Affected brother as the highest risk factor of type 1 diabetes development in children and adolescents: One center data before implementing type 1 diabetes national screening

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Abstract

Background. There is an increased risk for childhood type 1 diabetes (T1D) when T1D and type 2 diabetes (T2D) are reported in relatives.

Objectives. Our objective was to evaluate current family risk factors for T1D development before implementing a national screening program for T1D.

Materials and methods. A population of 879 Caucasian children and adolescents with T1D and 286 healthy controls were enrolled in the study. All participants completed the same questionnaire, which collected information about family history of diabetes over 3 generations. In statistical analyses, frequency tables and χ^2 tests evaluated possible multicollinearity among risk factors that were significantly associated with the outcomes.

Results. Family history of diabetes was more frequent in controls (n = 75, 26.2%) than in patients with T1D (n = 146, 16.6%, odds ratio (OR) = 1.785, 95% confidence interval (95% CI): 1.299–2.452, degrees of freedom (df) = 12.976, p = 0.004), especially with a family history of T2D (n = 62, 21.7% compared to n = 79, 9.0%, respectively, OR = 2.803, 95% CI: 1.948–4.034, df = 32.669, p < 0.001). Also, there was a tendency for the nuclear family of T1D patients to be more frequently affected by T1D (n = 74, 8.4%) than the controls (n = 15, 5.2%, OR = 1.605, 95% CI: 0.937–2.751, df = 3.081, p = 0.079). The risk of T1D was associated with the closest family members being affected and accelerated over generations. Indeed, it was highest in siblings, especially brothers (OR = 12.985, 95% CI: 0.782–215.743, Fisher's test: p < 0.001). A positive family history of T2D burden among second-degree relatives was 2.728 times more frequent in the control group than in the T1D group (OR = 2.728; 95% CI: 1.880–3.962, p < 0.001). Furthermore, a positive family history of T1D among first-degree relatives was less frequent in the controls than in the T1D group (OR = 0.124; 95% CI: 0.030–0.516, p = 0.004).

Conclusions. A family history of T1D, but not T2D, is a significant risk factor for T1D development. Indeed, the priority in screening for T1D should be given to first-degree relatives of T1D patients, starting from siblings.

Key words: type 2 diabetes mellitus, siblings, type 1 diabetes mellitus, first-degree relatives, family history of diabetes

Background

Type 1 diabetes (T1D) develops from interactions between several combinations of susceptibility genes and environmental exposures. Numerous studies have found an increased risk of T1D in children whose relatives have both type 1 and type 2 diabetes (T2D).[1–3] Previous studies demonstrated that individuals with first-degree relatives with T1D have an approx. 15-fold higher relative lifetime risk of developing T1D than the general population, and the prevalence of T1D by the age of 20 is around 5% compared to approx. 0.3% in the general population, making screening an effective approach to recruiting for preventive screening. However, over 85% of newly diagnosed patients have no family history.[4–6] Moreover, it is well established that the prevalence of autoimmunity and T1D in individuals with certain human leukocyte antigen (HLA) loci varies significantly, with a gradient that includes a range of highly susceptible protective loci.[7,8] Indeed, over 70 T1D genetic variants have been identified in genome-wide association studies.[9] Around half of them are HLA-DR and HLA-DQ loci. First-degree relatives who carry HLA-DR3-DQ2/DR4-DQ8 have an elevated risk of islet autoimmunity and T1D, which increases by about 20%.[10,11] In families living together, similar environmental risk factors for diabetes may also explain this observation.

Type 1 diabetes often occurs in combination with several endocrine and non-endocrine autoimmune disorders. Recent studies have shown a strong cluster of T1D and autoimmune diseases in patients and their first-degree relatives.[12] Annual serological and subsequent functional screening for autoimmune disorders in T1D patients and their first-degree relatives is recommended. Screening for T1D autoantibodies has positive clinical consequences, including reduced diabetic ketoacidosis events, improved glycemic control, and a positive impact on short-term and long-term complications.[13] In some regions of Poland, screening for T1D antibodies in first-degree relatives of patients with T1D has been conducted.[14] According to the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommendations, routine screening for family members as part of clinical care has been proposed as an intermediate step toward general population screening.[15] Such an approach would be highly recommended if effective immunotherapies that delay progression and preserve β-cell function are approved by regulatory bodies and the cost/benefit ratio related to screening is optimized.[16]

Objectives

This study aimed to assess T1D risk in children and adolescents with a positive family history of diabetes at our center prior to the implementation of a national T1D screening program.

Materials and methods

Our cohort study was conducted between 2017 and 2018 and involved 879 Caucasian children and adolescents with T1D and 286 healthy Caucasian children and adolescents. The T1D patients constituted an unselected group of patients and included 90% of all patients treated in our department, with a median age of 12.8 (9.2; 15.5) years. The T1D diagnosis was made according to the 2017 criteria of the Polish Diabetes Society.[17] The control group consisted of children and adolescents from public schools, representative of the general population.

