Comorbidity of attention deficit hyperactivity disorder and type 1 diabetes in children and adolescents: Analysis based on the multicentre DPV registry

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Background: The interaction between type 1 diabetes mellitus (T1DM) and attention deficit hyperactivity disorder (ADHD) in children and adolescents has been studied rarely. We aimed to analyse metabolic control in children and adolescents with both T1DM and ADHD compared to T1DM patients without ADHD.

Patients and methods: Auxological and treatment data from 56,722 paediatric patients (<20 years) with T1DM in the multicentre DPV (Diabetes Prospective Follow-up Initiative) registry were analysed. T1DM patients with comorbid ADHD were compared to T1DM patients without ADHD using multivariable mixed regression models adjusting for demographic confounders.

Results: We identified 1,608 (2.83%) patients with ADHD, 80.8% were male. Patients with comorbid ADHD suffered twice as often from diabetic ketoacidosis compared to patients without ADHD [10.2; 9.7–10.8 vs [5.4; 5.3–5.4] (P < .0001). We also found significant differences in HbA1c [8.6% (7.3–9.4); 66.7 mmol/mol (56.3–79.4) vs 7.8% (7.0–9.0); 62.1 mmol/mol (53.2–74.7)], insulin dose/kg [0.9 IU/kg (0.7–1.1) vs 0.8 IU/kg (0.7–1.0)], body mass index-standard deviation score (BMI-SDS) [0.2 (−0.5 to 0.8) vs 0.3 (0.3 – 0.9)], body weight-SDS [0.1 (−0.5 to 0.8) vs 0.3 (0.3 – 0.9)]; (all P < 0.0001), and systolic blood pressure after adjustment [mean: 116.3 vs 117.1 mm Hg]; (P < 0.005).

Conclusion: Paediatric patients with ADHD and T1DM showed poor metabolic control compared to T1DM patients without ADHD. Closer cooperation between specialized paediatric diabetes teams and paediatric psychiatry/psychology seems to be necessary to improve diabetes care and metabolic control in this group of patients.

KEYWORDS
attention deficit hyperactivity disorder, children, diabetic ketoacidosis, glycated haemoglobin (HbA1c), type 1 diabetes mellitus
1 | INTRODUCTION

Type 1 diabetes mellitus (T1DM) is the most frequent type of diabetes in childhood and adolescence with an incidence of 18/100 000 children under 14 years of age.1 In the general population attention deficit and hyperactivity disorder (ADHD) is the most common psychiatric disorder in childhood and adolescence and affects on average 4.8% of the population2 with different degrees of severity.3 However, in Germany the rate of stimulant therapy for ADHD has recently decreased.4 The interaction between T1DM and attention deficit hyperactivity disorder (ADHD) in children and adolescents has been studied rarely.

Symptoms in children affected with ADHD are more noticeable during school time compared to after school activities. According to current understanding, four behavioural symptoms are characteristic of ADHD: decreased ability to concentrate, problems in complying with sequences, impulsivity, and (optional) hypermotoric activity.3,5 Impulsive ADHD actions mean “thoughtless and spontaneous decisions.”6,7 Affected children without hyperactivity—predominantly girls—are often undiagnosed.8

Previous studies described that lack of concentration in diabetes-related tasks can lead to haphazard and even dangerous diabetes-related actions, resulting in an increased risk for metabolic crises.5,9 Moreover, children with ADHD were more likely to sustain injuries. The prevalence of injuries in children with ADHD who received treatment with ADHD medication is 14% in contrast to a prevalence of about 17% in children with ADHD not treated with ADHD drugs.10 Accidents were the most common cause of death in children with ADHD.5 Mahone et al identified several signs and symptoms as behavioural risk factors for ADHD in preschool children.6 Some of these symptoms may seriously interfere with diabetes treatment, for example avoiding activities that require attention for more than a couple of minutes, losing interest and doing something else after engaging in an activity for only a few minutes, being restless, getting into dangerous situations because of fearlessness, being consistently aggressive towards parents. Taking this behaviour in mind, the comorbidity of ADHD and T1DM can have serious consequences for diabetes self-management11,12 and metabolic outcome.13 but research in this area is still rare.

With the German-Austrian DPV-database (Diabetessoftware für prospektive Verlaufsbeobachtung, diabetes prospective follow-up),14 a metabolic characterization of this group of patients is possible.

