Worse Metabolic Control and Dynamics of Weight Status in Adolescent Girls Point to Eating Disorders in the First Years after Manifestation of Type 1 Diabetes Mellitus: Findings from the Diabetes Patienten Verlaufsdokumentation Registry

Thomas Reinehr, PhD[1], Barbara Dieris[1], Angela Galler, PhD[2], Martin Teufel, PhD[3], Gabriele Berger, PhD[4], Rainer Stachow, MD[5], Sven Golembowski, MD[6], Ute Ohlenschläger, MD[7], Martin Holder, MD[8], Michael Hummel, MD[9], Reinhard W. Holl, PhD[10,11], and Nicole Prinz, PhD[10,11]

Objective To assess indications of eating disorders in girls with type 1 diabetes mellitus (T1DM).

Study design In total 31 556 girls aged >6 months and <23 years of age with T1DM from the Diabetes Patienten Verlaufsdokumentation (DPV) cohort were analyzed including 155 (0.49%) girls with anorexia nervosa, 85 (0.27%) girls with bulimia nervosa, 45 (0.14%) girls with binge eating disorder, and 229 (0.73%) girls with eating disorders not otherwise specified. Patient characteristics, weight changes, numbers of patients with severe hypoglycemia and diabetic ketoacidosis (DKA), changes of glycosylated hemoglobin A1c (HbA1c) levels, use of pumps, and prevalence of celiac disease and autoimmune thyroiditis were compared between girls with and without eating disorders. Multiple logistic regression analyses were performed.

Results Eating disorders were significantly associated with late pubertal age, nonusage of pumps, no migration background, increased HbA1c levels, increased frequencies of DKA and severe hypoglycemia, and celiac disease were not related to eating disorders. Significant differences in HbA1c levels, prevalence of DKA and severe hypoglycemia between girls with and without eating disorders were already detectable in the first years after onset of T1DM. A decrease of body mass index (BMI)-SDS increased the risk for comorbid anorexia nervosa (7.1-fold [95% CI 3.6-14.3] compared with stable BMI-SDS, 6.9-fold [95%CI 3.4-14.1] compared with increase of BMI-SDS).

Conclusions Poor metabolic control and increased rates of DKA and severe hypoglycemia in the first years after manifestation of T1DM can be hints for eating disorders in girls with T1DM, and weight loss is specific for anorexia nervosa. These clinical features should lead to screening for eating disorders especially at a late pubertal age. *(J Pediatr 2019;207:205-12).*

Previous studies reported that diabetes mellitus type 1 (T1DM) seems to be associated with eating disorders or subthreshold variants in adolescents and adults.[1-3] One study revealed an almost 2-fold (95% CI 1.5-3.7) higher prevalence in females with T1DM compared with nondiabetic subjects,[4] and other studies reported eating disorders in 7%-33% of girls with T1DM.[5-7] In the Diabetes Patienten Verlaufsdokumentation (DPV) dataset, a large prospective observation study on children and adolescents with T1DM, eating disorders are documented in nearly 1% of the patients with T1DM with higher rates in girls.[2] This female predominance has also been reported in other studies.[1,8]

The combination of T1DM and untreated eating disorder contributes to a worse outcome in adults.[9] Eating disorders contribute to an increased risk of several complications of diabetes[7] such as abnormal lipid profiles,[10] diabetic ketoacidosis,[9] retinopathy,[2] neuropathy,[11] nephropathy,[12] and increased mortality.[13]

Although we and others have previously demonstrated that eating disorders are associated with worse metabolic control,[2,4,14-16] the time point of this metabolic deterioration during diabetes disease is unclear. Moreover, it is possible that clinical characteristics such as weight change could be hints for eating disorders in

BMI	Body mass index
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*
EDNOS	Eating disorders not otherwise specified
HbA1c	Glycosylated hemoglobin A1c
T1DM	Type 1 diabetes mellitus

From the [1]Department of Pediatric Endocrinology, Diabetes, and Nutrition Medicine, Vestische Hospital for Children and Adolescents, University of Witten/Herdecke, Witten; [2]Charité—Universitätsmedizin Berlin, Berlin; [3]Department of Psychosomatic Medicine and Psychotherapy, LVR-Hospital Essen, University of Duisburg-Essen, Essen,Germany; [4]Department of Pediatric and Adolescent Medicine, Medical University Vienna, Vienna, Austria; [5]Fachklinik Sylt for Children and Adolescents, Deutsche Rentenversicherung Nord, Sylt; [6]Department of Pediatrics, Sana Hospital Berlin Lichtenberg, Berlin; [7]Pediatric Endocrinology and Diabetology, Children University Hospital Frankfurt, Frankfurt; [8]Hospital Stuttgart, Olgahospital, Department of Pediatric Endocrinology and—Diabetology, Stuttgart; [9]Diabetes Center Rosenheim, Rosenheim; [10]Institute of Epidemiology and Medical Biometry, Central Institute for Biomedical Technology (ZIBMT), University of Ulm, Ulm; and [11]German Center for Diabetes Research (DZD), Munich-Neuherberg, Germany

Funded by the Federal Ministry of Education and Research within the German Center for Diabetes Research (DZD). Further funding has been received from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115797 (INNODIA) supported by the European Union's Horizon 2020 research and innovation program and "EFPIA," "JDRF," and "The Leona M. and Harry B. Helmsley Charitable Trust." The German Diabetes Association (DDG), the European Foundation for the Study of Diabetes (EFSD), and the German Robert Koch Institute (RKI) provided additional financial support. Sponsors were not involved in data acquisition or analysis. The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2018.11.037

children and adolescents because eating disorders in adults with T1DM are associated with weight loss in anorexia nervosa and weight gain in bulimia or binge eating disorder.[9,13,17]

Because studies identifying eating disorder-related factors in children with T1DM are rare, we analyzed the large pediatric DPV dataset of more than 60 000 patients with T1DM and longitudinal follow-up to identify covariates associated with the presence of eating disorders. We focused on girls because the prevalence of eating disorders in male adolescents with T1DM is low,[1,8] and the genesis and appearance of eating disorders might diverge between boys and girls. We hypothesized that girls with T1DM at pubertal age and without migration background, with celiac disease, and not using pumps (which allow the greatest flexibility in eating) had a higher risk for eating disorders. Furthermore, we analyzed whether baseline metabolic status, weight and height status, as well as the change of glycosylated hemoglobin A1c (HbA1c), body mass index (BMI) dynamics, frequency of severe hypoglycemia, or diabetic ketoacidosis are associated with specific eating disorders.

Methods

The basis for the present research was the German/Austrian/Luxembourgian and Swiss standardized, multicenter, prospective, computer-based diabetes data acquisition system DPV (www.d-p-v.eu). Within the DPV initiative, 462 specialized diabetes care centers currently use the DPV software for standardized documentation of diabetes diagnosis and patient care (list of participating centers in DPV is available in the **Appendix** [available at www.jpeds.com]). Patient demographics, type and onset of diabetes, metabolic control, treatment regimen, and comorbidities are entered into the electronic health record. Twice a year, participating centers transmit their locally documented data anonymously to Ulm, Germany, for central analyses and quality assurance.[18] In case of inconsistent data, participating centers are requested to correct data entries. All plausible data are aggregated into a cumulative database. The ethics committee of the University of Ulm approved the DPV initiative and the local review boards approved the anonymized data collection.

Until September 2017, demographic and clinical data of 480 244 patients with any type of diabetes were available in the database. For the present analysis, female patients with T1DM and age at diabetes onset between >6 months and <23 years, documented insulin dosage, body weight and height follow-up data of at least 1 year after diabetes manifestation, as well as no documented eating disorder in the first 4 weeks after manifestation of diabetes were included. The final study population was 31 556 pediatric and young-adult female patients with T1DM from 384 German, 2 Swiss, 1 Luxembourgian, and 37 Austrian centers.

To identify patients with eating disorders, the database was searched for the lifetime diagnosis of eating disorder. A total of 514 female patients were identified with comorbid eating disorder and were subdivided into 4 groups: (1) anorexia nervosa, (2) bulimia nervosa, (3) binge eating disorder, and (4) eating disorders not otherwise specified (EDNOS). Identification and classification of eating disorders was made using *International Classification of Diseases, 10th Revision/Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) codes[2,19] and the respective German terms entered by diabetologists at each site. Patients had either already received an eating disorder diagnosis based on *International Classification of Diseases, 10th Revision*/DSM-IV criteria by trained psychologists, or diabetologists made the diagnosis jointly with psychologists or child psychiatrists. For each patient included, the entire years of treatment were analyzed. In case of multiple data sets per patient, data were aggregated.

