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ORIGINAL DATA

German New Onset Diabetes in the Young Incident Cohort Study: DiMelli Study Design and First-Year Results

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■ Abstract

BACKGROUND: Diabetes incidence in childhood and youth is increasing worldwide, including autoimmune and non-autoimmune cases. Recent findings suggest that there is a larger than expected proportion of type 2 diabetes in youth, and potential cases of intermediate diabetes phenotypes. Most pediatric diabetes registries focus on type 1 diabetes. Also, there is an absence of reliable data on type 2 diabetes incidence in youth. **AIMS**: The DiMelli study aims to establish a diabetes incidence cohort registry of patients in Germany, diagnosed with diabetes mellitus before age 20 years. It will be used to characterize diabetes phenotypes by immunologic, metabolic, and genetic markers. DiMelli will assess the contribution of obesity and socio-demographic factors to the development of diabetes in childhood and youth. **METHODS**: Recruitment of patients started in 2009, and is expected to continue at a rate of 250 patients per year. **RESULTS**: 84% of the 216 patients recruited within the first year were positive for multiple islet autoantibodies, 12% for one islet autoantibody, and 4% were islet autoantibody-negative. Patients with multiple islet autoantibodies were younger and had lower fasting C-peptide levels, compared to islet autoantibody-negative patients (median age 10.0 vs. 14.1 years, $p < 0.01$). **CONCLUSIONS**: Results from the first year of the study show that DiMelli will help to reveal new knowledge on the etiology of diabetes, and the contribution of genetic predisposition and environmental risk factors to the different types of diabetes.

Keywords: type 1 diabetes · type 2 diabetes · diabetes registry · epidemiology · classification · identification · youth

Introduction

Worldwide, the incidence of diabetes in youth is increasing [1-3]. Below age 20 years, the majority of incident cases is of type 1 diabetes (T1D). However, findings from the SEARCH study indicate that there is a larger than expected proportion of type 2 diabetes (T2D); and potentially, there are cases of mixed T1D/T2D phenotype [4]. SEARCH showed that T2D occurs predominantly in high-risk ethnic groups in the US; but even among non-Hispanic whites above age 10 years, 14.9% of all diabetes cases were T2D. It is believed that there are overlaps in some aspects of T1D and T2D. Novel hypotheses have been proposed, suggesting that impaired insulin action (insulin resistance), and *a priori* impaired beta-cell function, may contribute to the development of islet autoimmunity and T1D [5-7]. This is supported by data showing that higher body weight is related to earlier age of diabetes onset [8-10], and that insulin resistance (calculated by HOMA-IR) is a risk factor for accelerated T1D progression in autoantibody-positive relatives [11-13].

Therefore, incidence monitoring, together with collection of detailed clinical and laboratory data, has become fundamental to correctly evaluate diabetes trends in youth, to ascribe optimal treatment to different cases, and to predict future trends and public health needs [14, 15]. Germany has a few isolated registries for monitoring diabetes incidence, but these are limited to patients diagnosed with T1D up to age 14 years, and do not collect patient material for standardized laboratory measurements [16-18]. Similar to SEARCH for the USA [19], the DiMelli study aims to establish a registry of patients diagnosed with diabetes mellitus below age 20 years, in Bavaria, Germany. The registry will be used to characterize diabetes phenotypes by immunologic, metabolic, and genetic markers. A number of sample collections and measurements, including the measurement of islet autoantibodies, have been harmonized to SEARCH [20]. Additional to SEARCH, the DiMelli study collects blood samples for the isolation and storage of peripheral blood mononuclear cells designated for cell-mediated immunity studies.

Abbreviations:
aab - autoantibody
ADA - American Diabetes Association
DiMelli Study - Diabetes Mellitus Incedence Cohort Study
EDTA - ethylenediaminetetraacetic acid
GADA - antibodies to glutamic acid decarboxylase 65
HbA1c - glycated hemoglobin
HDL/LDL - high/low-density lipoprotein
HLA - human leukocyte antigen
HOMA-IR - homeostasis model assessment of insulin resistance
IAA - insulin autoantibody
IA-2A - antibodies to insulinoma-associated protein 2
INS VNTR - insulin variable number of tandem repeats
KVB - Kassenaerztliche Vereinigung Bayerns (lit. Association of Statutory Health Insurance Physicians of Bavaria)
MODY - maturity onset diabetes of the young
SEARCH Study - Search for Diabetes in Youth Study
SNP - single-nucleotide polymorphisms
T1D/T2D - Type 1/2 Diabetes
TGCA - antibodies to transglutaminase C
TPOA - antibodies to thyroid peroxidase
WHO - World Health Organization
ZnT8A - antibodies to zinc transporter 8

