by Hughes et al. (22) with a corresponding age range was rather similar to our study.

Besides age, there might also be other reasons for the different prevalence rates. Lack of screening may underestimate the true prevalence of ADs. For T1D, the high prevalence may, in part, be explained by the Finnish policy to screen the thyroid status every fifth year.

The other possible reasons for the high prevalence of autoimmune hypothyroidism in the Finnish population is not known, but it can be speculated that it is linked to the high incidence of T1D in Finland. T1D-specific HLA subtypes have been observed to also increase the risk of autoimmune thyroid disease (23). Furthermore, individuals with β-cell autoantibodies appear to have a higher risk of developing thyroid antibodies (24). Individuals with increased levels of thyroid peroxidase antibodies may develop hypothyroidism or remain euthyroid.

Hyperthyroidism

Similar to hypothyroidism, autoimmune hyperthyroidism is also a multifactorial disease. It is a complex interplay of genetic and nongenetic factors that lead to the loss of immune tolerance to thyroid antigens and to the initiation of a sustained autoimmune reaction (25). Among nongenetic factors, smoking has been suggested to contribute to the development of the disease (25). That may be due to both a direct action of smoking metabolites on the immune system and by damage induced by smoking metabolites on the thyrocytes, thereby determining the exposure of thyroid antigens to the immune system (26). It is of note that in our study cohort, a significantly higher proportion of T1D individuals with hyperthyroidism had a history of smoking.

Celiac Disease

Celiac disease was the most prevalent AD on top of T1D after hyperthyroidism in concordance with previous observations (2). Finland has one of the highest incidence rates of celiac disease worldwide (27) in addition to the highest incidence of T1D (8). This might be indicative of an interaction between genetic and environmental factors that contribute to both T1D and celiac disease.

The prevalence of celiac disease shows a marked geographical variation, which may depend, in part, on the diagnostic criteria used and the intensity of screening. According to a recent meta-analysis, the global prevalence of celiac disease was 1.4%, when the diagnosis was based on tests for antitissue transglutaminase or antiendomysial antibodies, but only 0.7% when it was based on a duodenal biopsy (28). In previous studies on celiac disease in T1D, there were substantial differences in the proportion of individuals screened with biopsies, and the pooled prevalence of celiac autoantibodies varied from 5.3 to 12.7% depending on the type of antibody (2). Consequently, the prevalence of celiac disease ranged from 0.4 to 13.5% (2). In Finland, the ICD code for celiac disease is always based on a duodenal biopsy-confirmed diagnosis. If the diagnosis was based on antibody positivity, the prevalence of

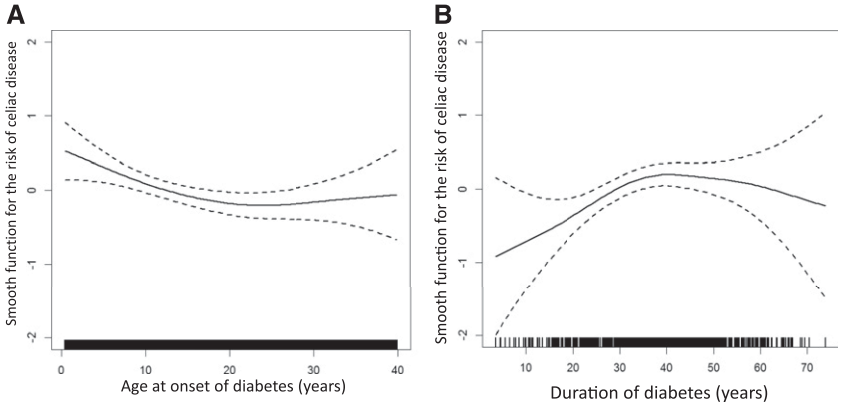

Figure 2—Plots of estimated smoothing splines of the association between the risk of celiac disease and the age at diagnosis of diabetes (*A*) and duration of diabetes (*B*). Dashed lines represent 95% CI. The area above zero represents increased risk, and the area under zero represents decreased risk.

celiac disease might have been even higher in the current study.