Migration background was defined if either the patient or at least 1 parent was born outside Germany/Austria/Switzerland/Luxembourg. BMI and height SDS (BMI-SDS respective height-SDS) were calculated using national reference data from the German Health Interview and Examination Survey for Children and Adolescents as described elsewhere.[20,21]

To adjust for differences among different laboratory methods, the multiple of the mean method was applied to mathematically standardize HbA1c measurements to the Diabetes Control and Complications Trial reference range (4.05%-6.05%; 20.7-42.6 mmol/mol).[22] Severe hypoglycemia was defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or other resuscitative actions or as a hypoglycemia with coma.[6,23] Diabetic ketoacidosis was diagnosed in patients with a blood pH value of <7.3 or a clinical diagnosis of diabetic ketoacidosis associated with inpatient care. Diagnosis of celiac disease was based on biopsy, and diagnosis of autoimmune thyroiditis was based on positive measurement of autoantibodies or a clinical diagnosis of autoimmune thyroiditis.

We used body surface in m^2 instead of body weight to interpret the daily insulin dosage because in underweight girls it is a better reference for daily insulin dosage than kilogram body weight.[2]

Data analysis was implemented using SAS v 9.4 (SAS Institute, Cary, North Carolina). Median with IQR (25th/75th percentile) was used as descriptive statistics for continuous variables and proportions for categorical variables. False discovery rate algorithm was applied to adjust for multiple comparisons. Age was categorized as <8 years, 8-12 years, and >12 years to account indirectly for pubertal stage. To adjust for potential confounding effects (age at onset of T1DM, diabetes duration at last observation, and migration background), multivariable logistic regression models were calculated for any eating disorder and for each type of eating disorder separately, including the categorical variables BMI-SDS at manifestation, BMI-SDS change, BMI-SDS last observation, HbA1c at manifestation, HbA1c last observation, DKA last observation, severe hypoglycemia last observation, pump use last observation, autoimmune thyroiditis, and celiac disease as independent factors, respectively. Because the number of girls with binge eating disorder was relatively low, they were not included in these analyses. Results are given as OR with 95% CI.

BMI-SDS, HbA1c, rate of DKA, and severe hypoglycemia were also analyzed longitudinally with a maximum follow-up of 10 years after diabetes onset. Values are adjusted for age

at diabetes onset and migration background. Two sided *P* values of <.05 were considered statistically significant.

Results

In this analysis, 31 556 girls with T1DM were included. Eating disorders were documented in 514 (1.62%) subjects, 155 (0.49%) anorexia nervosa, 85 (0.27%) bulimia nervosa, 45 (0.14%), binge eating disorder, and 229 (0.73%) eating disorders not otherwise specified [EDNOS]) (**Table I**; available at www.jpeds.com).

At onset of diabetes, girls with eating disorder did not differ significantly regarding to height-SDS, BMI-SDS, HbA1c, or prevalence of manifestation with diabetic ketoacidosis compared with girls without eating disorder (**Table I**). Girls with eating disorders were significantly older at manifestation of diabetes and had a significantly lower prevalence of migration background compared with girls without eating disorders (**Table I**).

In logistic regression analyses (**Table II**), higher age at diabetes manifestation (≥12 years and 8 to <12 years vs <8 years) was significantly related to eating disorder. Girls without migration background had an increased risk for eating disorder (especially girls with bulimia nervosa with 2.8-fold increased risk) compared with girls with migration background (**Table II**). By contrast, neither HbA1c nor BMI-SDS at manifestation was significantly associated with any eating disorder (**Table II**).

In the course of T1DM, girls with or without eating disorders did not differ significantly in prevalence of celiac disease (**Table I** and **Table II**). Autoimmune thyroiditis occurred significantly more often in girls with EDNOS (**Table II**), and other eating disorders were not associated with autoimmune thyroiditis.

The proportion of patients with events of diabetic ketoacidosis or severe hypoglycemia within the first 10 years after diabetes manifestation is demonstrated in **Figure 1**. Already 2 years after manifestation of diabetes, the proportion of patients with diabetic ketoacidosis was higher in girls with eating disorders compared with girls without eating disorders even after adjustment for age at manifestation and migration background. Moreover, already within the first year after manifestation of diabetes, severe hypoglycemia occurred more frequently in girls with eating disorders compared with girls without eating disorder.

Table II. ORs (95% CI) for the association with eating disorders

Type of eating disorder	Any eating disorder	Anorexia nervosa	Eating disorder other than anorexia nervosa	Bulimia nervosa	EDNOS
Variables	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]
Age at onset of T1DM					
<8 y vs ≥12 y	**0.64 [0.51-0.79]***	**0.64 [0.43-0.96]***	**0.63 [0.49-0.82]***	**0.42 [0.24-0.71]***	**0.72 [0.52-0.99]***
8 to <12 y vs <8 y	**1.46 [1.18-1.79]***	1.44 [0.99-2.10]	**1.46 [1.14-1.87]***	**1.74 [1.02-2.98]***	1.28 [0.94-1.74]
8 to <12 y vs ≥12 y	0.93 [0.75-1.15]	0.93 [0.63-1.38]	0.93 [0.71-1.12]	0.72 [0.44-1.20]	0.92 [0.66-1.28]
Native vs non-native	**1.64 [1.22-2.20]***	1.50 [0.89-2.52]	**1.71 [1.19-2.44]***	**2.76 [1.12-6.82]***	1.41 [0.93-2.14]
Diabetes duration at last observation					
≥5 y vs <5 y	**1.89 [1.53-2.35]***	**1.65 [1.13-2.39]***	**2.02 [1.56-2.62]***	**3.35 [1.78-6.31]***	**1.83 [1.33-2.51]***
BMI-SDS at manifestation†					
<25th vs ≥90th perc.	0.85 [0.43-1.67]	3.50 [0.47-26.06]	0.55 [0.26-1.17]	0.58 [0.07-5.27]	0.52 [0.22-1.22]
25th-<90th vs <25th perc.	1.29 [0.92-1.80]	0.86 [0.48-1.52]	1.58 [0.99-2.41]	2.43 [0.79-7.46]	1.62 [0.99-2.66]
25th-<90th vs ≥90th perc.	1.09 [0.56-2.10]	3.00 [0.41-22.17]	0.88 [0.43-1.77]	1.42 [0.18-10.90]	0.84 [0.38-1.87]
BMI-SDS change†					
<0 vs ≥1 SDS	**2.86 [1.91-4.28]***	**6.90 [3.37-14.10]***	1.69 [0.99-2.88]	2.17 [0.68-6.97]	1.79 [0.96-3.35]
0-<1 vs <0 SDS	**0.40 [0.27-0.59]***	**0.14 [0.07-0.28]***	1.22 [0.79-1.87]	0.35 [0.10-1.24]	0.77 [0.43-1.39]
0-<1 vs ≥1 SDS	1.14 [0.78-1.68]	0.93 [0.40-2.16]	0.72 [0.43-1.20]	0.77 [0.24-2.43]	1.38 [0.83-2.27]
BMI-SDS last observation†					
<25th vs ≥90th perc.	**3.01 [2.29-3.96]***	**14.71 [7.76-27.88]***	**1.46 [1.03-2.07]***	1.90 [0.92-3.94]	**1.54 [1.01-2.37]***
25th-<90th vs <25th perc.	**0.28 [0.22-0.34]***	**0.12 [0.09-0.17]***	**0.49 [0.36-0.66]***	**0.49 [0.27-0.91]***	**0.46 [0.32-0.66]***
25th-<90th vs ≥90th perc.	0.83 [0.66-1.06]	1.76 [0.93-3.33]	**0.71 [0.54-0.92]***	0.94 [0.54-1.63]	**0.70 [0.51-0.97]***
HbA1c at manifestation†					
≥9% vs <9%	1.13 [0.74-1.74]	0.96 [0.47-1.98]	1.23 [0.72-2.09]	0.97 [0.28-3.41]	1.45 [0.75-2.82]
HbA1c last observation					
≥7.5% vs <7.5%†	**1.63 [1.34-2.00]***	1.16 [0.83-1.63]*	**1.93 [1.50-2.48]***	**1.73 [1.05-2.86]***	**1.94 [1.42-2.65]***
DKA last observation					
Yes vs no†	**2.62 [1.78-3.87]***	**3.43 [1.85-6.38]***	**2.27 [1.38-3.72]***	1.19 [0.30-4.88]	**2.47 [1.37-4.45]***
Severe hypoglycemia last observation					
Yes vs no†	**1.45 [1.10-1.91]***	**1.69 [1.05-2.70]***	1.35 [0.96-1.89]	1.00 [0.46-2.17]	**1.59 [1.07-2.36]***
No pump vs pump last observation†	**1.38 [1.14-1.67]***	**1.95 [1.36-2.81]***	1.20 [0.95-1.50]	1.13 [0.71-1.81]	1.22 [0.93-1.62]
Autoimmune thyroiditis					
Yes vs no†	**1.27 [1.04-1.56]***	1.23 [0.84-1.79]	**1.29 [1.01-1.65]***	1.10 [0.65-1.86]	**1.37 [1.01-1.84]***
Celiac disease					
Yes vs no†	0.76 [0.40-1.43]	1.01 [0.37-2.75]	1.54 [0.68-3.47]	n.a.	0.66 [0.24-1.78]

n.a., not available because of the low number of patients
Values in bold indicate significant association.
**P* < .05.
†Adjusted for age at onset, diabetes duration at last observation and migration background by multivariable regression; because of the low number of patients with binge eating disorder, they were not included in this analysis.