The Ethics Committee of Jagiellonian University approved the study (approval No. 1072.6120.206.2017). All parents/legal guardians of the study participants gave their written informed consent by completing a family interview questionnaire. All participants completed the same questionnaire, which was prepared by the authors of the study. Family history collected information about diabetes over 3 generations (defined as grandparents, i.e., both of the parent's parents, parents, siblings of parents, i.e., aunts and uncles, and the children of parents' siblings, i.e., cousins and siblings). Data on the number of relatives with diabetes, the age of disease onset, and the use of insulin in those diagnosed with diabetes were obtained. The questionnaire used the term latent autoimmune diabetes in adults (LADA) for T1D diagnosed in adults according to the then valid classification. In addition, we asked about autoimmune diseases in diabetic family members, specifically celiac disease, autoimmune thyroiditis, including Graves' disease, and non-celiac autoimmune bowel diseases, to minimize the risk of T1D overdiagnosis among diabetic relatives treated with insulin. The interviewers were medical students from a scientific group working in our department. Data on study participants were mostly obtained from their parents (predominantly from mothers).

Statistical analyses

All statistical analyses employed IBM SPSS v. 25 (IBM Corp., Armonk, USA) and Statistica v. 13 with the medical kit (StatSoft, Tulsa, USA). Results are presented as medians with upper and lower quartiles. The normality of data distribution was assessed using the Shapiro–Wilk test (for a relatively small sample size <50) and the Kolmogorov–Smirnov test (for a large sample size). Due to interval data with non-parametric distribution in parameters such as age and the T1D diagnosed age, which occurred in at least 1 of the 2 examined groups of children (Table 1,2), the Mann–Whitney U test for 2 independent samples was used. Frequency tables and χ^2 tests assessed possible collinearity among risk factors that were significantly associated with the outcomes.

For subsets of data with smaller numbers, the χ^2 test with Yates' correction and Fisher's exact test of independence were used. The chi-square automatic interaction detection (CHAID) decision tree algorithm proposed by Kass

Table 1. Values of normality tests for age in the entire examined population (n = 1165), the group of children with T1D (n = 879) and control group (n = 286), taking gender into account

Groups	D statistics (D) and p-values in the Kolmogorov–Smirnov tests	W statistics (W) and p-values in the Shapiro–Wilk tests
Entire examined population (n = 1165)	D = 0.073827 p < 0.001	W = 0.968583 p < 0.001
Group of children with T1D (n = 879)	D = 0.081427 p < 0.001	W = 0.954083 p < 0.001
Control group (n = 286)	D = 0.137104 p < 0.001	W = 0.47486 p < 0.001
Entire examined boy population (n = 588)	D = 0.081074 p < 0.001	W = 0.964077 p < 0.001
Entire examined girl population (n = 570)	D = 0.070772 p = 0.006	W = 0.971673 p < 0.001
Group of boys with T1D (n = 451)	D = 0.084905 p = 0.003	W = 0.949227 p < 0.001
Group of girls with T1D (n = 428)	D = 0.086927 p = 0.003	W = 0.957016 p < 0.001
Boys in the control group (n = 137)	D = 0.157911 p = 0.002	W = 0.936828 p < 0.001
Girls in the control group (n = 142)	D = 0.132553 p = 0.013	W = 0.950827 p < 0.001

T1D – type 1 diabetes; T2D – type 2 diabetes; n – number of children.

Table 2. Values of normality tests for age at diagnosis of T1D in the group of children with T1D (n = 879) depending on family history of T1D and T2D, taking gender into account

Groups	D statistics (D) and p-values in the Kolmogorov–Smirnov test	W statistics (W) and p-values in the Shapiro–Wilk test
Group of children with T1D (n = 879)	D = 0.081427 p < 0.001	W = 0.954083 p < 0.001
Group of boys with T1D (n = 451)	D = 0.097346 p < 0.001	W = 0.954009 p < 0.001
Group of girls with T1D (n = 428)	D = 0.053759 p = 0.162	W = 0.944326 p < 0.001
Group of children with T1D with a positive family history of T2D (n = 79)	D = 0.0661 p = 0.858	W = 0.980561 p = 0.271
Group of children with T1D with a negative family history of T2D (n = 800)	D = 0.073228 p < 0.001	W = 0.949314 p < 0.001
Group of children with T1D with a positive family history of T2D burden among second-degree relatives (n = 76)	D = 0.069974 p = 0.825	W = 0.978839 p = 0.235
Group of children with T1D with a negative family history of T2D among second-degree relatives (n = 803)	D = 0.072574 p < 0.001	W = 0.949625 p < 0.001
Group of children with T1D with a positive family history of T2D burden among grandparents (n = 73)	D = 0.081854 p = 0.681	W = 0.974688 p = 0.149
Group of children with T1D with a negative family history of T2D burden among grandparents (n = 806)	D = 0.072066 p < 0.001	W = 0.949656 p < 0.001

T1D – type 1 diabetes; T2D – type 2 diabetes; n – number of children.

identified the main determinants of T1D at younger ages (84 months and below). These decision trees operate through a series of steps, including merging, splitting and retaining, based on user-specified criteria, and split the data into more homogeneous groups.[18] Multivariate logistic regression models determined the odds of avoiding T1D. A 95% confidence interval (95% CI) was used to estimate the precision of the odds ratio (OR). A two-tailed p-value <0.05 was considered statistically significant.

