Comorbidity of Type 1 Diabetes and Juvenile Idiopathic Arthritis

Gerhard Hermann, MA[1], Angelika Thon, MD[2], Kirsten Mönkemöller, MD[3], Eggert Lilienthal, MD[4], Christof Klinkert, MD[5], Martin Holder, MD[6], Thomas Hörtenhuber, MD[7], Petra Vogel-Gerlicher, MD[8], Holger Haberland, MD[9], Martin Schebek, MD[10], and Reinhard W. Holl, MD, PhD[1], on behalf of the Diabetes Patienten Verlaufsdokumentation-initiative and the Federal Ministry of Education and Research Competence Network Diabetes Mellitus*

Objective To analyze the prevalence of juvenile idiopathic arthritis (JIA) and diabetes end points in pediatric patients with type 1 diabetes.

Study design Patients with type 1 diabetes, recorded from 1995 up to September 2013 in the Diabetes Patienten Verlaufsdokumentation database (n = 54 911, <16 years of age, 47% girls), were analyzed. The patients' height, weight, and body mass index SDS, glycosylated hemoglobin A1c (HbA1c); insulin dose; hypertension and dyslipidemia prevalence; rate of hypoglycemic events; and ketoacidosis were compared between patients with and without JIA. To adjust for age, sex, diabetes duration, and migration background, data were analyzed in hierarchic multivariable regression models.

Results The prevalence of JIA in type 1 diabetes was 106 of 54 911 patients; 66% were girls. Diabetes onset was earlier in children with JIA (7.2 years vs 8.3 years, $P = .04$). Children with JIA were smaller (SDS: −0.22 vs 0.09, $P = .004$). Correspondingly, weight SDS was lower in patients with JIA (−0.02 vs 0.22, $P = .01$). Body mass index SDS did not differ. HbA1c was marginally lower in children with JIA (63 mmol/mol [8.0%] vs 67 mmol/mol [8.3%], $P = .06$). Insulin requirement was greater in patients with JIA (1.03 vs 0.93 insulin units/weight/day, $P = .003$). Hypertension and dyslipidemia were comparable in both groups.

Conclusions The JIA-prevalence in patients with type 1 diabetes (0.19%) was considerably greater than in the general population (0.05%). Growth is influenced negatively by JIA. Surprisingly, HbA1c was somewhat lower in children with JIA, possibly because of a more intensive treatment or a latent hemolysis caused by the inflammation. *(J Pediatr 2015;166:930-5)*.

Type 1 diabetes mellitus is known to be associated with juvenile idiopathic arthritis (JIA), autoimmune thyroiditis (AIT), and celiac disease (CD).[1-3] Reports describing the comorbidity of type 1 diabetes and JIA in larger cohorts are rare.[3-5] JIA is the most common chronic arthritis in childhood and encompasses heterogeneous forms of chronic arthritis. Worldwide, the prevalence of JIA varies significantly (7-400 of 100 000 children).[6] Reported differences in the prevalence and incidence resulted mainly from different diagnostic and classification criteria, as well as regional variation.[6] Fifteen years ago, the prevalence was reported to be 15-20 of 100 000 German children, with girls (18-23 of 100 000) more frequently affected than boys (13-17 of 100 000).[7,8] Today, the prevalence is estimated up to 100 of 100 000 children.[9,10] Worldwide, AIT was reported to be present in 7%-40% and CD in 1%-16% of children and adolescents with type 1 diabetes.[11-13]

It is known that autoimmune diseases frequently occur in type 1 diabetes patients.[1-3,14,15] However, little information on the clinical data and the prevalence of JIA in subjects with type 1 diabetes based on larger populations are available. One goal of the present study was to determine the prevalence of JIA in Germany and Austria in a large number of children and adolescents with type 1 diabetes. We hypothesized that in patients with type 1 diabetes with JIA, anthropometry is affected by the comorbid rheumatic disease. Patients with JIA may be smaller than patients without JIA. Diabetes treatment also may differ between patients with or without the rheumatic disease. A greater prevalence of JIA in females was reported in studies analyzing smaller

AIT	Autoimmune thyroiditis
BMI	Body mass index
CD	Celiac disease
HbA1c	Glycosylated hemoglobin A1c
JIA	Juvenile idiopathic arthritis

From the [1]Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm, Ulm; [2]Department of Pediatric Pneumology, Allergology & Neonatology, Children's Hospital, Hanover Medical School, Hanover; [3]Children's Hospital, Hospitals of the City of Cologne, Cologne; [4]Department of Pediatrics, Ruhr University of Bochum, Bochum; [5]Pediatric Practice, Herford; [6]Department of Pediatric Endocrinology and Diabetology, Olgahospital, Stuttgart Clinical Center, Stuttgart, Germany; [7]Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria; [8]German Center for Pediatric and Adolescent Rheumatology with Center for Social Pediatrics, Garmisch-Partenkirchen; [9]Hospital for Children and Adolescents, Sana Hospital Lichtenberg, Berlin Lichtenberg; and [10]Department of Pediatrics and Adolescent Medicine, Kassel Clinical Center, Kassel, Germany

*List of participating centers of the Diabetes Patienten Verlaufsdokumentation-initiative and the Federal Ministry of Education and Research Competence Network Diabetes Mellitus is available at www.jpeds.com (**Appendix 1**).