We hypothesized that symptoms of ADHD have relevant negative effects on diabetes outcome in children and adolescents. We expected an increased risk for severe hypoglycaemia and/or diabetic ketoacidosis as well as worse metabolic control, as reflected by HbA1c, in patients with both T1DM and ADHD compared to T1DM patients without ADHD. The aim of our study was to describe paediatric patients with ADHD and T1DM with regard to auxological parameters, diabetes control, insulin therapy and acute diabetes complications. In addition, we compared ADHD-patients with and without stimulant therapy.

2 | PATIENTS AND METHODS

We investigated T1DM patients from the standardized longitudinal DPV database,14 which comprises treatment and outcome of routine diabetes care as well as demographic data from >90% of all diabetic children in Germany/Austria. Data were collected locally at 391 specialized centers from Germany and Austria during routine care between January 2003 and March 2015 and transmitted twice a year in anonymous form for central analysis. Implausible data were verified or corrected at the participating centers. Sex, age, diabetes duration, type of diabetes, migration background, body mass index (BMI), height, weight, insulin requirement, number of severe hypoglycaemia, ketoacidosis, glycated haemoglobin (HbA1c) levels, and other parameters are documented in the system. Migration background is defined as at least one parent not born in Germany or Austria.

Diagnosis of ADHD was reported by the families at diabetes consultation or based on psychologic or psychiatric evaluation and recorded by the treating diabetes centers in the database. Drugs used to treat ADHD8,15 included orally administered methylphenidate, amphetamine and atomoxetine in various formulations.

Insulin therapy was documented as daily insulin dose per kilogramme body weight (IU/kg), number of injections per day, and percentage of patients on continuous subcutaneous insulin infusion (CSII).

Height, weight and BMI values were adjusted for age and sex using standard deviation scores and calculated by the LMS method of Cole. National reference data from Kromeyer-Hauschild16 were used. Systolic and diastolic blood pressure (BP) SDS-values were calculated according to KiGGS. BP values above the >95th percentile were interpreted as elevated.17 To assess metabolic control, locally measured HbA1c values were mathematically standardized to the diabetes control and complications trial (DCCT) reference range (4.05–6.05%: 20.77–42.62) using the multiple of the mean method (MoM method).18 HbA1c is reported in both SI (IFCC) and national glycohaemoglobin standardization program (NGSP)/DCCT units.

DKA was defined as glycosuria with ketonuria, hyperglycaemia and acidosis (bicarbonate <15 mmol/L or pH <7.3) according to the consensus guidelines of the international society for paediatric and adolescent diabetes (ISPAD).18 Severe hypoglycaemic episodes were defined as unconsciousness, convulsion, or being unable to take glucose. Without help from others. As younger children almost always need the help of a parent or caregiver when experiencing hypoglycaemia, severe hypoglycaemia in younger children was defined as an altered mental state due to which the child cannot assist in care.18

Screening for microalbuminuria was performed by the following methods: (1) measurement of the urine albumin-to-creatinine ratio (UAC) in a random spot collection, (2) 24-h collection and (3) timed (eg, overnight) collection. Microalbuminuria was defined as at least two increased urine albumin tests during the follow-up period. Thresholds were albumin excretion rate (AER) ≥20 μg/min or albumin-to-creatinine ratio (UAC) ≥2.5 mg/mmol according to guidelines of the American Diabetes Association.14,19

2.1 | Statistical analysis

Data are presented as median and interquartile range for continuous variables and as percentage and rates for categorical variables. Results of regression models are presented as adjusted means (LS Means), rates or odds ratios (OR) with their corresponding 95% confidence intervals (CI). Differences between groups were tested...
using Wilcoxon rank sum tests for continuous variables, X² tests for categorical variables, and Poisson regression models for rates. Adjustments for multiple comparisons were made using the Bonferroni step-down correction (method of Holm).

Hierarchical multiple linear, logistic and Poisson regression models adjusted for age, gender, diabetes duration and migration background were used to compare T1DM patients with ADHD to T1DM patients without ADHD. We included differences between treatment centers as a random effect. Parameter estimation was based on restricted pseudo-likelihood using the Newton–Raphson optimization method. Statistical analysis was performed using SAS for Windows version 9.4 (SAS Institute Inc., Cary, North Carolina). A two-sided P-value < .05 was considered statistically significant.

### 3 RESULTS

In our analysis, we included 56,722 patients aged <20 years with complete data during the most recent year of observation. Median age was 15.3 years (Q1–Q3: 11.6–17.5), median age at diabetes onset was 8.6 years (5.0–11.9) and median diabetes duration was 5.0 years (2.0–8.5). A subgroup of patients (n = 1,608; 2.83%) was diagnosed with ADHD based on clinical diagnosis (n = 1,222) and/or stimulant therapy (n = 1,136). During individual years of the study period between 2003 and 2015, the percentage of documented patients with comorbid ADHD ranged from 1.91% (2003) to 2.93% (2011) (Table 1).