Study objectives

The DiMelli study objectives are to determine incidence trends, and phenotype changes of T1D and T2D diabetes, and to identify mixed/overlapping diabetes syndromes in childhood and adolescence. This will be achieved by establishing a representative prospective model diabetes incidence cohort for Germany, with detailed standardized characterization of autoimmunity, T1D and T2D associated genotypes, beta-cell function, and lipid metabolism. Furthermore, the study aims to improve diabetes therapy, and eventually reduce long term complications through refined classification and awareness of intervention trials. It is planned to integrate follow-up data on diabetes outcome to assess the relevance of diabetes phenotype on diabetes control and outcome. The principal research questions are:

1. What are incidence rates and trends for autoimmune and non-autoimmune diabetes below age 20 years in Germany?
2. What are the immunologic and metabolic characteristics of different diabetes types?
3. What is the prevalence of overweight, obesity, and insulin resistance in children and adolescents with respect to diabetes phenotype in Germany?
4. What is the contribution of T1D and T2D associated genotypes to risk for autoimmune and non-autoimmune diabetes below age 20 years?
5. What are the socio-economic factors in Germany that are associated with diabetes in children and adolescents?
6. Is the biomarker defining diabetes phenotype associated with short term diabetes outcome?

We expect that this project will be a model for research, clinical, and public health interaction and translation in Germany.

Study population

This study is a population-based incidence cohort study of children and adolescents with recent onset of any type of diabetes mellitus. Diagnosis of diabetes must meet the criteria developed by ADA/WHO [21]. The cohort comprises of children and young adults below age 20 years at diabetes onset, who are registered within six months after diagnosis, and who are residents of Bavaria, Germany. Patients are recruited by physicians in pediatric hospitals, and primary care practicioners mainly specialized in diabetology throughout Bavaria. Each patient, and/or parent, must sign an informed consent to participate.

Study organization

The DiMelli study is part of the German Competence Network Diabetes Mellitus [22], and is a

collaboration between the Forschergruppe Diabetes (Diabetes Research Group), Klinikum rechts der Isar (lit. Hospital on the right hand side of the river Isar), Technical University of Munich, and the Kassenaerztliche Vereinigung Bayerns (KVB, lit. Association of Statutory Health Insurance Physicians of Bavaria).

The incident cases are obtained state-wide involving all pediatric hospitals and primary care practicioners specialized in diabetology. Thus, about 90% of all new diabetes cases in this age group are covered. Registration includes completion of a questionnaire, and obtaining a blood sample (fasting in children aged 3 years and older). Questionnaires and material for collecting blood samples are provided to the local health care provider. Results of autoantibody status and fasting C-peptide are provided to the patient's local physician. The central laboratory and sample repository is at the Forschergruppe Diabetes in Munich. The database with data from pseudonymized questionnaires is coordinated by the KVB. The study was approved by the ethical committee of Bavaria, Germany (Bayerische Landesaerztekammer, #08043). Recruitment of patients started in 2009, and is planned to continue for at least 10 years. A rate of 250 registered patients per year is expected.

Data items to be analyzed

Information about clinical onset and demographics is obtained by a structured questionnaire completed by the local physician. The questionnaire includes:

- Diagnosis of diabetes
- Duration of symptoms
- Weight loss prior to diagnosis
- Ketoacidosis
- Current medication
- Known autoimmune diseases associated with diabetes
- Family history of diabetes
- Demographic factors (parent nationality, level of education)

Weight, height, waist, and hip circumference, as well as blood pressure and tanner stages, are assessed at the clinical site by trained staff. Fasting glucose is measured at the clinical site.

A fasting venous blood sample is obtained by the local physician, and sent to the central laboratory at the Forschergruppe Diabetes by overnight express. Samples are processed into serum, plasma, peripheral blood mononuclear cells, and DNA.