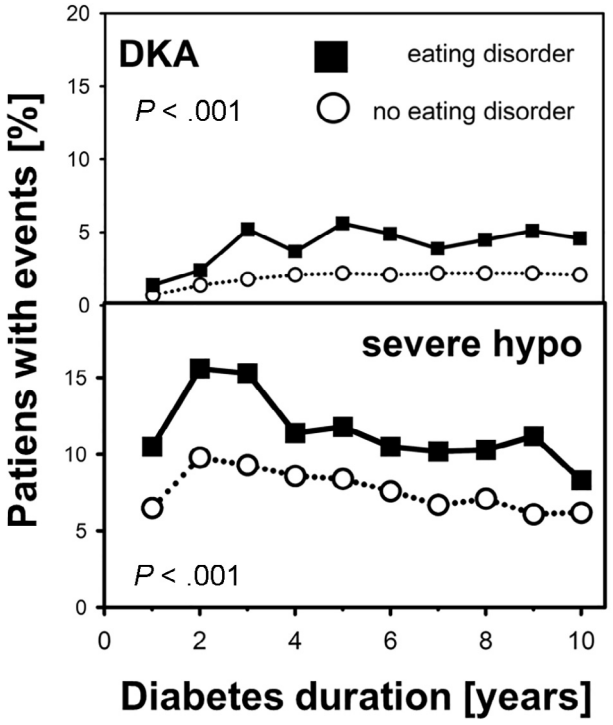


Figure 1. Proportion of patients with DKA or severe hypoglycemia over time in girls with and without eating disorder. Adjusted means from logistic regression models with adjustments for age at onset and migration background. *P* value is given for trend. Because of the low number of patients with events, analysis could not be stratified by type of eating disorder.

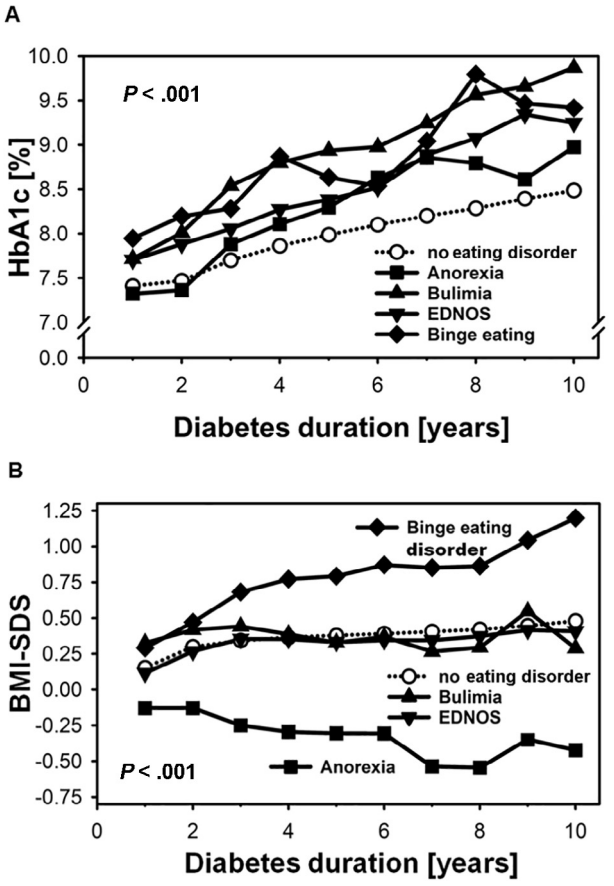


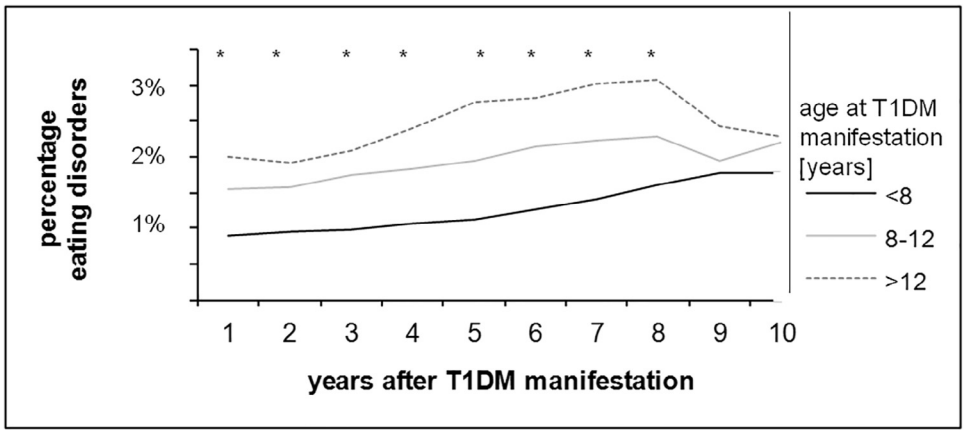
Figure 2. **A,** HbA1c and **B,** BMI-SDS during follow-up stratified by type of eating disorder; Adjusted means from linear regression models with adjustments for age at onset and migration background. P value is given for trend.

The changes of HbA1c in the course of diabetes are demonstrated in **Figure 2**. Regardless of the type of eating disorder, HbA1c was significantly higher in girls with eating disorders compared with girls without eating disorders three years after onset of diabetes even after adjustment for age at manifestation and migration background. In the first and second year after diabetes manifestation, except for anorexia nervosa, all other eating disorders demonstrated also higher HbA1c levels.

Although the change of BMI-SDS in the first 3-6 months after diabetes manifestation did not differ significantly between groups, BMI-SDS change between manifestation and last observation differed significantly (**Table I**). In girls with anorexia nervosa, a decrease was observed, whereas an increase was present in girls with any other eating disorder or without eating disorder. Within the first 10 years after diabetes manifestation, a significant difference between groups was found (**Figure 2**). Girls with anorexia nervosa showed a lower BMI-SDS at each time point during follow-up compared with girls without eating disorder, and girls with binge eating disorder had a higher BMI-SDS starting 3 years after diabetes manifestation (**Figure 2**). In logistic regression analyses adjusted for age at manifestation, diabetes duration at last observation and migration background, a decrease of BMI-SDS during the course of T1DM was associated with a greater than 6-fold likelihood of developing anorexia nervosa compared with girls with a BMI-SDS increase ≥1 SDS, and a BMI-SDS increase between 0 and <1 SDS during the course of diabetes was associated with a lower chance (0.14 [0.07-0.28]) for developing anorexia nervosa compared with girls with a BMI-SDS reduction during follow-up (**Table II**).

The changes of height-SDS between manifestation and 3-6 months later as well as between manifestation and last observation did not differ significantly between groups (**Table I**).

Unadjusted group comparisons are summarized in **Table I**. In logistic regression analyses, longer diabetes duration was significantly related to eating disorders (**Table II**). An underweight status was associated with a higher likelihood of anorexia nervosa or EDNOS compared with normal weight or overweight status. HbA1c levels ≥7.5% at last visit were associated with a greater than 1.7-fold likelihood for suffering from bulimia nervosa and a nearly 2-fold odds for EDNOS compared with girls with HbA1c levels <7.5% (**Table II**). Diabetic ketoacidosis or severe hypoglycemia in the year before the last visit increased the likelihood for anorexia nervosa or EDNOS, and bulimia nervosa was not associated with diabetic ketoacidosis or severe hypoglycemia (**Table II**). Injection therapy was not related to any eating disorder except for



*: $P < .01$

Figure 3. Prevalence of eating disorders in the course of T1DM stratified by age at manifestation diabetes.

anorexia nervosa. The usage of pump decreased the likelihood for anorexia nervosa by almost one-half.

Stratifying the girls according to age at diabetes onset demonstrated that the prevalence of eating disorder after 10 years of diabetes duration did not differ significantly ($P = .424$) (**Figure 3**). However, in the first 8 years after diabetes manifestation, the prevalence of eating disorder was significantly different according to age at manifestation of diabetes, with lower rates in younger girls. The increase of eating disorder prevalence over time started 5 years after diabetes manifestation in girls with an age at manifestation <8 years and 2 years after manifestation in girls with an age between 8 and 12 years at diabetes manifestation or >12 years at diabetes manifestation.

Discussion

We were able to demonstrate that higher HbA1c and higher rate of diabetic ketoacidosis or severe hypoglycemia in the course of diabetes were associated with eating disorders. In contrast to the well-known phenomenon that BMI-SDS increases after diagnosis of T1DM in children and adolescents,[24] BMI-SDS decreased in our study in girls with anorexia nervosa. A decrease of BMI-SDS increases the risk nearly 7-fold for suffering from anorexia nervosa.