Results

The study included 879 children with T1D, among them 451 (51%) boys and 428 (49%) girls (Fig. 1). The median age in the male subgroup with T1D amounted to 154 months (110.5; 187) and did not differ from the female subgroup (149 months (109;185.5); U = 94804, p = 0.346). In the group of children with T1D, the median age at T1D diagnosis was 84 months (49; 124), which did not differ

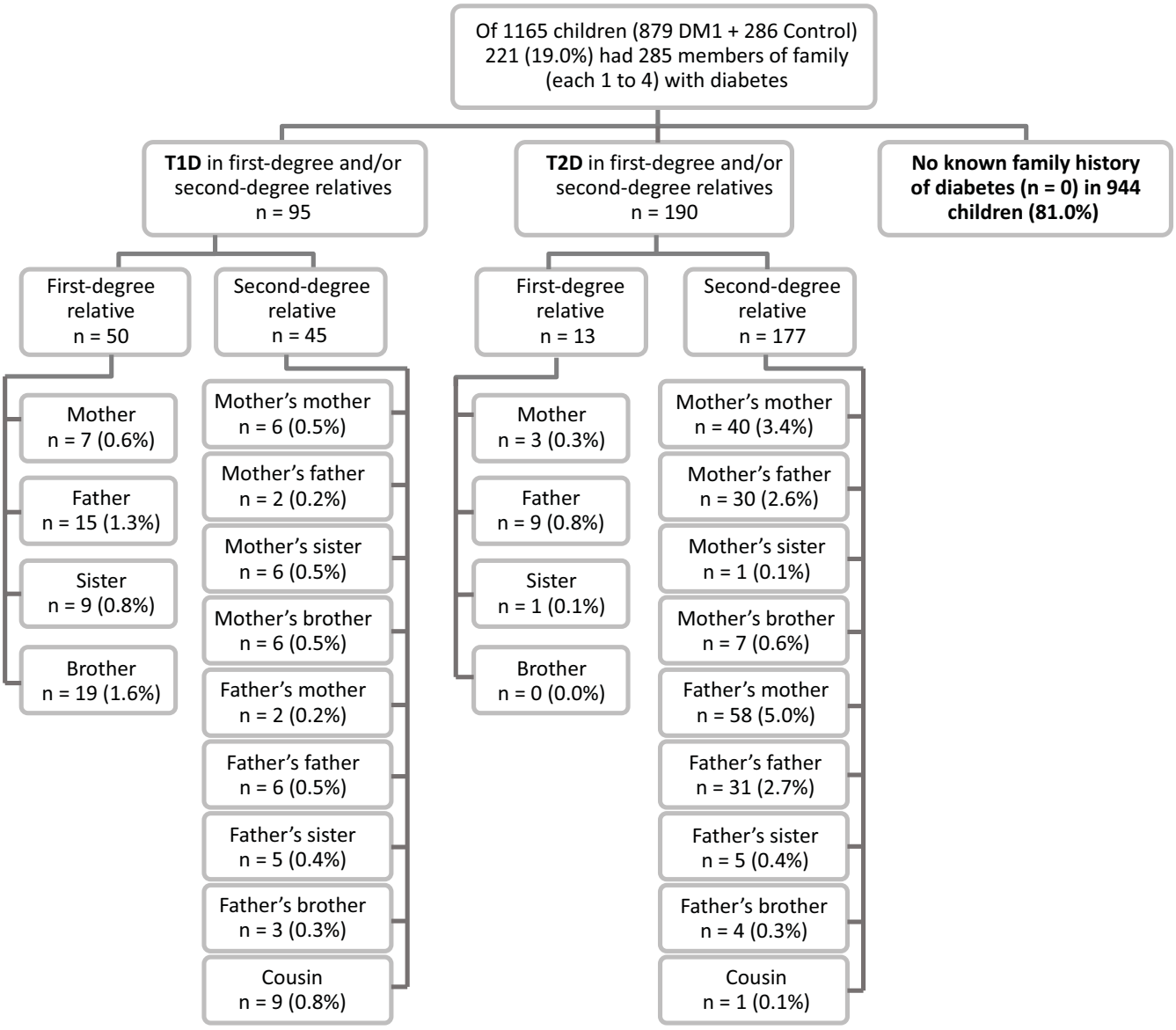

Fig. 1. Flowchart presenting the numbers (n) and proportions of participants with relatives affected by type 1 diabetes (T1D) and type 2 diabetes (T2D) in the total cohort of 1165 children

between genders (U = 91937, p = 0.224). The 286 healthy individuals in the control group consisted of 137 boys (48%) and 142 girls (50%), with gender not specified in 7 (2%) questionnaires. The gender distribution (boys compared to girls) was similar in the control group compared to the T1D group (degrees of freedom (df) = 0.412, p = 0.521).