Non-adjusted comparisons between T1DM with and without ADHD are given in Table 2. The proportion of male patients (80.8%) in the group with ADHD was significantly higher than in T1DM patients without ADHD (51.9%, P < .0001). Patient age and age at diabetes onset were similar for both groups, but diabetes duration at the time of examination was significantly longer in T1DM with ADHD (6.0 years; 2.9–9.4) compared to T1DM controls (4.9 years; 2.0–8.5) (P < .0001). BMI-SDS with 0.2 [-0.5 to 0.8] vs 0.3 [-0.3 to 0.9], body weight-SDS with 0.1 [-0.5 to 0.8] vs 0.3 [0.3–0.9] and height-SDS with −0.1 [-0.7 to 0.7] vs 0.1 [-0.6 to 0.8] were significantly lower in T1DM patients with ADHD compared to T1DM patients without ADHD (all P < .0001). Diastolic BP was significantly higher in T1DM with ADHD compared to T1DM only. There were no significant differences for total cholesterol, LDL-cholesterol, HDL-cholesterol or triglycerides before adjustment for confounders.

With regard to acute diabetes complications, diabetic ketoacidosis (DKA/100 patient years) occurred significantly more often in T1DM with ADHD compared to T1DM without ADHD (Table 2, P < .0001). After adjustment for demographic confounders, ADHD patients suffered twice as often from diabetic ketoacidosis than non-ADHD patients (10.2 vs 5.0 events/100 patient years, P < .0001). In contrast, the rate of severe hypoglycaemia did not differ. After adjustment, 15.5 severe hypoglycaemic events/100 patient years occurred in T1DM with ADHD compared to 14.9 events in T1DM controls (n.s.).

There was a significant difference in metabolic control with a higher HbA1c in the group with ADHD (8.6%; 7.3–9.4, 66.7 mmol/ mol; 56.3–79.4) compared to the group without ADHD (7.8%; 7.0–9.0) 62.1 mmol/mol; 53.2–74.7), (P < .0001). Results did not change after adjustment for age, diabetes duration, and gender. There was no significant difference for HbA1c comparing patients with ADHD and stimulant therapy (n = 1.136) to patients with ADHD without psychopharmacological medication (n = 472).

Patients with T1DM and additional ADHD required a significantly higher dose of insulin compared to patients with T1DM only: 0.9 IU/kg [0.7–1.1] vs 0.8 IU/kg [0.7–1.0]; P < .0001. Results persisted after adjustment for gender, age and diabetes duration (P < .0001). We observed no difference in frequency of CSII therapy between the groups. Comparing ADHD patients with and without stimulant therapy, insulin dose did not differ significantly. In patients with ADHD on injection therapy, slightly more frequent applications of insulin per day have been documented (5.0 vs 4.0, P < .0001). After adjustment for confounders (age, diabetes duration and sex), the difference in diastolic BP did not persist, but there was a significant difference in systolic BP with lower values in patients with comorbid ADHD (116 vs 117 mm Hg, P < .002). After additional adjustment for the use of ADHD medication also the difference in systolic BP was no longer significant (P = .07).

There were no significant differences for total cholesterol, LDL-cholesterol, HDL-cholesterol or triglycerides before adjustment for confounders. Details are given in Table 2. After adjustment for confounding effects of age, diabetes duration and sex differences for total cholesterol (183.4 mg/dL vs. 178.9 mg/dL; P < .0002), LDL-cholesterol (103.8 mg/dL vs 100.5 mg/dL; P < .002) and triglycerides (142.5 mg/dL vs 131.3 mg/dL; P = .0005) were all significant. Dyslipidaemia was significantly more prevalent in patients with T1DM and ADHD (46.1% vs 41.0%). After adjustment, 15.5 severe hypoglycaemic events/100 patient years occurred in T1DM with ADHD compared to 14.9 events in T1DM controls (n.s.).

### 4 DISCUSSION

The aim of our analysis was to compare paediatric T1DM patients with and without ADHD documented in the DPV registry, to better
characterize the interaction between the two chronic disorders and to investigate the possible impact of ADHD on diabetes outcome and acute complications. As both disorders are based on very different pathogenesis we hypothesized that disease co-occurrence is probabilistic.20,21

A total of 2.84% of T1DM patients in our patient population were diagnosed with ADHD. This is less than 4–5% currently reported for the general population,2 however the rate of pharmacologically treated patients is decreasing in Germany.4 A possible explanation could be that ADHD might not have been diagnosed in all diabetes patients. Another reason could be that the endocrinologists and diabetes care teams at the participating centres were unaware of the comorbid diagnosis of ADHD. Stratified for individual treatment years, our patient sample showed no significant differences in the frequency of ADHD (see Table 1).