It has been hypothesized that individuals with T1DM getting overweight may be more likely to develop eating disorders because a higher BMI increases the drive for thinness, thus, making these individuals more susceptible.[6,25,26] However, we found no higher incidence of any eating disorder in girls with higher BMI-SDS.

Girls developing eating disorders were characterized by a deterioration of their HbA1c levels during follow-up. A HbA1c level of >7.5% at last observation was associated with a 1.7-fold likelihood for suffering from bulimia nervosa and a nearly 2-fold odds for EDNOS compared with girls with HbA1c levels of <7.5%. Higher HbA1c levels in patients with eating disorder have been reported previously.[2,4,14-16]

Furthermore, eating disorders were characterized by a higher rate of diabetic ketoacidosis. This is in line with a previous analysis reporting higher rates of inpatient-treated diabetic ketoacidosis in female patients aged 11-21 years with T1DM who scored positive on a screening questionnaire for disordered eating.[27] Interestingly, in our study, a higher prevalence of diabetic ketoacidosis occurred already 2 years after manifestation of diabetes in girls with eating disorders. The higher prevalence of diabetic ketoacidosis in eating disorders is also associated with longer hospitalization stays and an increased prevalence of retinopathy as demonstrated previously in the DPV cohort.[2]

Reasons for the worse metabolic control in girls with eating disorders already in the first years after manifestation could be blood glucose fluctuations due to overeating or binge eating, lack of adherence to treatment regimen, insulin omission, or underdosing ("insulin purging").[2,3,14,28,29] "Insulin purging" is a unique tool to reduce weight in diabetes and has been reported in many patients with eating disorder.[3,7,28,30,31] It is regarded as characteristic for eating disorders in T1DM and an important mediator between eating disorders and poor metabolic control.[7] Beside the catabolism of lipids, the induced glycosuria results in excretion of calories with the urine and contributes to weight loss. Although restricting or omitting insulin can be appropriate in some circumstances (eg, to avoid hypoglycemia or prior to exercise), it is considered a diabetes-specific purging behavior in eating disorders when used for weight loss. Up to 44% of female adolescents and young women with T1DM were reported to use this weight-loss strategy.[32] The reason for the intention to reduce body weight might be that a large proportion of girls with eating disorders reported body dissatisfaction as reflected by a discrepancy between their actual body size and ideal body shape.[25] In our study, the lower reported insulin dosage per body surface in patients with anorexia nervosa or bulimia nervosa might indicate insulin omission, underdosing, or under- reporting. Another explanation for the lower insulin dosage might be enhanced insulin sensitivity due to excessive

physical activity or, in patients with anorexia nervosa, due to empty glycogen storages. Rate of severe hypoglycemia was higher in girls with eating disorders in our study already in the first year after manifestation of diabetes. Severe caloric restriction (to achieve weight loss) and empty glycogen storages may lead to higher rates of hypoglycemia.[33] Importantly, insulin misuse for weight loss purposes is associated with the main finding in patients with eating disorders in our study, higher HbA1c levels,[14,27,34] which leads in turn to a higher morbidity and an earlier mortality.[14,35]

The prevalence of 1.6% documented eating disorders was lower than the reported rate of 7% up to 33% suspected eating disorders based on anonymous questionnaires in female adolescents with T1DM.[5,6] Higher rates of eating disorder are more likely to be reported when anonymity occurs in contrast to our study.[36] Usually, eating disorder rates are higher in studies using specific screening tools targeted for the detection of eating disorders than in patient registries such as DPV.[5,36,37] Likely, many cases of eating disorders are undiagnosed in clinical registries of T1DM. Disordered eating is often denied or downplayed by patients. A clinical diagnosis of eating disorder might not always be reported to diabetologists by patients or their psychologists. In addition, the wide age range also including prepubertal children in our study may explain the lower eating disorder prevalence compared with previous studies focusing mainly on adolescents.

Age is an important risk factor for eating disorders because of eating disorders usually are not diagnosed before puberty.[7,38] In our study, the prevalence of eating disorders increased after 5 years of diabetes duration in girls with T1DM manifestation before the age of 8 years suggesting a prepubertal stage at manifestation, and the prevalence of eating disorders increased already 2 years after diabetes manifestation in girls aged 8-12 years at diabetes manifestation. These findings point toward a manifestation of eating disorders predominately at late pubertal age. This observation fits well to studies reporting that female adolescents aged 12-18 years being the most vulnerable for eating disorder.[3,7,25,38]

Several behavioral factors may increase the likelihood of eating disorder among adolescents with T1DM. One example is focussing on food and dieting as part of diabetes management such as counting carbohydrates and restrictive dietary behaviors.[28] In this context, the use of a pump, which allows the most flexibility in eating, was associated with a lower prevalence of anorexia nervosa in our study as well as in a previous small study.[31] However, diabetologists may recommend usage of pumps more frequently in girls without eating disorder. Because we found no relationship between celiac disease and eating disorders in our study, this finding points against the hypotheses that eating disorders in T1DM are simply caused by focusing on food and eating pattern.

We found lower odds of eating disorders in girls with migration background suggesting that also cultural, social, or genetic factors influence the prevalence of eating disorder in girls with T1DM. Future studies are necessary to understand why girls in Western culture are more susceptible for eating disorders.

Several limitations have to be kept in mind. First, eating disorders might be under-reported in the database. The documentation of a comorbid eating disorder was made by diabetologists and not by mental health professionals in the DPV registry. There may be a lack of systematic screening for eating disorders in the diabetes care centers. Furthermore, patients not allowing the documentation of eating disorder were classified as T1DM patients without eating disorder. Second, subclinical eating disorders or subtypes of eating disorder could not be considered. For example, we have not analyzed separately the restrictive or binge/purging type of anorexia nervosa. Third, in our multiple regression models, we have analyzed the changes between baseline and last visit, probably missing changes of BMI-SDS or HbA1c during the course of the eating disorder. This is of importance especially in those girls, whose eating disorders have been well-controlled before the last visit. However, eating disorders are frequently life-long diseases and the changes of HbA1c and BMI-SDS over time are plotted in **Figure 2**. Fourth, it is possible that DSM-IV criteria used for classification have not been met in the strictest sense in some patients. Hence, there could be an overlap in the diagnostic categories. Fifth, it has been suggested to screen for eating disorders in patients with T1DM with specific validated and reliable screening tools (eg, Diabetes Eating Problem Survey-Revised).[37,39] Sixth, we do not know the exact onset of eating disorder because the diagnosis of eating disorders is usually delayed,[33] which might have influenced our findings. In this line it is possible that weight changes occurred before clinical diagnosis of eating disorder. Seventh, we have summarized all girls with migration background, and it is possible that ethnicity and cultural background are more important factors than migration itself. Eighth, we have not enough data concerning pubertal stage, which would be helpful because eating disorders seem to start in our study at pubertal age. Finally and most importantly, our study design does not allow differentiating whether the eating disorder-related factors are the cause or the consequence of eating disorder.

In summary, worse metabolic control, as demonstrated by elevated HbA1c levels, increased prevalence of diabetic ketoacidosis, and severe hypoglycemia already in the first years after manifestation of T1DM and especially in late pubertal age, are significant hints for eating disorder. In addition, BMI-SDS decrease after T1DM manifestation was related to nearly 7-fold increased odds for comorbid anorexia nervosa. Therefore, these clinical features in girls with T1DM should lead diabetologists to initiate a work-up for eating disorders. Future research including longitudinal and intervention studies based on the suggested theoretical frameworks[28,40] is necessary to prevent and treat eating disorders. ■

*We thank A. Hungele and R. Ranz for the development of the DPV documentation software and K. Fink and E. Bollow for the DPV data management and statistical analysis (clinical data managers and software developers, Ulm University). We are grateful to all participating centers contributing data for the present analysis (**Appendix**).*

Submitted for publication Jul 12, 2018; last revision received Nov 20, 2018; accepted Nov 20, 2018

Reprint requests: Thomas Reinehr, PhD, Department of Pediatric Endocrinology, Diabetes, and Nutrition Medicine, Vestische Kinder-und Jugendklinik, University of Witten/Herdecke, Dr F. Steiner Str. 5, 45711 Datteln, Germany. E-mail: t.reinehr@kinderklinik-datteln.de