Family history of diabetes mellitus

Of the 879 children with T1D, 109 (12.4%) had 1 family member (first- or second-degree relative) with diabetes (all types) (Fig. 2), 30 (3.4%) had 2 family members, 6 (0.7%) had 3 family members and only 1 (0.1%) had 4 family members with diabetes. In summary, 16.6% (n = 146) of children with T1D had at least 1 family member (first- or second-degree relative) affected by diabetes. Of the 286 control children, 58 (20.3%) had 1 family member (first- or second-degree relative) with diabetes (all types) (Fig. 3), 15 (5.2%) had 2 affected members and only 2 (0.7%) had 3 family members with diabetes. To sum up, 26.2% (n = 75) of children from the control group had at least 1 family member (first- or second-degree relative) with diabetes.

Family history of diabetes mellitus type 1

Of the 879 children with T1D, 69 (7.8%) had 1 family member (first- or second-degree relative) affected by T1D (Fig. 2), 4 (0.5%) had 2 such family members and only 1 (0.1%) had 3 family members affected by T1D. Overall, 8.4% (n = 74) of children with T1D had at least 1 family member (first- or second-degree relative) affected by T1D. Of the 286 children in the control group, 15 (5.2%) had 1 family member (first- or second-degree relative) affected by T1D.

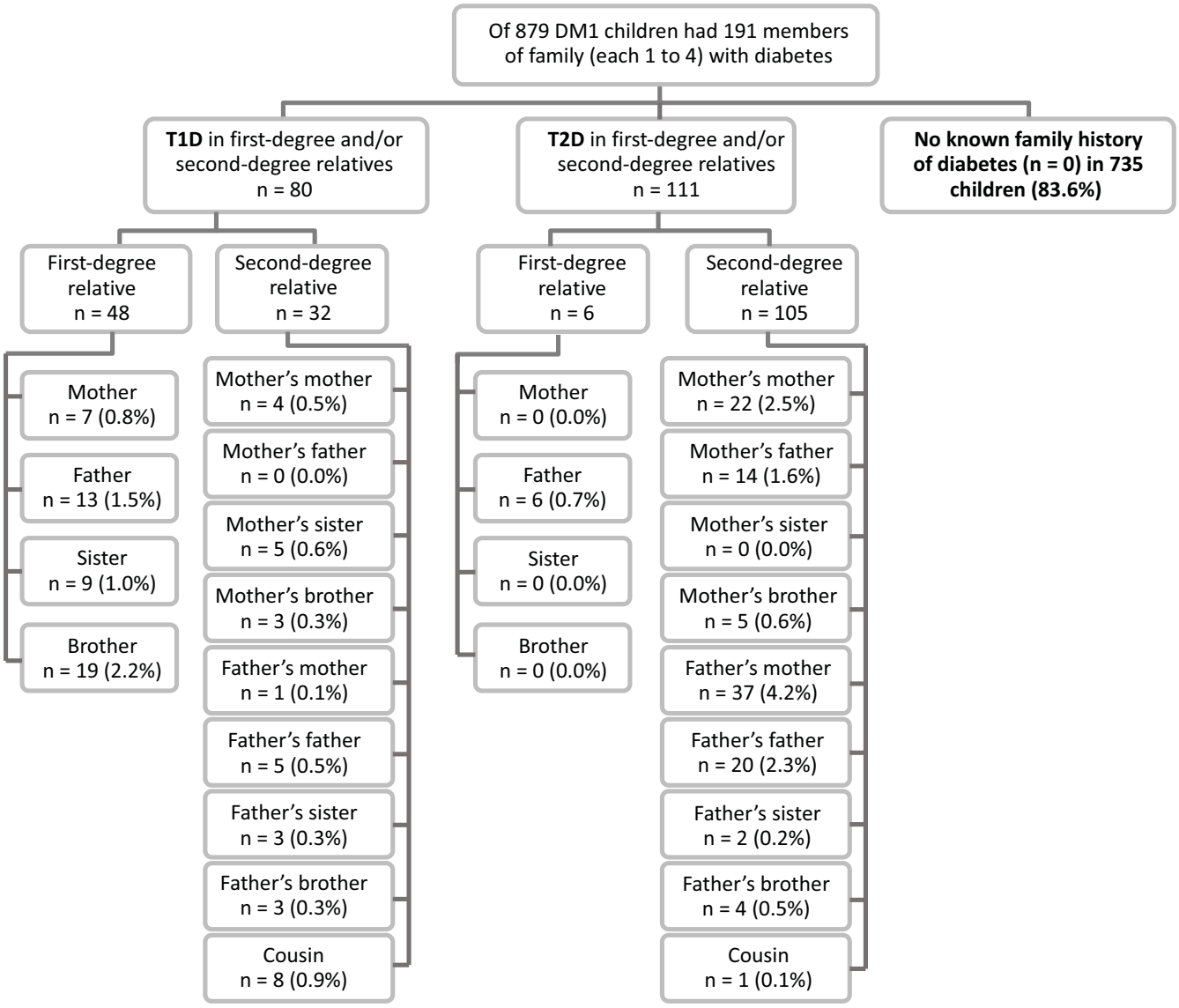

Fig. 2. Flowchart presenting the numbers (n) and proportions of participants with relatives affected by type 1 diabetes (T1D) and type 2 diabetes (T2D) in a group of 879 children diagnosed with T1D

Of the 879 T1D patients, 13 (1.5%) had a T1D father and 7 (0.8%) had an affected mother. In addition, 19 patients (2.2%) had a brother with T1D and 9 (1.0%) had an affected sister. Of the 286 children in the control group, 2 (0.7%) had a father with T1D (Fig. 3). There were no cases of affected mothers or affected siblings in this group. The incidence of T1D in first- and second-degree relatives is detailed in Fig. 2 and Fig. 3.