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populations.[7,8] On the basis of data from a large registry in the present study, we investigated whether sex differences exist between children and adolescents with and without JIA.

Methods

Since 1995 standardized longitudinal data are recorded in the diabetes data acquisition system for prospective surveillance (Diabetes Patienten Verlaufsdokumentation).[16] In diabetes health care centers, which used the Diabetes Patienten Verlaufsdokumentation software, all data were entered by physicians, nurses, or other staff members. The centers exported anonymized data and sent them twice a year to the Institute of Epidemiology and Medical Biometry at the University of Ulm, Germany, for aggregated cumulative central analysis. Implausible and inconsistent data were sent back for verification and correction. The ethics committee of the University of Ulm approved analysis of anonymized DPV data.

Data of 54 911 patients with type 1 diabetes mellitus, who were younger than 16 years of age, were analyzed. In this observational study, based on information from the Diabetes Patienten Verlaufsdokumentation registry, 330 centers (308 in Germany, 22 in Austria) participated in the prospective data collection from 1995 up to September 2013. The selection of the study population can be seen in a flow chart (**Figure 1**; available at www.jpeds.com).

The measurements herein from each patient's recent treatment year were extracted from Diabetes Patienten Verlaufsdokumentation. Height and weight were measured, and body mass index (BMI) was calculated. To compare height, weight, and BMI values, the age- and sex-adjusted SDS was determined with contemporary national reference values.[17] A patient had a migration background if either the patient or at least one parent was not born in Germany or Austria. Glycemic control was assessed by glycosylated hemoglobin A1c (HbA1c). Each patient's aggregated HbA1c of the last treatment year was used. To adjust for possible differences between participating centers, HbA1c was standardized to the Diabetes Control and Complication Trial Research Group reference range of 4.05%-6.05% (International Federation of Clinical Chemistry and Laboratory Medicine: 20-42 mmol/mol) by applying the multiple of the mean method.[13] Values are displayed in percent and mmol/mol. The number of blood glucose self-measurements per week and the insulin dose per kilogram and day were self-reported by the children and adolescents, their parents, or caregivers.

Blood pressure was measured after current guidelines and hypertension was defined by increased systolic and/or diastolic blood pressure (>95th percentile),[18] or when patients used antihypertensive drugs. Blood lipids were evaluated in comparison with national reference values.[19] Dyslipidemia was defined by the use of lipid-lowering medication and/or by increased values of one or several blood lipids. Cut-off values for blood lipids were as follows: total cholesterol >200 mg/dL, high-density lipoprotein cholesterol <35 mg/dL, low-density lipoprotein cholesterol >130 mg/dL, and triglycerides >150 mg/dL.

Acute metabolic complications, such as severe hypoglycemia (help of another person needed or coma) and ketoacidosis (admission with blood pH less than 7.3), were recorded as number of incidences per year.

To select patients with JIA, the Diabetes Patienten Verlaufsdokumentation database was searched for the diagnosis and/or therapy of JIA as comorbidity with search terms and *International Classification of Diseases, 10th revision* codes according to current guidelines.[20] Terms for the diagnosis were "JIA," "JRA," "JCA," "(systemic) idiopathic arthritis," "SJIA," "rheumatoid/chronic arthritis," "Still's disease," "oligoarthritis," "polyarthritis," "psoriatic arthritis/JIA," "enthesitis-related arthritis/JIA," "articular/joint rheumatism," "ankylosing spondylitis," "monoarthritis," and *International Classification of Diseases, 10th revision* codes M05, M08, and M45. Search terms for disease-modifying antirheumatic drugs or common biologics were additionally applied (**Appendix 2**: list of drugs). When a patient was found only through treatment search terms, his or her records were reviewed to rule out that the medication was used because of another disease. Such cases were excluded from the analysis.

AIT was ascertained when patients were diagnosed with Hashimoto thyroiditis, or if positive thyroid antibodies (thyroid peroxidase antibodies, antithyroglobulin antibodies) greater than 100 U/mL were detected. Patients had CD when confirmed by biopsy.

Insulin therapy was classified according to the reported injection frequency per day. Conventional therapy was ascertained when 1-3 injection time points per day were documented. An intensified conventional therapy was determined if more than 3 injection time-points per day were recorded. The documentation of continuous subcutaneous insulin infusion corresponded to pump-therapy.

Data were analyzed with SAS 9.3 (SAS Institute Inc, Cary, North Carolina). To compare groups, Kruskal-Wallis test was used for continuous variables and χ^2; test for dichotomous variables. To compare event rates, a Poisson distribution was assumed. Missing data were not imputed. Data analysis was conducted in regression models (SAS proc glimmix). Regression models were created to adjust for differences in age, sex, diabetes duration, and migration background (in the model for "age at diabetes onset," diabetes duration was not included; in all sex-stratified models, sex was not included). In additional models for HbA1c and insulin dose per kilogram and day, the confounder "therapy form" was included, to adjust for a possible influence of the applied diabetes therapy. All confounders were fixed effects, and the treatment center was set as random intercept. The models' estimates were calculated based on observed marginal frequencies. P values <.05 were considered statistically significant.