References

1. Peveler RC, Fairburn CG, Boller I, Dunger D. Eating disorders in adolescents with IDDM. A controlled study. Diabetes Care 1992;15:1356-60.
2. Scheuing N, Bartus B, Berger G, Haberland H, Icks A, Knauth B, et al. Clinical characteristics and outcome of 467 patients with a clinically recognized eating disorder identified among 52,215 patients with type 1 diabetes: a multicenter german/austrian study. Diabetes Care 2014;37:1581-9.
3. Colton PA, Olmsted MP, Wong H, Rodin GM. Eating disorders in individuals with type 1 diabetes: case series and day hospital treatment outcome. Eur Eat Disord Rev 2015;23:312-7.
4. Jones JM, Lawson ML, Daneman D, Olmsted MP, Rodin G. Eating disorders in adolescent females with and without type 1 diabetes: cross sectional study. BMJ 2000;320:1563-6.
5. Young V, Eiser C, Johnson B, Brierley S, Epton T, Elliott J, et al. Eating problems in adolescents with Type 1 diabetes: a systematic review with meta-analysis. Diabet Med 2013;30:189-98.
6. Hanlan ME, Griffith J, Patel N, Jaser SS. Eating disorders and disordered eating in Type 1 diabetes: prevalence, screening, and treatment options. Curr Diab Rep 2013;13:909-16.
7. Colton PA, Olmsted MP, Daneman D, Farquhar JC, Wong H, Muskat S, et al. Eating disorders in girls and women with Type 1 Diabetes: a longitudinal study of prevalence, onset, remission, and recurrence. Diabetes Care 2015;38:1212-7.
8. Wisting L, Bang L, Skrivarhaug T, Dahl-Jorgensen K, Ro O. Adolescents with Type 1 diabetes—the impact of gender, age, and health-related functioning on eating disorder psychopathology. PLoS ONE 2015;10:e0141386.
9. Affenito SG, Backstrand JR, Welch GW, Lammi-Keefe CJ, Rodriguez NR, Adams CH. Subclinical and clinical eating disorders in IDDM negatively affect metabolic control. Diabetes Care 1997;20:182-4.
10. Affenito SG, Lammi-Keefe CJ, Vogel S, Backstrand JR, Welch GW, Adams CH. Women with insulin-dependent diabetes mellitus (IDDM) complicated by eating disorders are at risk for exacerbated alterations in lipid metabolism. Eur J Clin Nutr 1997;51:462-6.
11. Rydall AC, Rodin GM, Olmsted MP, Devenyi RG, Daneman D. Disordered eating behavior and microvascular complications in young women with insulin-dependent diabetes mellitus. N Engl J Med 1997;336:1849-54.
12. Takii M, Uchigata Y, Tokunaga S, Amemiya N, Kinukawa N, Nozaki T, et al. The duration of severe insulin omission is the factor most closely associated with the microvascular complications of Type 1 diabetic females with clinical eating disorders. Int J Eat Disord 2008;41:259-64.
13. Nielsen S, Emborg C, Molbak AG. Mortality in concurrent type 1 diabetes and anorexia nervosa. Diabetes Care 2002;25:309-12.
14. Goebel-Fabbri AE, Fikkan J, Franko DL, Pearson K, Anderson BJ, Weinger K. Insulin restriction and associated morbidity and mortality in women with type 1 diabetes. Diabetes Care 2008;31:415-9.
15. Grylli V, Hafferl-Gattermayer A, Schober E, Karwautz A. Prevalence and clinical manifestations of eating disorders in Austrian adolescents with type-1 diabetes. Wien Klin Wochenschr 2004;116:230-4.
16. Bernstein CM, Stockwell MS, Gallagher MP, Rosenthal SL, Soren K. Mental health issues in adolescents and young adults with type 1 diabetes: prevalence and impact on glycemic control. Clin Pediatr (Phila) 2013;52:10-5.
17. Herpertz S, Albus C, Wagener R, Kocnar M, Wagner R, Henning A, et al. Comorbidity of diabetes and eating disorders. Does diabetes control reflect disturbed eating behavior? Diabetes Care 1998;21:1110-6.
18. Hofer SE, Schwandt A, Holl RW. Standardized documentation in pediatric diabetology: experience from Austria and Germany. J Diabetes Sci Technol 2016;10:1042-9.
19. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington (DC): American Psychiatric Association Press; 2000.
20. Rosario AS, Schienkiewitz A, Neuhauser H. German height references for children aged 0 to under 18 years compared to WHO and CDC growth charts. Ann Hum Biol 2011;38:121-30.
21. Kurth BM, Kamtsiuris P, Holling H, Schlaud M, Dolle R, Ellert U, et al. The challenge of comprehensively mapping children's health in a nationwide health survey: design of the German KiGGS-Study. BMC Public Health 2008;8:196-9.
22. Rosenbauer J, Dost A, Karges B, Hungele A, Stahl A, Bachle C, et al. Improved metabolic control in children and adolescents with type 1 diabetes: a trend analysis using prospective multicenter data from Germany and Austria. Diabetes Care 2012;35:80-6.
23. American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005;28:1245e9.
24. Frohlich-Reiterer EE, Rosenbauer J, Bechtold-Dalla PS, Hofer SE, Schober E, Holl RW. Predictors of increasing BMI during the course of diabetes in children and adolescents with type 1 diabetes: data from the German/Austrian DPV multicentre survey. Arch Dis Child 2014;99:738-43.
25. Araia E, Hendrieckx C, Skinner T, Pouwer F, Speight J, King RM. Gender differences in disordered eating behaviors and body dissatisfaction among adolescents with type 1 diabetes: results from diabetes MILES youth-Australia. Int J Eat Disord 2017;50:1183-93.
26. Meltzer LJ, Johnson SB, Prine JM, Banks RA, Desrosiers PM, Silverstein JH. Disordered eating, body mass, and glycemic control in adolescents with type 1 diabetes. Diabetes Care 2001;24:678-82.
27. Bachle C, Stahl-Pehe A, Rosenbauer J. Disordered eating and insulin restriction in youths receiving intensified insulin treatment: results from a nationwide population-based study. Int J Eat Disord 2016;49:191-6.
28. Goebel-Fabbri AE. Disturbed eating behaviors and eating disorders in type 1 diabetes: clinical significance and treatment recommendations. Curr Diab Rep 2009;9:133-9.
29. Peterson CM, Fischer S, Young-Hyman D. Topical review: a comprehensive risk model for disordered eating in youth with type 1 diabetes. J Pediatr Psychol 2015;40:385-90.
30. Ackard DM, Vik N, Neumark-Sztainer D, Schmitz KH, Hannan P, Jacobs DR Jr. Disordered eating and body dissatisfaction in adolescents with type 1 diabetes and a population-based comparison sample: comparative prevalence and clinical implications. Pediatr Diabetes 2008;9(4 Pt 1):312-9.
31. Powers MA, Richter S, Ackard D, Gerken S, Meier M, Criego A. Characteristics of persons with an eating disorder and type 1 diabetes and psychological comparisons with persons with an eating disorder and no diabetes. Int J Eat Disord 2012;45:252-6.
32. Neumark-Sztainer D, Patterson J, Mellin A, Ackard DM, Utter J, Story M, et al. Weight control practices and disordered eating behaviors among adolescent females and males with type 1 diabetes: associations with sociodemographics, weight concerns, familial factors, and metabolic outcomes. Diabetes Care 2002;25:1289-96.
33. Daneman D, Olmsted M, Rydall A, Maharaj S, Rodin G. Eating disorders in young women with type 1 diabetes. Prevalence, problems and prevention. Horm Res 1998;50(Suppl 1):79-86.
34. d'Emden H, Holden L, McDermott B, Harris M, Gibbons K, Gledhill A, et al. Disturbed eating behaviours and thoughts in Australian adolescents with type 1 diabetes. J Paediatr Child Health 2013;49:E317-23.
35. Peveler RC, Bryden KS, Neil HA, Fairburn CG, Mayou RA, Dunger DB, et al. The relationship of disordered eating habits and attitudes to clinical outcomes in young adult females with type 1 diabetes. Diabetes Care 2005;28:84-8.
36. Keel PK, Crow S, Davis TL, Mitchell JE. Assessment of eating disorders: comparison of interview and questionnaire data from a long-term follow-up study of bulimia nervosa. J Psychosom Res 2002;53:1043-7.

37. Wisting L, Froisland DH, Skrivarhaug T, Dahl-Jorgensen K, Ro O. Psychometric properties, norms, and factor structure of the diabetes eating problem survey-revised in a large sample of children and adolescents with type 1 diabetes. Diabetes Care 2013;36:2198-202.
38. Takii M, Uchigata Y, Kishimoto J, Morita C, Hata T, Nozaki T, et al. The relationship between the age of onset of type 1 diabetes and the subsequent development of a severe eating disorder by female patients. Pediatr Diabetes 2011;12(4 Pt 2):396-401.
39. Markowitz JT, Butler DA, Volkening LK, Antisdel JE, Anderson BJ, Laffel LM. Brief screening tool for disordered eating in diabetes: internal consistency and external validity in a contemporary sample of pediatric patients with type 1 diabetes. Diabetes Care 2010;33:495-500.
40. Olmsted MP, Colton PA, Daneman D, Rydall AC, Rodin GM. Prediction of the onset of disturbed eating behavior in adolescent girls with type 1 diabetes. Diabetes Care 2008;31:1978-82.

