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Original article

Family history of type 1 and type 2 diabetes and risk of latent autoimmune diabetes in adults (LADA)

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ABSTRACT

Background. – A family history of diabetes (FHD) is a strong predictor of diabetes risk, yet has rarely been investigated in latent autoimmune diabetes in adults (LADA). This study therefore investigated the risk of LADA and type 2 diabetes (T2D) in relation to FHD, taking into account the type of diabetes in relatives.
Methods. – Data from a population-based study were used, including incident cases of LADA [glutamic acid decarboxylase antibody (GADA)-positive, $n = 378$] and T2D (GADA-negative, $n = 1199$), and their matched controls ($n = 1484$). First-degree relatives with disease onset at age < 40 years and taking insulin treatment were classified as type 1 diabetes (T1D) or, if otherwise, as T2D. Odds ratios (ORs) were adjusted for age, gender, BMI, education and smoking. Cases were genotyped for high- and low-risk HLA genotypes.
Results. – Both FHD–T1D (OR: 5.8; 95% CI: 3.2–10.3) and FHD–T2D (OR: 1.9; 95% CI: 1.5–2.5) were associated with an increased risk of LADA, whereas the risk of T2D was associated with FHD–T2D (OR: 2.7; 95% CI: 2.2–3.3), but not FHD–T1D. In LADA patients, FHD–T1D vs FHD–T2D was associated with higher GADA but lower C-peptide levels, lower prevalence of low-risk HLA genotypes (5.0% vs 28.6%, respectively; $P = 0.038$) and a tendency for higher prevalence of high-risk genotypes (90.0% vs 69.1%, respectively; $P = 0.0576$).
Conclusion. – The risk of LADA is substantially increased with FHD–T1D but also, albeit significantly less so, with FHD–T2D. This supports the idea of LADA as a mix of both T1D and T2D, but suggests that the genes related to T1D have greater impact. LADA patients with FHD–T1D had more T1D-like features, emphasizing the heterogeneity of LADA.

Introduction

A family history of diabetes (FHD) encompasses both genetic and shared environmental factors, and is a strong predictor of diabetes risk. Previous studies have indicated that diabetes in first-degree relatives confers a ninefold greater risk of type 1 diabetes (T1D) [1] and a threefold greater risk of type 2 diabetes (T2D) [2]. The genetic risk of T1D is mainly attributed to genes in the human leucocyte antigen (HLA) region, which are estimated to

Abbreviations: ANDIS, All New Diabetics in Scania; ANDiU, All New Diabetics in Uppsala; ESTRID, Epidemiological Study of Risk Factors for LADA and Type 2 Diabetes; FHD-T1D, Family history of type 1 diabetes; FHD-T2D, Family history of type 2 diabetes; GADA, Glutamic acid decarboxylase antibody; HLA, Human leucocyte antigen; LADA, Latent autoimmune diabetes in adults.

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explain around 30–50% of familial clusterings [3]. Recent studies have identified several genes related to T2D, of which variants within the *TCF7L2* gene have the strongest effect [4]. The currently identified genes, however, can only explain about 20% of the genetic heritability of T2D [5] and only a fraction of its familial aggregation [2]. Therefore, FHD remains an important, easily obtained predictor of diabetes risk [2].

Latent autoimmune diabetes in adults (LADA) is thought to be a genetic mix of both T1D and T2D [6], and linked to HLA *DQB1* risk genotypes associated with autoimmunity [7,8] as well as genes associated with T2D, including *TCF7L2* [9–11]. Consequently, a family history of both type 1 diabetes (FHD–T1D) and type 2 diabetes (FHD–T2D) may promote LADA. Findings from prospective data indicate that FHD increases LADA risk two- to fourfold [12,13], while cross-sectional studies also reveal a high prevalence of FHD [14,15]. While studies of the relative importance of FHD–T1D *vs* FHD–T2D are scarce, data from a few small-scale studies support links to both T1D and T2D [16–20]. Also, in a prospective follow-up study of a non-diabetic population, FHD–T1D conferred a twofold greater risk of developing non-insulin-dependent diabetes [13].

Our aim was to clarify the role of FHD–T1D and FHD–T2D in relation to LADA and T2D. To this end, data were taken from a novel Swedish population-based study to create the largest study to date of FHD and LADA.