The male predominance of ADHD with a 5:1 ratio of boys to girls corresponds with the typical sex distribution of ADHD.22,23 Children and teenagers are more easily diagnosed when presenting with hyperactivity, regardless of gender.8 This is likely to apply to diabetic patients as well. Girls with ADHD but without hyperactive symptoms (inattentive type, ADD) are often undiagnosed.22 However, not hyperactivity, but impulsivity and the lack of attention seem to be responsible for the risk of a dysfunctional diabetes self-treatment in comorbid patients12 and therefore leads to an increase in diabetes complications.

Previous studies reported that insulin mismanagement is most important for glycaemic control in T1DM patients with comorbid ADHD.23–25 Studies have shown that typical symptoms of ADHD3 lead to not only a higher risk of DKA,25–28 but also increase the risk of severe hypoglycaemia.29 In our study, we observed a significant difference for DKA only. One explanation for DKA might be missed insulin injections due to lack of attention and/or impulsivity in the diet with uncontrolled eating habits. Attention deficit and impulsivity may lead to gaps in treatment of diabetes and severe metabolic imbalance in patients with ADHD,12,30 as confirmed by the significantly higher HbA1c values and the increased rate of DKA in comorbid patients from our study. Therefore, it is important to diagnose ADHD and recognize irrational treatment decisions, even in the absence of hyperactivity.

Reasons for missed injections might differ between ADHD patients on stimulant therapy and those on psychotherapy only or untreated, but data related to prescription dosage and adherence are

| TABLE 2 | T1DM with and without ADHD: non-adjusted comparison1 |
|-----------------|------------------|-------------------|
| **Patient demographics** | | |
| Patient number | 55.114 | 1.608 |
| Male (%) | 51.9 | 80.8 |
| Female (%) | 48.1 | 19.2 |
| Chronological age (y) | 15.3 (11.5 to 17.5) | 15.4 (12.8 to 17.3) |
| Duration of diabetes (y) | 4.9 (2.0 to 8.5) | 6.0 (2.9 to 9.4) |
| Age at manifestation (y) of diabetes | 8.6 (5.0 to 12.0) | 8.5 (5.2 to 11.5) |
| Migration background (%) | 16.2 | 11.8 |
| **Anthropometry and cardiovascular risk** | | |
| Weight-SDS | 0.3 (−0.3 to 0.9) | 0.1 (−0.5 to 0.8) |
| Height-SDS | 0.1 (−0.6 to 0.8) | −0.1 (−0.7 to 0.7) |
| BMI-SDS | 0.3 (−0.3 to 0.9) | 0.2 (−0.5 to 0.8) |
| HbA1c (%) | 7.8 (7.0 to 9.0) | 8.3 (7.3 to 9.4) |
| HbA1c (mmol/mol) | 62.1 (53.2 to 74.7) | 66.7 (56.3 to 79.4) |
| Total cholesterol (mg/dL) | 173.0 (152.0 to 198.0) | 174.0 (153.0 to 198.0) |
| HDL (mg/dL) | 59.6 (50.0 to 70.0) | 58.0 (49.0 to 68.0) |
| LDL (mg/dL) | 95.0 (77.0 to 116.0) | 96.2 (77.0 to 117.0) |
| Triglycerides (mg/dL) | 96.0 (67.0 to 146.0) | 101.0 (69.0 to 161.0) |
| Systolic blood pressure (mm Hg) | 119.0 (110.0 to 127.5) | 120.0 (110.5 to 127.0) |
| Diastolic blood pressure (mm Hg) | 69.0 (63.0 to 75.0) | 70.0 (64.0 to 75.5) |
| **Diabetes-related parameters** | | |
| Insulin dose (IE/kg bodyweight) | 0.8 (0.7 to 1.0) | 0.9 (0.7 to 1.1) |
| Number of injections/day, Injection patients only (n = 36.148) | 4.0 | 5.0 |
| CSII (%) | 32.6 | 33.1 |
| Microalbuminuria (%) | 8.4 | 8.0 |
| Severe hypoglycaemia (100 pat. y) | 14.8 (14.7 to 14.9) | 16.4 (15.7 to 17.1) |
| Hypoglycaemic coma (100 pat. y) | 3.6 (3.5 to 3.7) | 3.9 (3.6 to 4.3) |
| DKA (100 pat. y) | 5.4 (5.3 to 5.4) | 10.3 (9.7 to 10.8) |

CSII, insulin pump therapy; pat, patient; y, years.