50 Years Ago in *The Journal of Pediatrics*

A Note on Hypertension in Children and Adolescents. II. Drug Therapy

Loggie J. J Pediatr 1969;74:640-54

In 1969, Loggie described the pharmacologic management of children and adolescents with hypertension. At that time, the efficacy, side effects, and metabolism of these drugs had not been studied in this population, and the rationale for their use was extrapolated from studies in adults, making each therapeutic decision an educated guess at best. This situation has changed significantly since then, especially in the last 2 decades, as more medications have been systematically studied, encouraged by federal legislation.[1] Today, pharmacotherapy is tailored based on blood pressure categories and is usually reserved for patients with symptomatic or persistent hypertension and those with end-organ damage or comorbidities. Nonetheless, the principles remain the same: treatment should start with the lowest dose known to be effective, and it is preferable to use one drug to its maximum tolerated effectiveness before adding a second agent.

As we gained more insight into the mechanisms controlling blood pressure, new medications were developed. Drugs affecting the renin-angiotensin system or the long-acting calcium channel blockers have shown to reduce morbidity and mortality with fewer side effects and thus have largely replaced other options, such as reserpine, diazoxide, ganglionic blocking drugs, phentolamine, and sodium nitroprusside. Thiazides, on the other hand, have endured the passage of time and are still considered first-line treatment.

In the past, a low-sodium diet and physical exercise were considered poorly effective in lowering blood pressure in children. Today, nonpharmacologic measures, such as salt restriction, weight reduction, and regular physical activity, are crucial aspects of treatment for all patients with hypertension regardless of etiology or severity, and have been suggested to increase the beneficial effect of some antihypertensive drugs.

Despite this progress, the prevalence of hypertension among children and adolescents has increased over the last several years, with the obesity epidemic being a significant contributor to this trend. We must continue to strive for early identification of hypertension and optimal treatment to improve the long-term outcomes of cardiovascular disease in children and adolescents.

Karla Lorena Chavez Caraza, MD
Oscar Garcia Valencia, MD
Pediatrics Residency Program
Tecnologico de Monterrey
Escuela de Medicina y Ciencias de la Salud
Monterrey, Nuevo León, Mexico

Reference

1. Chaturvedi S, Lipszyc DH, Licht C, Craig JC, Parekh R. Pharmacological interventions for hypertension in children. Cochrane Database Syst Rev 2014;2:CD008117.

Appendix

List of participating centers in DPV

Aachen—Innere RWTH
Aachen—Uni-Kinderklinik RWTH
Aalen Kinderklinik
Ahlen St Franziskus Kinderklinik
Aidlingen Praxisgemeinschaft
Altötting Zentrum Inn-Salzach
Altötting-Burghausen Innere Medizin
Amberg Kinderklinik St Marien
Arnsberg-Hüsten Karolinenhosp Kinderabteilung
Asbach Kamillus-Klinik Innere
Aue Helios Kinderklink
Augsburg IV Med Klinik
Augsburg Josefinum Kinderklinik
Augsburg Kinderklinik Zentralklinikum
Aurich Kinderklinik
Bad Aibling Internist Praxis
Bad Driburg/Bad Hermannsborn Innere
Bad Hersfeld Innere
Bad Hersfeld Kinderklinik
Bad Kreuznach-Viktoriastift
Bad Kösen Median Kinderklinik
Bad Lauterberg Diabeteszentrum Innere
Bad Mergentheim—Diabetesfachklinik
Bad Mergentheim—Gemeinschaftspraxis DM-dorf Althausen
Bad Oeynhausen Herz-und Diabeteszentrum NRW
Bad Orb Spessart Klinik
Bad Orb Spessart Klinik Reha
Bad Reichenhall Kreisklinik Innere Med.
Bad Salzungen Kinderklinik
Bad Säckingen Hochrheinklinik Innere
Bad Waldsee Kinderarztpraxis
Bautzen Oberlausitz KK
Bayreuth Innere Medizin
Berchtesgaden CJD
Berchtesgaden MVZ Innere Med
Berlin DRK-Kliniken Mitte Innere
Berlin DRK-Kliniken Pädiatrie
Berlin Endokrinologikum
Berlin Evang. Krankenhaus Königin Elisabeth
Berlin Klinik St Hedwig Innere
Berlin Lichtenberg—Kinderklinik
Berlin Oskar Zieten Krankenhaus Innere
Berlin Schlosspark-Klinik Innere
Berlin St Josephskrankenhaus Innere
Berlin Virchow-Kinderklinik
Berlin Vivantes Hellersdorf Innere
Bern Universitätsklinik InselSpital Innere Medizin
Bielefeld Kinderarztpraxis
Bielefeld Kinderklinik Gilead
Bocholt Kinderklinik
Bochum Universitäts St Josef
Bochum Universitätskinderklinik St Josef
Bonn Uni-Kinderklinik
Bottrop Knappschaftskrankenhaus Innere
Braunfels-Wetzlar Innere
Braunschweig Kinderarztpraxis
Bremen—Kinderklinik Nord
Bremen—Mitte Innere
Bremen Zentralkrankenhaus Kinderklinik
Bremerhaven Kinderklinik
Bruchweiler Edelsteinklinik Kinder-Reha
Böblingen Kinderklinik
Castrop-Rauxel Evangelisches Krankenhaus
Castrop-Rauxel Rochus-Hospital
Celle Klinik für Kinder- und Jugendmedizin
Chemnitz Kinderklinik
Chemnitz-Hartmannsdorf Innere Medizin—DIAKOMED-1
Coburg Innere Medizin
Coburg Kinderklinik
Coesfeld Kinderklinik
Coesfeld/Dülmen Innere Med
Darmstadt Innere Medizin
Darmstadt Kinderklinik Prinz. Margaret
Datteln Vestische Kinderklinik
Deggendorf Gemeinschaftspraxis
Deggendorf Kinderklinik
Deggendorf Medizinische Klinik II
Deggendorf Pädiatrie-Praxis
Delmenhorst Kinderklinik
Dessau Kinderklinik
Detmold Kinderklinik
Dinslaken Kinderklinik
Dornbirn Innere Medizin
Dornbirn Kinderklinik
Dortmund Kinderklinik
Dortmund Knappschaftskrankenhaus Innere
Dortmund Medizinische Kliniken Nord
Dortmund-Hombruch Marienhospital
Dortmund-St Josefshospital Innere
Dortmund-West Innere
Dresden Neustadt Kinderklinik
Dresden Uni-Kinderklinik
Duisburg Evang. und Johanniter Krhs Innere
Duisburg Malteser Rhein-Ruhr St Anna Innere
Duisburg Malteser St Johannes
Duisburg Sana Kinderklinik
Duisburg-Huckingen
Duisburg-Huckingen Malteser Rhein-Ruhr, St Johannes
Duisburg-St Johannes Helios
Düren-Birkesdorf Kinderklinik
Düsseldorf Uni-Kinderklinik
Eberswalde Klinikum Barnim Werner Forßmann—Innere
Eisleben Lutherstadt Helios-Klinik
Erfurt Kinderklinik
Erlangen Uni Innere Medizin
Erlangen Uni-Kinderklinik
Essen Diabetes-Schwerpunktpraxis
Essen Elisabeth Kinderklinik
Essen Kinderarztpraxis
Essen Uni-Kinderklinik