The close relationship between celiac disease and T1D can be largely explained by a common genetic background. In a recent international prospective birth cohort study (The Environmental Determinants of Diabetes in the Young), for children carrying high-T1D-risk HLA genotypes and having both T1D and celiac disease, the development of autoantibodies for T1D usually precedes that of the transglutaminase autoantibodies (7). Also, a significantly greater co-occurrence was observed in children with a family history of T1D (7). Interestingly, there is a genetic link between very young onset T1D, familial aggregation of T1D, and celiac disease (29–31). In line with this, we also found that young age at onset of diabetes increased the risk of celiac disease. In previous studies, no such associations have been shown unequivocally. The results seem to vary depending on the type of screened antibody because different celiac disease antibodies are associated with age or duration of diabetes differently (2).

Addison Disease

Addison disease is rare. The most conspicuous feature in this study was its high degree of coexistence with additional ADs; 89% of the individuals with T1D and Addison disease also had a third AD. Such a phenomenon was also found in a previous study by Fichna et al. (32) where 85% of individuals with Addison disease had at least one additional AD. They further observed that serum ZnT8 antibodies indicated an elevated risk for an additional AD. In our study, Addison disease clustered most often with thyroid ADs in accordance with a recent Swedish nationwide observational cohort study (33). Unlike in another Swedish study (34) where persons with T1D developed Addison disease at a younger age, no association with age at diabetes diagnosis, duration of diabetes, or age was detected in the Finnish cohort.

We found that the T1D individuals with Addison disease had higher LDL cholesterol and lower HDL cholesterol compared with the other T1D groups. This observation is in line with a previous study, where adverse lipid profiles and cardiovascular risk factors were observed in South African and Swedish T1D cohorts with Addison disease (35). Uncontrolled diabetes, hypothyroidism, and chronic over-replacement with glucocorticoids are known to adversely influence the blood lipid profile and may negatively influence the cardiovascular profile. However, it remains uncertain whether these are due to Addison disease, per se, or its management.

Atrophic Gastritis

The T1D individuals diagnosed with atrophic gastritis were older; their T1D was diagnosed at older age; and they had longer T1D duration compared with those with or without an additional AD.

Taking into consideration that autoimmune gastritis and pernicious anemia are common autoimmune disorders, being present in up to 2% of the general population and being increased threefold to fivefold in T1D (36), the prevalence in our Finnish cohort is apparently low. In Finland, parietal cell autoantibodies or intrinsic factor are not recommended to be screened routinely (Finnish Current Care Guidelines). Instead, an annual examination of the peripheral blood is recommended in order to reveal possible macrocytosis and anemia. Thus, it is probable that atrophic gastritis is an underdiagnosed disorder and is diagnosed at a rather late phase. Since vitamin B12 deficiency may result in pernicious anemia and may predispose to gastric carcinoid tumors or adenocarcinomas in up to 10% of individuals, there is a strong rationale for screening, early diagnosis, and treatment of atrophic gastritis in individuals with T1D (36).

Strengths and Limitations

The main strengths of this study are the large cohort of well-characterized patients with T1D and the possibility to identify ADs through the Finnish national health registers during long periods of time. Therefore, with long diabetes duration and relatively old age at the end of the study, there was enough time for individuals to develop additional ADs. Importantly, having age- and sex-matched control subjects enabled us to quantify the excess risk of ADs in individuals with T1D and separately for men and women. Because the peak incidences of different ADs varies a lot, it is crucial to have sex- and age-matched control subjects that were studied during the same time period in order to achieve reliable estimates of the excess risk of ADs in T1D.

However, there are also limitations in our study. One of the limitations was the absence of detailed clinical data for the control individuals at baseline, which would have helped in identifying associated predictive factors. Another limitation is that we were not able to get age at onset data for all ADs, and therefore, we were not able to determine the peak incidences for ADs. Since individuals who had an early diagnosis of T1D decades ago and died or who had died before they reached the age of 18 years would not have been recruited to the FinnDiane study, the prevalence rates of some of the ADs might even be underestimated. This is particularly true for those ADs that develop later in life.

In conclusion, this nationwide study showed that 22.8% of individuals with T1D have an additional AD. Hypothyroidism, celiac disease, and hyperthyroidism are the most prevalent ADs. Late onset of T1D and aging increases the risk of hypothyroidism. Screening for celiac disease is important during childhood, since age $\leq$10 years at onset of T1D but not aging, per se, increases the risk of celiac disease. ADs should be screened throughout life equally for both sexes and more often in those with a family history of T1D. More studies are needed to identify the associated predictive factors for combinations of ADs in T1D. However, it is unclear whether screening and early detection of additional ADs may improve the clinical outcomes in individuals with T1D.

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