1 Data are given as median and interquartile range.

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not available in the DPV database. However, the higher insulin dose and more frequent insulin injections reported by patients with T1DM and comorbid ADHD may be the therapeutic reaction of diabetologists and patients/families to persistently high glucose/HbA1c values.

In our study diastolic BP was slightly higher in T1DM with comorbid ADHD, however this difference did not persist after adjustment. Systolic BP was even lower when demographic confounders were taken into account. This finding is in line with a large and representative national sample of German adolescents displaying a significant association between low BP and ADHD symptoms. However, we observed an increased BP in patients taking methylphenidate, an alpha-adrenergic substance. This has repeatedly been reported in individual patients, both with methylphenidate as well as with atomoxetine. This observation resulted in a warning message from the European Medicine Agency (EMA) and the recommendation to measure BP during therapy. However, alterations in BP in attention-deficit/hyperactivity disorder (ADHD), specifically during dopaminergic stimulant intake, are still not fully understood.

Previous reports on height, weight and BMI in patients with ADHD are inconsistent. Numerous studies described an association between attention-deficit/hyperactivity disorder (ADHD) and overweight/obesity in children and adolescents; however, most studies adjusted only for a limited number of possible confounders. In a community-based sample of the adult German population, de Zwaan et al showed that ADHD in adulthood was associated with obesity. In contrast, our data on children and adolescents with diabetes did not support these results. However, this may be due to the simultaneous effect of diabetes therapy on weight gain in this group of patients or psychosocial confounders. Our results are in line with a previous report by Gurbuz et al. In their study, 34 patients with ADHD out of 48 developed lack of appetite during treatment with methylphenidate. In this subgroup body weight SDS, BMI, and BMI SDS were significantly reduced. In our patient cohort BMI-SDS was significantly lower in the group with ADHD, even more pronounced after adjustment. Lower BMI might be explained by three mechanisms: (1) Children and adolescents with ADHD have higher physical activity than adults. (2) The appetite-reducing effect of methylphenidate. This would be compatible with the fact that BMI-SDS was significantly higher in untreated patients with ADHD in our study. (3) Insufficiently treated diabetes in ADHD with worse metabolic control results in increased lipolysis and glucosuria with subsequent weight-loss.

In 2008 Spahis et al reported abnormalities of serum lipids in patients with ADHD. Our study confirmed these findings, as dyslipidaemia was more prevalent in patients with ADHD and T1DM after adjustment for confounders.

In summary, our study describes significant differences between paediatric patients with or without comorbid ADHD, related to auxology, diabetes therapy and treatment outcomes. The risks for diabetic ketoacidosis and for poor metabolic control are considerably increased in patients with ADHD. Unrecognized as well as inadequately treated comorbid ADHD should be considered as a serious challenge for successful diabetes treatment.

Our study has several limitations. In this multicentre analysis it was difficult to standardize the diagnosis of psychiatric disorders like ADHD, especially for patients without stimulant therapy. A consistent diagnosis of ADHD is challenging, as demonstrated by regional differences of ADHD prevalence. The DPV database is focussed on diabetes, therefore we were not able to provide details on psychological testing, on stimulant dosage or on adherence to pharmacological and non-pharmacological therapy.

The strength of our study was the large multicentre observational database covering more than 90% of paediatric patients with T1DM in Germany and Austria. We clearly described relevant detrimental consequences of a comorbid diagnosis of ADHD on the long-term outcome in T1DM. Further research and studies are necessary to better understand the impact of ADHD on diabetes control and acute complications in order to give evidence-based advice and improve both diabetes therapy as well as psychiatric help for this group of patients. A closer collaboration of paediatric diabetologists with paediatric psychologists/psychiatrists seems to be an important step. Increased awareness for behavioural patterns in everyday management is needed to improve diabetic care and outcome in diabetes patients with ADHD comorbidity.

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Conflict of Interest
No potential conflicts of interest relevant to this article were reported.

Author Contributions
DH and MM conceptualized together with RWH the study design and interpreted the data, DH and KK wrote and edited the manuscript, MM provided specific knowledge, contributed to interpretation of the results and reviewed the manuscript, BB provided specific knowledge, contributed to interpretation of the results, reviewed/edited the manuscript. KPO, RL and ES reviewed/edited the manuscript. EB performed statistical analysis and contributed to interpretation of the results. RWH designed the statistical analysis, supervised the study, contributed to interpretation of results critically revised the manuscript. All authors read and approved the final manuscript.

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