Esslingen Klinik für Kinder und Jugendliche
Eutin Kinderklinik
Eutin St-Elisabeth Innere
Feldkirch Kinderklinik
Filderstadt Kinderklinik
Flensburg Diakonissen Kinderklinik
Forchheim Diabeteszentrum SPP
Frankenthal Kinderarztpraxis
Frankfurt Diabeteszentrum Rhein-Main-Erwachsenendiabetologie (Bürgerhospital)
Frankfurt Diabeteszentrum Rhein-Main-pädiat. Diabetologie (Clementine-Hospital)
Frankfurt Uni-Kinderklinik
Frankfurt Uni-Klinik Innere
Frankfurt-Sachsenhausen Innere
Frankfurt-Sachsenhausen Innere MVZ
Freiburg Kinder-MVZ
Freiburg St Josef Kinderklinik
Freiburg Uni Innere
Freiburg Uni-Kinderklinik
Freudenstadt Kinderklinik
Friedberg Innere Klinik
Friedrichshafen Kinderklinik
Fulda Innere Medizin
Fulda Kinderklinik
Fürth Kinderklinik
Gaissach Fachklinik der Deutschen Rentenversicherung Bayern Süd
Garmisch-Partenkirchen Kinderklinik
Geislingen Klinik Helfenstein Innere
Gelnhausen Innere
Gelnhausen Kinderklinik
Gelsenkirchen Kinderklinik Marienhospital
Gera Kinderklinik
Gießen Ev Krankenhaus Mittelhessen
Gießen Uni-Kinderklinik
Graz Uni Innere
Graz Uni-Kinderklinik
Greifswald Uni-Kinderklinik
Göppingen Innere Medizin
Göppingen Kinderklinik am Eichert
Görlitz Städtische Kinderklinik
Göttingen Uni Gastroenterologie
Göttingen Uni-Kinderklinik
Güstrow Innere
Hachenburg Kinderpraxis
Hagen Kinderklinik
Halberstadt Innere Med. AMEOS Klinik
Halberstadt Kinderklinik AMEOS
Halle Uni-Kinderklinik
Halle-Dölau Städtische Kinderklinik
Hamburg Altonaer Kinderklinik
Hamburg Endokrinologikum
Hamburg Kinderklinik Wilhelmstift
Hamburg-Nord Kinder-MVZ
Hameln Kinderklinik
Hamm Kinderklinik
Hanau Kinderklinik
Hanau St Vincenz—Innere
Hannover DM-SPP
Hannover Henriettenstift—Innere
Hannover Kinderklinik MHH
Hannover Kinderklinik auf der Bult
Haren Kinderarztpraxis
Heide Kinderklinik
Heidelberg St Josefskrankenhaus
Heidelberg Uni-Kinderklinik
Heidelberg Uniklinik Innere
Heidenheim Arztpraxis Allgemeinmed
Heidenheim Kinderklinik
Heilbronn Innere Klinik
Heilbronn Kinderklinik
Herdecke Kinderklinik
Herford Innere Med I
Herford Kinderarztpraxis
Herford Klinikum Kinder and Jugendliche
Heringsdorf Inselklinik
Hermeskeil Kinderpraxis
Herne Evan. Krankenhaus Innere
Herten St Elisabeth Innere Medizin
Hildburghausen Hennebergklinik
Hildesheim GmbH—Innere
Hildesheim Kinderarztpraxis
Hildesheim Kinderklinik
Hinrichsegen-Bruckmühl Diabetikerjugendhaus
Hof Kinderklinik
Hohenmölsen Diabeteszentrum
Homburg Uni-Kinderklinik Saarland
Idar Oberstein Innere
Ingolstadt Klinikum Innere
Innsbruck Uni-Kinderklinik
Innsbruck Universitätsklinik Innere
Iserlohn Innere Medizin
Itzehoe Kinderklinik
Jena Uni-Kinderklinik
Jena diabetol. Schwerpunktpraxis
Kaiserslautern Kinderarztpraxis
Kaiserslautern-Westpfalzklinikum Kinderklinik
Kamen Klinikum Westfalen Hellmig Krankenhaus
Karlsburg Klinik für Diabetes and Stoffwechsel
Karlsruhe Städtische Kinderklinik
Kassel Klinikum Kinder- und Jugendmedizin
Kassel Städtische Kinderklinik
Kaufbeuren Innere Medizin
Kempen Heilig Geist—Innere
Kempten Oberallgäu Kinderklinik
Kiel Städtische Kinderklinik
Kiel Universitäts-Kinderklinik
Kirchen DRK Krankenhaus Kinderklinik
Kirchheim-Nürtingen Innere
Klagenfurt Innere Med I
Kleve Innere Medizin
Koblenz Kemperhof 1. Med. Klinik
Koblenz Kinderklinik Kemperhof

Konstanz Innere Klinik
Konstanz Kinderklinik
Krefeld Alexianer Innere
Krefeld Innere Klinik
Krefeld Kinderklinik
Krefeld-Uerdingen St Josef Innere
Kreischa-Zscheckwitz Klinik Bavaria
Köln Kinderklinik Amsterdamerstrasse
Köln Uni-Kinderklinik
Landau Innere
Landshut Kinderklink
Lappersdorf Kinderarztpraxis
Leer Klinikum—Klinik Kinder and Jugendmedizin
Leipzig Uni-Kinderklinik
Leoben LKH Kinderklinik
Leverkusen Kinderklinik
Lienz BKH Kinderklinik
Lienz Diabetesschwerpunktpraxis für Kinder und Jugendliche
Lilienthal Diabeteszentrum
Limburg Innere Medizin
Lindenfels Luisenkrankenhaus Innere
Lindenfels Luisenkrankenhaus Innere 2
Lingen Kinderklinik St Bonifatius
Linz AKH—2 Med
Linz KUK MedCampus IV Kinderklinik
Linz Krankenhaus Barmherzige Schwestern Kardiologie Abt Int II
Linz Krankenhaus der Barmherzigen Schwestern Kinderklinik
Lippstadt Evangelische Kinderklinik
Ludwigsburg Kinderklinik
Ludwigshafen Kinderklinik St Anna-Stift
Ludwigshafen diabetol. SPP
Luxembourg—Centre Hospitalier
Lübeck Uni-Kinderklinik
Lübeck Uni-Klinik Innere Medizin
Lüdenscheid Hilfswerk Kinder and Jugendliche
Lüdenscheid Märkische Kliniken—Kinder and Jugendmedizin
Lünen Klinik am Park
Magdeburg Städtisches Klinikum Innere
Magdeburg Uni-Kinderklinik
Mainz Uni-Kinderklinik
Mannheim Uni-Kinderklinik
Mannheim Uniklinik Innere Medizin
Marburg—UKGM Endokrinologie and Diabetes
Marburg Uni-Kinderklinik
Marburg Uni-Kinderklinik
Marktredwitz Innere Medizin
Marpingen-SPP
Mechernich Kinderklinik
Meissen Kinderklinik Elblandklinikum
Melk Kinderklinik
Memmingen Internistische Praxis
Memmingen Kinderklinik
Merzig Kinderklinik
Minden Kinderklinik
Moers—St Josefskrankenhaus Innere
Moers Kinderklinik
Murnau am Staffelsee—diabetol. SPP
Mutterstadt Kinderarztpraxis
Mödling Kinderklinik
Mölln Reha-Klinik Hellbachtal
Mönchengladbach Kinderklinik Rheydt Elisabethkrankenhaus
Mühlacker Enzkreiskliniken Innere
Mühldorf am Inn Kinderarztpraxis
München 3. Orden Kinderklinik
München Diabetes-Zentrum Süd
München Kinderarztpraxis diabet. SPP
München Schwerpunktpraxis
München von Haunersche Kinderklinik
München-Gauting Kinderarztzentrum
München-Harlaching Kinderklinik
München-Schwabing Kinderklinik
Münster Herz Jesu Innere
Münster Ludgerus-Kliniken GmbH
Münster St Franziskus Kinderklinik
Münster Uni-Kinderklinik
Münster pädiat. Schwerpunktpraxis
Münsterlingen Kinderklinik
Nagold Kreiskrankenhaus Innere
Nauen Havellandklinik
Neuburg Kinderklinik
Neumarkt Innere
Neunkirchen Innere Medizin
Neunkirchen Marienhausklinik Kohlhof Kinderklinik
Neuruppin Kinderklinik
Neuss Lukas-Krankenhaus Kinderklinik
Neuss Lukaskrankenhaus Kinderklinik
Neuwied Kinderklinik Elisabeth
Neuwied Marienhaus Klinikum St Elisabeth Innere
Nidda Bad Salzhausen Klinik Rabenstein/Innere-2 Reha
Nürnberg Cnopfsche Kinderklinik
Nürnberg Med. Klinik 4
Nürnberg Zentrum f Neugeb./Kinder and Jugendl.
Oberhausen Innere
Oberhausen Kinderklinik
Oberhausen Kinderpraxis
Oberhausen St Clemens Hospitale Sterkrade
Oberndorf Gastroenterologische Praxis Schwerpunkt Diabetologie
Oberwart—Burgenländische Krankenanstalten Pädiatrie
Offenbach/Main Innere Medizin
Offenbach/Main Kinderklinik
Offenburg Kinderklinik
Oldenburg Kinderklinik
Oldenburg Schwerpunktpraxis
Olpe pädiatrische Gemeinschaftspraxis
Oschersleben MEDIGREIF Bördekrankenhaus
Osnabrück Christliches Kinderhospital
Osterkappeln Innere
Ottobeuren Kreiskrankenhaus
Oy-Mittelberg Hochgebirgsklinik Kinder-Reha
Paderborn St Vincenz Kinderklinik
Papenburg Marienkrankenhaus Kinderklinik
Passau Kinderarztpraxis