We observed a tendency for the nuclear family of patients with T1D to be more frequently affected by T1D (n = 74, 8.4%) than the control group (n = 15, 5.2%, OR = 1.605, 95% CI: 0.937–2.751, df = 3.081, p = 0.079). Children with T1D had parents with T1D more often (OR = 4.070, 95% CI: 1.900–8.733) than they had grandparents with T1D (df = 15.173, p < 0.001). In the control group, the numbers of parents and grandparents with T1D were similar (OR = 0.665, 95% CI: 0.065–3.747; Fisher's exact test, p = 0.726). A positive family history of T1D among first-degree relatives was more frequent (n = 48, 5.4%, OR = 8.202, 95% CI: 1.981–33.963) in the T1D group (Fisher's exact test, p < 0.001) than in the control group (n = 2, 0.7%). A positive family history of T1D among second-degree relatives was as common in the T1D group (n = 27, 3.1%, df = 1.414, p = 0.234) as it was in the control group (n = 13, 4.5%).

A positive family history of T1D among siblings was more frequent (n = 28, 19.0%, OR = 19.173, 95% CI: 1.167–315.137) in the T1D group (Fisher's exact test, p < 0.001) than in the control group (n = 0, 0%). A positive family history of T1D among brothers was more frequent (n = 19, 2.2%, OR = 12.985, 95% CI: 0.782–215.743) in the T1D group (Fisher's exact test, p = 0.006) than in controls (n = 0, 0%).

Parental family history of T1D was similar between the T1D group (Fisher's exact test, p = 0.130) and the control group, although there was a tendency for male family members of T1D children to have a more frequent positive