Methods

Study population and design

The present study used data from the Epidemiological Study of Risk Factors for LADA and Type 2 Diabetes (ESTRID), a population-based study including incident cases. A detailed description of the study design has been previously reported [21]. Briefly, ESTRID is a substudy of ANDIS (All New Diabetics in Scania) [22], a detailed study aiming to characterize all new cases of diabetes in the Swedish county of Scania. For ESTRID, all newly diagnosed LADA patients and a random sample of newly diagnosed T2D cases (four per each LADA case) were invited to participate from 2010 onwards. For each case of LADA, six diabetes-free controls, aged $\geq$ 35 years (to match the definition of LADA), were randomly selected from the general population of Scania, and matched by time and region (incidence density sampling) [23]. After 2012, cases and controls were also recruited from Uppsala county through ANDiU (All New Diabetics in Uppsala) [24], a sister study to ANDIS. Response rate was high: 80% *vs* 64% for cases *vs* controls, respectively. Thus, the analytical sample of the present study included 378 cases of LADA, 1199 cases of T2D and 1484 controls—all of the participants included in ESTRID up to 31 July 2015—with complete information on their age, gender, FHD, body mass index (BMI), education and smoking (99.5% of the total sample).

The study was approved by the ethics review board in Stockholm (reference number: 2010/336-31/2), and all participants provided their written informed consent.

Biochemical analysis and case definition

At diagnosis, all patients provided blood samples, which were analyzed for glutamic acid decarboxylase antibody (GADA), C-peptide and glucose at the central laboratories of the university hospitals of Scania and Uppsala. GADA was analyzed in serum by enzyme-linked immunosorbent assay (ELISA; RSR Ltd, Cardiff, UK). Levels $\geq$ 10 IU/mL were regarded as positive, as per instructions in the kit. At a cut-off level of 10.7 IU/mL, sensitivity was 84% and specificity 98% [25]. Fasting (overnight) levels of C-peptide in plasma were measured by an IMMULITE 2000 (Siemens Healthcare Diagnostics Product Ltd., Caernarfon, UK) or Cobas e 601 (Roche Diagnostics, Mannheim, Germany) analyzer [26]. LADA patients had onset at age $\geq$ 35 years, were GADA-positive ($\geq$ 10 IU/mL) and had C-peptide levels above the lower limit of normal range [$\geq$ 0.2 nmol/L (IMMULITE) or $\geq$ 0.3 nmol/L (Cobas e 601)]. T2D patients had onset at age $\geq$ 35 years, were GADA-negative and had C-peptide levels $>$ 0.6 nmol/L (IMMULITE) or $>$ 0.72 nmol/L (Cobas e 601). While there is no established definition of LADA, this is in line with previously used criteria [6] except for C-peptide, which was used as an indicator of any remaining insulin production. This criterion distinguished LADA patients from those with adult-onset T1D (C-peptide $<$ 0.2 or 0.3 nmol/L), who were not recruited into ESTRID. C-peptide may be regarded as a more objective measurement than the more commonly used insulin criteria [27].

Homoeostasis model assessment (HOMA) was used to assess insulin resistance (HOMA-IR), insulin sensitivity (HOMA-S) and β-cell function (HOMA-β), based on the relationship between fasting glucose and C-peptide [28]. DNA was extracted and genetic analyses were performed at the central laboratory in Scania by running the iPLEX Gold Assay (Sequenom Inc, San Diego, CA, USA). As per the previously described methodology [29], three single-nucleotide polymorphisms (SNPs) in the MHC region (rs3104413, rs2854275, rs9273363) were combined to identify carriers of the high- and low-risk HLA *DR* and *DQ* genotypes known to be associated with autoimmune diabetes (*DR3/4, DR3/3, DR4/4, DR3/X, DR4/X, DR4-DQ7, DR4/3-DQ8, DR4-DQ8, DRX/X*), where the greatest risk of T1D is found in subjects heterozygous for these types [29,30]. Genetic information was available for 70.1% of LADA cases and 68.6% of T2D cases. No genetic and clinical information was available for the controls.

Questionnaire

Cases and controls answered an extensive questionnaire with items on heredity, previous health, and lifestyle and demographic socioeconomic and psychosocial factors. Cases were given the questionnaire following diagnosis (within a median time of 6 months), and were carefully instructed to report conditions as they were prior to diagnosis.

Family history of diabetes

Information on FHD entailed questions on diabetes in first-degree relatives (mother, father, sisters, brothers, daughters, sons) as well as in maternal and paternal grandparents. Also, the questionnaire asked about the total number of other, second-degree relatives (grandchildren, aunts, uncles, nephews, nieces) and first cousins with diabetes. (This report included first cousins as second-degree relatives as they could not be distinguished from other relatives.) For first-degree relatives, information on age at diagnosis and modalities of treatment were also obtained. Relatives were classified as FHD–T1D if they had onset at age $<$ 40 years and were taking insulin treatment or, if otherwise, as FHD–T2D.

Covariates

Self-reported information on current body weight together with height was used to calculate BMI (kg/m^2). For these patients, this information correlated significantly with information from medical records (r = 0.92). Information on smoking was obtained through questions about current and previous tobacco use, and included duration and average number of cigarettes smoked per day. Physical activity was assessed by validated questions about leisure-time physical activity during the preceding year [31].

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