The blood sample is analyzed centrally for the following parameters:

1. Autoantibodies to insulin (IAA), glutamic acid decarboxylase (GADA), insulinoma-associated protein 2 (IA-2A), and zinc transporter 8 (ZnT8A)
2. Autoantibodies to tissue transglutaminase C (TGCA) and thyroid peroxidase (TPOA)
3. Fasting C-peptide and insulin
4. Glycated hemoglobin A1c (HbA1c)
5. Triglycerides, total cholesterol, HDL, LDL
6. Genotyping for HLA DR/DQ, INS VNTR, MODY, and single-nucleotide polymorphisms (SNP) associated with T1D and T2D

Peripheral blood mononuclear cells for studies of autoreactive T cells, and additional serum, and plasma, are stored at a biobank of the Forschergruppe Diabetes in Munich. The diabetes-associated autoimmune response is characterized in detail using NIDDK standardized methods for GADA and IA-2A [20], highly sensitive methods for IAA, the novel ZnT8A, and sub-specificities of these four antibodies, as previously described [23-25]. To detect TPOA that is associated with autoimmune thyroiditis, a direct radiobinding assay is performed according to the manufacturer's instructions (CentAK anti-TPO, Medipan, Dahlewitz/Berlin, Germany), as described previously [26]. Also as previously described, radiobinding assay is used to measure celiac disease-associated IgA TGCA [27]. Fasting C-peptide and insulin concentrations are measured in aprotinin-stabilized EDTA plasma samples using an automated immunoassay analyzer (AIA 360, Tosoh, San Francisco, CA, USA). Genotyping is carried out using the Illumina Human Linkage-12 Genotyping Beadchip, which contains 6,090 single nucleotide polymorphisms, as described [28, 29]. Data on body mass index (BMI) is adjusted for gender and exact age at examination. BMI is expressed as the BMI percentile [30], with reference to national data provided by the study group Adipositas im Kindes- und Jugendalter (Adiposity in Childhood and Youth) [31].

Data management and analysis

Pseudonymized clinical data from questionnaires are entered into a database. Diabetes phe-

notypes are characterized by autoantibody pattern, beta-cell function, insulin resistance, lipid status, BMI, and genotypes associated with T1D, T2D, or MODY.

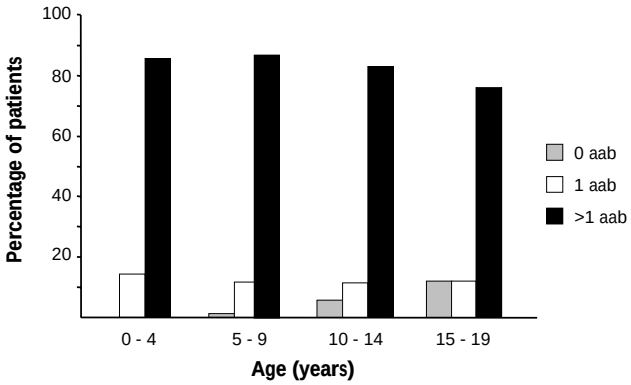

Figure 1. Islet autoantibody frequency in different age groups. The figure shows the prevalence of single (1 autoantibody, white bars) and multiple (>1 autoantibody, black bars) islet autoantibodies, and the frequency of children without antibodies (0 autoantibodies, grey bar). aab: autoantibody.

Based on autoantibody data, diabetes cases are described as autoimmune, non-autoimmune, and intermediate. For each of the autoimmune, non-autoimmune, and intermediate groups, the clinical and laboratory data with respect to age, beta-cell reserve, insulin resistance, other autoimmunity, BMI, genotypes, and demographics are described, and compared using parametric or non-parametric tests, as appropriate. Autoantibody profiles, including detailed characterization of subspecificities, are compared by age, HLA genotype, and properties of intermediate and autoimmune diabetes cases. Measurements relative to insulin action, obesity, and lipid metabolism help to define the phenotype (T1D, T2D, or intermediate) on the basis of standard laboratory and clinical parameters. Also, these measurements provide a baseline description of beta-cell function and lipids at diabetes diagnosis in Germany.

Trends in diabetes incidence are assessed by Poisson regression for the total diabetes cases and for the autoimmune, non-autoimmune, and intermediate cases. The study is designed to reveal any increase in the order of 7%, or greater, with a power of 80% at a bilateral test on significance level of 5% (alpha = 5%). This requires a study population of at least 1,500 children.