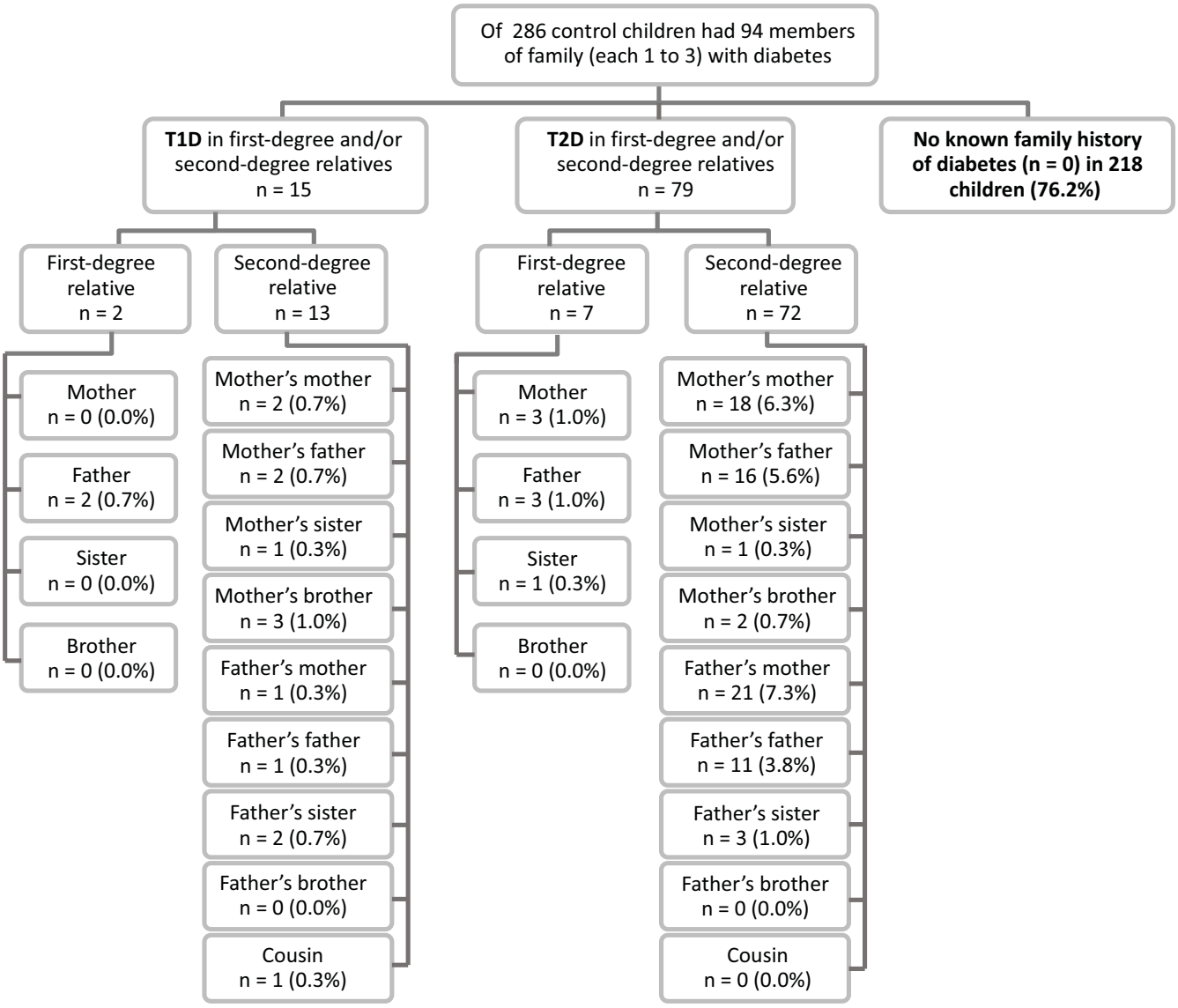

Fig. 3. Flowchart presenting the numbers (n) and proportions of participants with relatives affected by type 1 diabetes (T1D) and type 2 diabetes (T2D) in the control group (286 children).

history of T1D (df = 2.900, p = 0.089). A family history of T1D in aunts, uncles and cousins was similar in the T1D and control groups.

Family history of diabetes mellitus type 2

Among the 879 children with T1D, 53 (6.0%) had 1 family member (first- or second-degree relative) affected by T2D (Fig. 2), 21 (2.4%) had 2 such members, 4 (0.5%) had 3 members, and only 1 (0.1%) had 4 family members affected by T2D. Overall, 9.0% (n = 79) of children with T1D had at least 1 family member (first- or second-degree relative) affected by T2D. Of the 286 control children, 47 (16.4%) had 1 family member (first- or second-degree relative) affected by T2D (Fig. 3), 13 (4.5%) had 2 such family members and only 2 children (0.7%) had 3 family members affected by T2D. Overall, 21.7% (n = 62) of the children in the control group had at least 1 family member (first- or second-degree relative) affected by T2D.

Family history of T2D was more frequent in the control group (OR = 2.803, 95% CI: 1.948–4.034, df = 32.669, p < 0.001) than T1D. Grandparents with T2D were statistically more frequent than parents with T2D in both groups (OR = 5.143; 95% CI: 2.213–11.947, df =17.903, p < 0.001 for the T1D group and OR = 11.956; 95% CI: 5.067–28.211, df = 47.971, p < 0.001 for the control group). In patients with T1D and a positive family history of T2D burden among grandparents, T1D was diagnosed later (U = 24505, p = 0.018, median age (25; 75%): 107 months (77; 127)) than in patients with a negative family history of T2D (81 months (48; 124)). This finding corresponded with, among other things, decision tree (CHAID) results, which showed that the children with a positive family history of T2D among grandparents were more frequent (OR = 2.342; 95% CI: 1.153–4.755) in the older T1D diagnosis group (df = 8.785, p = 0.003) than in the younger group (84 months and below).

Family history of diabetes mellitus: comparison of diabetes types

In children with a positive family history of T2D, T1D was diagnosed later (U = 26469, p = 0.018, median age of 103 months (73.5; 126.5), n = 79) than in the group with a negative history (81 months (48; 124)). In cases with a family history of T1D, there were no such observations (U = 27512, p = 0.278; median age of 97 (49.25; 137) compared to 84 (49; 124) months).

The logistic regression model showed a significant impact of T2D scores on the chances of second-degree relatives avoiding T1D in the entire study population (F = 27.133, p < 0.001). In order to describe this phenomenon more precisely, the model included an additional T1D variable in the family member(s) burden among first-degree relatives (F = 42.867, p < 0.001; Table 2). After using a least absolute shrinkage and selection operator (LASSO) logistic regression model, the full logistic regression model included 2 variables (T2D in family member(s) burden among second-degree relatives and T1D in family member(s) burden among first-degree relatives) to assess the chance of avoiding T1D in the entire study population (Table 3,4). In the final model, children with a positive family history of T2D burden among second-degree relatives were classified more frequently by an average of 2.727 times (OR = 2.728; 95% CI: 1.880–3.962, p < 0.001) in the control group than in the T1D group, but children with a positive family history of T1D burden among first-degree relatives were classified less frequently (OR = 0.124; 95% CI: 0.030–0.516, p = 0.004) in the control group than in the T1D group.