Passau Kinderklinik
Pforzheim Kinderklinik
Pfullendorf Innere Medizin
Pirmasens Städtisches Krankenhaus Innere
Plauen Vogtlandklinikum
Rastatt Gemeinschaftspraxis
Rastatt Kreiskrankenhaus Innere
Ravensburg Kinderklink St Nikolaus
Recklinghausen Dialysezentrum Innere
Regensburg Kinderklinik St Hedwig
Remscheid Kinderklinik
Rendsburg Kinderklinik
Reutlingen Kinderarztpraxis
Reutlingen Kinderklinik
Reutlingen Klinikum Steinenberg Innere
Reutte Tirol BKH Kinderklinik
Rheine Mathiasspital Kinderklinik
Ried Innkreis Barmherzige Schwestern
Rodalben St Elisabeth
Rosenheim Innere Medizin
Rosenheim Kinderklinik
Rosenheim Schwerpunktpraxis
Rostock Uni-Kinderklinik
Rostock Universität Innere Medizin
Rotenburg/Wümme Agaplesion Diakonieklinikum Kinderabteilung
Rüsselsheim Kinderklinik
Saaldorf-Surheim Diabetespraxis
Saalfeld Thüringenklinik Kinderklinik
Saarbrücken Kinderklinik Winterberg
Saarbrücken Kinderklinik Winterberg 2
Saarlouis Kinderklinik
Salzburg Universitäts-Kinderklinik
Scheibbs Landesklinikum
Scheidegg Prinzregent Luitpold
Scheidegg Reha-Kinderklinik Maximilian
Schw. Gmünd Stauferklinik Kinderklinik
Schweinfurt Kinderklinik
Schwerin Innere Medizin
Schwerin Kinderklinik
Schwäbisch Hall Diakonie Innere Medizin
Schwäbisch Hall Diakonie Kinderklinik
Siegen Kinderklinik
Singen—Hegauklinik Kinderklinik
Singen Kinderarztpraxis
Sinsheim Innere
Spaichingen Innere
Speyer Diakonissen Stiftungskrankenhaus Pädiatrie
St Augustin Kinderklinik
St Johann Tirol Kinderklinik
St Pölten Universitäts-Kinderklinik
St Pölten Universitätsklinik Innere
Stade Kinderklinik
Stockerau Landeskrankenhaus
Stolberg Kinderklinik
Stuttgart Olgahospital Kinderklinik
Stuttgart Sana Klinik Bethesda
Suhl Kinderklinik
Sylt Rehaklinik
Tettnang Innere Medizin
Timmendorfer Strand
Traunstein Kinderklinik
Traunstein diabetol. Schwerpunktpraxis
Trier Kinderklinik der Borromäerinnen
Trostberg Innere
Tübingen Uni-Kinderklinik
Ulm Endokrinologikum
Ulm Schwerpunktpraxis Bahnhofsplatz
Ulm Uni Innere Medizin
Ulm Uni-Kinderklinik
Vechta Kinderklinik
Viersen Kinderkrankenhaus St Nikolaus
Villach Kinderklinik
Villingen-Schwenningen SPP
Villingen-Schwenningen Schwarzwald Baar Klinikum Kinderklinik
Villingen-Schwenningen Schwarzwald-Baar-Klinikum Innere
Vöcklabruck Kinderklinik
Waldshut Kinderpraxis
Waldshut-Tiengen Kinderpraxis Biberbau
Wangen Oberschwabenklinik Innere Medizin
Waren-Müritz Kinderklinik
Weiden Kinderklinik
Weingarten Kinderarztpraxis
Weisswasser Kreiskrankenhaus
Wels Klinikum Pädiatrie
Wernberg-Köblitz SPP
Werningerode MVZ
Wesel Marienhospital Kinderklinik
Wetzlar Schwerpunkt-Praxis
Wien 3. Med. Hietzing Innere
Wien Preyersches Kinderspital
Wien Rudolfstiftung
Wien SMZ Ost Donauspital
Wien Uni Innere Med III
Wien Uni-Kinderklinik
Wien Wilhelminenspital 5. Med. Abteilung
Wiesbaden Helios Horst-Schmidt-Kinderkliniken
Wiesbaden Kinderklinik DKD
Wilhelmshaven Klinikum Kinderklinik
Wilhelmshaven St Willehad Innere
Winnenden Rems-Murr Kinderklinik
Wismar Kinderklinik
Wittenberg Innere Medizin
Wittenberg Kinderklinik
Wolgast Innere Medizin
Worms—Weierhof
Worms Kinderklinik
Wuppertal Kinderklinik
Wörth am Main SPP
Würzburg Kinderarztpraxis
Zweibrücken Ev. KH. Innere
Zweibrücken Kinderarztpraxis
Zwettl Landesklinikum Gmünd-Waidhofen Kinderklinik

Table I. Clinical characteristics of girls at onset of T1DM and in the course of the disease stratified by presence or absence of eating disorder during follow-up

Type of eating disorder	Without eating disorders	Any eating disorder	Anorexia nervosa	Eating disorder other than anorexia nervosa	Binge eatingdisorder	Bulimia nervosa	EDNOS
Numbers	31 042	514	155	359	45	85	229
at baseline							
Age, y	8.7 (5.2-11.8)	9.9 (6.6-12.3)*	10.1 (6.4-12.5)*	9.9 (6.6-12.3)*	9.2 (7.0-11.7)	10.7 (7.6-12.8)*	9.9 (6.4-12.1)*
Height-SDS	0.31 (–0.41-1.04)	0.28 (–0.33-1.12)	0.18 (–0.33-0.82)	0.35 (–0.30-1.15)	0.56 (–0.53-2.01)	0.38 (–0.44-1.10)	0.34 (–0.24-1.11)
BMI-SDS	–0.37 (–1.13-0.39)	–0.27 (–0.91-0.41)	–0.53 (–1.20-0.28)	–0.19 (–0.82-0.48)	–0.25 (–0.98-0.70)	–0.25 (–0.58-0.04)	–0.11 (–0.82-0.52)
Manifestation with ketoacidosis [%]	19.3	17.3	23.0	14.6	18.8	11.1	14.6
HbA1c [%]	11.2 (9.6-13.0)	11.7 (10.1-13.8)*	11.7 (9.8-13.5)*	11.8 (10.1-14.0)*	11.2 (9.2-12.2)*	12.3 (9.8-14.1)*	11.8 (10.5-14.0)*
Migration background [%]	14.7	9.5*	10.3	9.2*	6.7	5.9*	10.9
Associated diseases							
Celiac disease [%]	2.8	1.9	2.6	1.7	4.4	0	1.7
Autoimmune thyroiditis [%]	19.4	23.9*	23.2	24.2*	24.4	21.2	25.3*
Changes between manifestation and 3-6 mo							
Change of height-SDS	–0.08 (–0.27-0.08)	–0.07 (–0.19-0.07)	–0.08 (–0.19-0.01)	–0.06 (–0.19-0.08)	–0.12 (–0.18–-0.05)	–0.05 (–0.16-0.03)	–0.04 (–0.20-0.11)
Change of BMI-SDS	+0.48 (0.13-0.94)	+0.50 (0.12-0.87)	+0.61 (0.08-1.11)	+0.46 (0.13-0.82)	+0.81 (0.08-1.23)	+0.44 (0.21-0.87)	+0.43 (0.09-0.74)
Changes between manifestation and last observation							
Change of height-SDS	–0.13 (–0.58-0.22)	–0.25 (–0.81-0.16)	–0.12 (–0.61-0.10)	–0.28 (–0.87-0.16)	–0.35 (–1.25-0.21)	–0.28 (–0.51-0.16)	–0.28 (–0.86-0.14)
Change of BMI-SDS	+0.78 (0.24-1.37)	+0.56 (–0.15-1.11)*	–0.04 (–1.13-0.82)*	+0.80 (0.06-1.30)	+0.88 (0.59-1.67)	+0.56 (–0.18-1.24)	+0.76 (0.05-1.16)
Last observation							
Diabetes duration [y]	7.2 (3.9-11.5)	8.5 (5.4-13.8)*	8.5 (5.1-13.9)*	8.6 (5.8-13.8)*	8.3 (5.6-11.6)	11.3 (7.0-17.6)*	8.2 (5.4-12.5)*
HbA1c [%]	7.9 (7.1-8.9)	8.4 (7.4-10.3)*	8.3 (7.3-10.7)*	8.5 (7.5-10.1)*	8.5 (8.0-10.5)	8.4 (7.5-10.3)*	8.6 (7.6-9.9)*
Insulin doses [IU] per d	50.0 (34.8-65.0)	50.0 (34.2-67.0)	43.0 (26.0-62.7)*	52.7 (38.0-69.5)*	56.4 (42.6-76.0)	44.0 (32.0-62.0)*	53.3 (39.5-70.7)
Insulin doses [IU] per body surface and d	30.1 (22.9-38.0)	29.7 (20.9-38.9)	27.4 (17.2-37.3)*	30.5 (22.4-39.6)	31.8 (23.8-43.4)	27.7 (19.9-33.3)	31.8 (23.2-40.0)
Pump usage [%]	45.1	36.4*	29.0*	39.7	39.0	41.1	39.4
Patients with ketoacidosis [%]	2.3	5.4*	7.1*	4.7*	6.7	2.4	5.2*
Patients with severe hypoglycemia [%]	8.0	11.3*	12.9*	10.6	6.7	8.2	12.3*

Data as median and IQR or as percentage.
*Significant difference between eating disorder and no eating disorder ($P < .05$, adjusted for multiple comparisons).