Preliminary results from the first year of DiMelli

Of 216 patients recruited in 2009, 84% were classified as autoimmune diabetes (multiple islet autoantibody positive), 4% as non-autoimmune diabetes (islet autoantibody-negative), and 12% as intermediate cases (positive to one islet autoantibody). The prevalence of multiple islet autoantibodies was highest in children below 15 years of age. Non-autoimmune cases were more frequent in adolescents over age 10 years (Figure 1). The prevalence of IAA decreased with age at onset. It was highest in children below 4 years, and lowest in adolescents over age 15 years (96% vs. 29%, $p < 0.01$). Frequencies of GADA, IA-2A, and ZnT8A were similar in all age groups. TGCA (celiac disease) were positive in 11%, and TPOA (autoimmune thyroiditis) in 6% of patients.

Patients tested positive for multiple autoantibody were younger (median age 10.0 vs. 14.1 years, $p < 0.01$), and had lower fasting C-peptide levels (median C-peptide 1.2 nmol/l vs. 2.1 nmol/l, $p < 0.01$) than autoantibody-negative patients. Fasting C-peptide levels were age-dependent, and were lower in younger patients ($p < 0.01$, Figure 2). Patients with autoimmune diabetes had a lower BMI percentile at onset than patients with intermediate, or non-autoimmune, diabetes (median BMI percentile 18 vs. 43 vs. 69, $p < 0.01$).

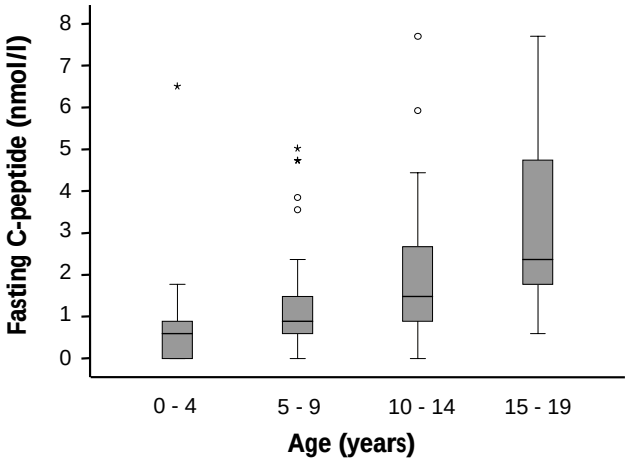

Figure 2. C-peptide in different age groups. C-peptide levels correlate positively with age at diabetes onset ($r = 0.49$, $p < 0.01$). The boxes indicate lower quartile, median, and upper quartile. Whiskers indicate lowest or highest data within 1.5 inter quartile range (IQR). Median C-peptide levels in nmol/l in children and adolescents were 0.6 (0-4 years), 0.9 (5-9 years), 1.5 (10-14 years), and 2.4 (15-19 years).

Discussion

First-year study results show that the DiMelli study provides an intense characterization of diabetes phenotypes at onset in youth at an immunological, metabolic, and genetic level. This will help to generate new hypotheses about the etiology of diabetes, and the contribution of genetic predisposition and environmental risk factors to the disease. Establishing a biobank of sera and peripheral blood mononuclear cells of a large cohort of diabetes patients will facilitate future hypothesis testing, and will permit comparison of German incident cases to other national registries.

First results from DiMelli indicate that the majority of incident cases in Bavaria have autoimmune diabetes (positive for multiple islet autoantibodies). The data also confirm previous findings from other studies, suggesting a positive correlation between fasting C-peptide levels and age at diabetes onset. Possibly, this reflects a more aggressive beta-cell destruction, and a higher rate of metabolic decompensation in younger patients [8, 19, 32, 33].

The increasing incidence of diabetes in youth, and the relationship to global increases in body weight and obesity, necessitate early implementation of measures to halt these trends. This is particularly important in Germany where obesity was recently reported to be at world peak levels [34-36]. This study will provide new knowledge to scientists and planning bodies, as well as feedback to health care workers and patients. Performing the study will provide Germany with realistic prognoses for diabetes trends according to diabetes phenotypes. Also, it will inform the changes needed to health and governmental policies to improve therapy, and to halt the upward incidence rates.

The results of this project will have an important impact on clinical practice in Germany, with improved communication between ambulatory and clinical health care services. Since study findings will be reported to practicing doctors, this should improved diabetes awareness, and contribute to proper treatment in clinical health care service. The standardized classification should result in more appropriate treatment of patients, which in turn, should reduce future complications. More intense interaction between public health care and clinical science will increase recruitment of patients and their family members into clinical trials of diabetes reversal, or prevention. With respect to pathogenesis, the study will contribute to our understanding of the contribution of T2D risk factors for diabetes diagnosed in the German population under age 20 years.

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