Discussion

The results of our study confirm that a positive family history of T1D in first-degree relatives is more common in children with T1D than in healthy controls (p < 0.001). Our data show that 5.4% of children with T1D had at least 1 first-degree relative affected by T1D, which was statistically significantly higher than in the control group (0.7%). In the USA, data from the SEARCH study suggest that the risk of developing T1D in a child is 1.54 per 1000, or 0.154%.[19] The risk of developing T1D in a child is higher if one of the parents has T1D, and the risk of T1D in siblings is 6%.[20] When analyzing the immediate family members in our T1D group, 1.5% had a father with T1D, 0.8% had a mother with T1D, 2.2% had a brother with T1D, and 1.0% had a sister with T1D. It is worth emphasizing that children with a negative family history of T1D among brothers were more frequent in the control group than in the T1D group (p = 0.005). Interestingly, T1D parents were statistically more common than T1D grandparents (p < 0.001), but in the control group, the number of T1D parents and T1D grandparents was similar (p = 0.726); perhaps this is the effect of the epigenetic phenomenon of acceleration in subsequent generations.

Interestingly, male family members carry a higher risk of developing T1D. In previous studies, the risk of developing familial T1D has been reported to be more than 2 times higher in the offspring of affected fathers than in those of affected mothers. Familial T1D characteristics in first-degree relatives were investigated in children diagnosed before the age of 15 using data from an international

Table 3. Comparison of the 2 logistic regression models explaining the chance of avoiding T1D in the entire examined population (n = 1165) – before and after adding a new variable (T1D in member(s) family) to the basic model, which includes 1 variable: T2D in member(s) family burden among first-degree relatives (χ^2 test: 15.733; p = 0.001)

Statistical parameters	Model including 1 variable: T2D in member(s) family burden among second-degree relatives	Extended model with a new variable: T1D in member(s) family burden among first-degree relatives
F	27.133	42.867
p-value	<0.001	<0.001
df	1	2
R^2 Nagelkerke (goodness-of-fit measure)	0.034	0.054

T1D – type 1 diabetes; T2D – type 2 diabetes; n – number of children; F – F statistic; df – degrees of freedom.

Table 4. Restricted model in logistic regression explaining the chance of avoiding T1D in the entire examined population (n = 1165)

Parameters	B	SE(B)	95% CI for B		Wald statistic	p-value	Exp(B)	95% CI for Exp(B)	
			lower	upper				lower	upper
T2D in member(s) of the family burden among second-degree relatives	1.010	0.189	0.640	1.381	28.5407	<0.001	2.746	1.896	3.978
Constant	1.263	0.075	−1.411	−1.116	282.482	<0.001	0.283	0.244	0.328

B – regression coefficient in Wald statistic; SE(B) – standard error in Wald statistic; Exp(B) – odds ratio; 95% CI – 95% confidence interval; T2D – type 2 diabetes.

population registries network and a case-control study, and showed a positive association between the population-based incidence rate of T1D and the incidence of T1D in fathers of affected children.[21] Pooled results from all centers showed that a higher proportion of fathers (3.4%) of affected children had T1D than mothers, giving a hazard ratio (HR) of 1.8. These data are consistent with our observations (HR of 1.86 in children with T1D), although we only noticed a trend towards a higher positive history of T1D in male family members of children with T1D. The hypothesis was built suggesting that index children with an affected father may have a more aggressive disease process at diagnosis than those with other affected first-degree relatives. Moreover, the hypothesis stated that maternal insulin treatment protects against T1D. A Finnish group reported that the index children with an affected father or mother were younger than those with an affected sibling.[22] After age- and sex-adjusted analyses, index children with an affected father presented more often with ketoacidosis and exhibited more weight loss before diagnosis than those with an affected mother.

Recent data from an international study report that the risk of developing multiple autoantibodies was lower in children with maternal T1D. For the whole group, the risk of developing multiple autoantibodies was independent of birthweight but was greater in those with increased height velocity during the first 2 years of life. However, the risk associated with paternal T1D diabetes was not linked to differences in birthweight or early growth.[23] Also, Verge et al. reported that the offspring of a father with T1D were more likely to seroconvert to positivity for diabetes-related autoantibodies than the offspring of an affected mother.[24] Similarly, the risk of developing multiple islet autoantibody positivity tended to be higher in the offspring of affected fathers compared with affected mothers in the BABYDIAB study.[25] In a German study, compared with the reference population, individuals with T1D had significantly fewer children and were more often childless, and more men (51.1%) than women (35.7%, $p < 0.001$) were childless.[26] This report refutes the hypothesis that affected fathers bring T1D risk to offspring more frequently because women with T1D decide not to have children due to fears over pregnancy, its complications and defects in their offspring.

The beneficial effects of estrogen with regard to insulin action and secretion in healthy women are well known.[27] However, there is no direct data that suggest that estrogens protect against autoimmune insulitis. Moreover, estrogen's action could not explain why young, especially prepubertal male members of the family carry a higher risk of developing T1D. Rather, some genes on the Y chromosome increase the risk of T1D development. Azulay et al. demonstrated that the predominance of the HLA-DRB1*03 and DRB1*04 alleles in conferring an increased risk in a Brazilian population and being more frequently related to the ancestry of the European Y chromosome suggests that, in this population, the risk of T1D can be transmitted by European ancestors through miscegenation.[28]

Finnish data from 2013 indicate that 12.2% of T1D patients had a first-degree relative with T1D (6.2% father, 3.2% mother and 4.8% sibling) and 11.9% had a second-degree relative affected. Given an extended family history of T1D, the rate of sporadic diabetes can be reduced to less than 80%. In this cited study, a positive family history of T1D was associated with less severe metabolic decompensation at diagnosis, even if only second-degree relatives were affected. Autoantibody profiles were similar in familial and sporadic T1D diabetes, suggesting similar pathogenetic mechanisms.[29] We did not analyze the associations between a positive family history and the metabolic status of our patients at the time of diagnosis of T1D, but certainly, knowledge about the disease could help avoid metabolic decompensation when diagnosed in subsequent family members. This is the most important premise for the planned introduction of T1D screening tests in our country. Even screening for T1D among close relatives of children with T1D would play an important role, although the latest Finnish data from 2019 indicate that all clinical and metabolic variables were significantly worse in children with sporadic diabetes than familial diabetes.[22] Also, an Italian study found that children whose first- or second-degree relatives were affected by T1D had earlier disease onset and showed lower glycated hemoglobin (HbA1C) levels that were negatively associated with a positive family history of T1D, fasting C-peptide levels and some autoantibody levels. Milder metabolic decompensation in children with a positive family history of T1D is probably explained by families' awareness of early T1D symptoms, while younger age of onset and higher levels of autoantibodies may suggest greater genetic susceptibility associated with a more aggressive autoimmune process.[30] However, the latest data from the literature indicate that T1D in non-nuclear relatives is an important risk factor for islet autoimmunity and progression to clinical disease in HLA-susceptible children.[31] Therefore, national screening is important for all.

Our results are at odds with previous reports of an increased positive family history of T2D in T1D patients. In our study, 9% of children with T1D had at least 1 family member (first- or second-degree relative) affected by T2D, while 21.7% of control children had at least 1 family member affected by T2D. A 2021 Finnish study found that characteristics associated with T2D, such as increased weight, older age at diagnosis and lack of autoantibodies, are more likely to be present at T1D diagnosis in children with a positive family history of T2D. Considering the cited report, one should be aware of the clinical picture of T1D in obese children.[32] This observation is difficult to explain. Recent evidence indicates that both T1D and T2D represent a model of an immunological continuum of endotypes lying between the 2 extremes, "insulin-resistant" and "autoimmune β-cell targeting," shaped by environmental and genetic factors that contribute to determining specific immune-conditioned

outcomes.[33] However, T2D is rather associated with insulin resistance. In our study, children with a positive family history of T2D among second-degree relatives were diagnosed with T1D later than those with a negative family history ($p = 0.028$), which may suggest that insulin resistance delays the onset of autoimmune β-cell destruction. Another explanation would be that a positive family history of diabetes implies a reduction in family intake of simple carbohydrates, which may prolong the time to T1D symptom onset. This is partly in line with Wilkin's accelerator hypothesis, which assumes that the pathogenesis of both types of diabetes is related to the interaction between insulin resistance (including, i.a., an abnormal lifestyle) and genetic determinants (which are connected, especially in T1D, with autoimmune β-cell destruction).[34] However, there is no objective clinical data to support our hypothesis. The observation of a much later onset of T1D associated with a maternal history of T1D and T2D was reported by Holstein et al.[26]

Limitations

The strength of our study is the cohort of a homogenous Caucasian population of participants, almost all of whom lived within nuclear families with the same environmental risk factors of developing T1D. Compared to other studies, the weaknesses are the lack of verification of data obtained from parents/legal guardians based on medical documents.

Conclusions

Our research has shown that a family history of T1D, but not T2D, is a significant risk factor for developing T1D. The risk of T1D is associated with affected members of the immediate family and accelerates from generation to generation. It is greatest in siblings, and therefore first-degree relatives of T1D patients, especially siblings, should have priority in T1D screening. An interesting finding worthy of further studies is that male family members carry a higher risk of developing T1D.

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