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PSYCHOLOGICAL ASPECTS OF DIABETES

Association of insulin-manipulation and psychiatric disorders: A systematic epidemiological evaluation of adolescents with type 1 diabetes in Austria

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Background/Objective: The aim of this study was to systematically assess the association of insulin-manipulation (intentional under- and/or overdosing of insulin), psychiatric comorbidity and diabetes complications.

Methods: Two diagnostic interviews (Diabetes-Self-Management-Patient-Interview and Children's-Diagnostic-Interview for Psychiatric Disorders) were conducted with 241 patients (age 10-22) with type 1 diabetes (T1D) from 21 randomly selected Austrian diabetes care centers. Medical data was derived from medical records.

Results: Psychiatric comorbidity was found in nearly half of the patients with insulin-manipulation (46.3%) compared to a rate of 17.5% in patients, adherent to the prescribed insulin therapy. Depression (18.3% vs 4.9%), specific phobia (21.1% vs 2.9%), social phobia (7.0% vs 0%), and eating disorders (12.7% vs 1.9%) were elevated in patients with insulin-manipulation. Females (37.7%) were more often diagnosed (P = 0.001) with psychiatric disorders than males (18.4%). In females, the percentage of psychiatric comorbidity significantly increased with the level of non-adherence to insulin therapy. Insulin-manipulation had an effect of +0.89% in HbA1c (P = <0.001) compared to patients adherent to insulin therapy, while there was no association of psychiatric comorbidity with metabolic control (HbA1c 8.16% vs 8.12% [65.68 vs 65.25 mmol/mol]). Ketoacidosis, severe hypoglycemia, and frequency of outpatient visits in a diabetes center were highest in patients with insulin-manipulation.

Conclusions: This is the first study using a systematic approach to assess the prevalence of psychiatric disorders in patients who do or do not manipulate insulin in terms of intentional under- and/or overdosing.

Internalizing psychiatric disorders were associated with insulin-manipulation, especially in female patients and insulin-manipulation was associated with deteriorated metabolic control and diabetes complications.

KEYWORDS

adolescent, diabetes complications, medication adherence, mental disorders, psychology

1 | INTRODUCTION

Puberty and adolescence are a challenging time in diabetes therapy. Adolescents with T1D are known to show deteriorated metabolic control and have the highest rate of acute diabetes complications.[1,2] The etiology of decreased metabolic control is multifactorial and

Abbreviations: DKA, diabetic ketoacidosis; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; T1D, type 1 diabetes mellitus

cannot only be explained by physiological changes during puberty; psychosocial factors contribute to this phenomenon.[3–5] In addition to the developmental demands of this age period, new but complex therapy regimes like multiple daily injections or insulin pump therapy require self-responsible adaptation and application of the daily insulin dosages within provided algorithms.[6] In older children and adolescents, decisions relating to diabetes therapy are increasingly transferred from parents to the adolescents, who have to take on autonomy that is sometimes disproportionate to their psychological maturation. Being overburdened with this responsibility or family conflicts about autonomy can result in poor adherence to diabetes therapy.[7] Therefore, T1D can lead to psychological distress.[8]

Prevalence rates of mental illness are estimated to be 13.4% to 25.7% in adolescents without a chronic disease[9–12] and might even be pronounced in adolescent patients with T1D.[8,13–15] In particular, internalizing disorders comprising depressive and anxiety symptoms as well as eating disorders seem to be elevated.[8] In a recent study, Cooper et al[14] reported a 2.3 times higher risk for specific diagnoses such as anxiety, eating-, mood-, personality, and behavior disorders in young patients with T1D. The prevalence of depression is estimated to be 10% to 26% in T1D[13,16,17] vs 4.7% to 6.2% in somatically healthy children and adolescents,[18,19] of anxiety disorders it is 9% to 19% in T1D[13,16] vs 3.8% to 7.4%[19] and in eating disorders it is also elevated to 7% to 11.5% in T1D[20–22] vs 2.8% in the general population. However, there are also studies showing no increased rates of psychiatric diagnoses.[23,24] Methodological differences in study design, diagnostic tools, and diagnostic criteria between the studies contribute to the differences in rates. An association of psychiatric comorbidity with deteriorated metabolic control and acute diabetes complications including ketoacidosis and severe hypoglycemia is suspected[14,25–32] but there is also some literature suggesting only a weak association.[33,34] The mediating factors in the relationship between psychiatric comorbidity and metabolic control have not yet been completely clarified.[35–37] Hormonal changes associated with stress in the hypothalamic-pituitary-adrenal-axis, with elevated catecholamines and cortisol resulting in elevated blood glucose levels might contribute[38] but also less adherence to treatment could play an important role.[27,39–43]

One common way of non-adherence to diabetes treatment is "insulin-manipulation" which can be performed by: (a) intentional insulin-underdosing and omission or by (b) intentional overdosing of insulin and additional injections. In a prior analysis of this study, we found this behavior in almost a third of adolescents with diabetes (29.5%). The majority were both under- and overdosing (59.2%), some were only overdosing (18.3%), some only underdosing or omitting insulin (22.5%) (data published elsewhere).[44] A link between insulin-omission and psychiatric comorbidity has been established for eating disorders. The so-called "insulin-purging" is a unique way of weight control in T1D by omitting insulin to lose weight by glucosuria and ketonaemic state, reported in many studies focusing on disordered eating behavior[20,45–49] and is acknowledged in the Diagnostic and Statistical Manual of mental disorders (5th ed.) as a diabetes specific inappropriate compensatory behavior.[50] Several studies describe insulin-omission in patients without eating disorders, but the underlying reasons have not been assessed systematically.[49,51] Furthermore, insulin-omission was found to be associated with deteriorated metabolic control, higher rates of diabetes complications and mortality.[52–54] Increasing the dose or administering additional insulin seems to be as frequent as insulin-omission,[44] but scientific evaluation of this behavior is scarce. A recent case report and review of Bauman et al[55] describes 39 cases of factitious hypoglycemia due to intentional insulin-overdosing. The wish to eat more, depression, and a cry for help and attention were described as common reasons. In case reports and studies on suicidal behavior in diabetes patients, insulin-overdosing was reported in the course of suicidal attempts or ideations,[56–59] but whether insulin-manipulation, particularly insulin-overdosing, is associated with other psychiatric comorbidities, is still unknown. A better understanding of possible underlying reasons for insulin-manipulation is important to identify patients at risk and to develop targeted psychological interventions.

Therefore, the aim of our study was to systematically assess the association between intentional insulin-manipulation and psychiatric comorbidity.

Our hypotheses were that (1) insulin-manipulation is associated with the occurrence of psychiatric disorders and (2) insulin-manipulation and psychiatric comorbidity are associated with deteriorated metabolic control. Furthermore, we aimed to assess if insulin-manipulation and psychiatric comorbidity are associated with diabetes complications (severe hypoglycemia, number of hospital admissions due to diabetic ketoacidosis [DKA]) and with the frequency of outpatient visits in the diabetes care centers.

2 | METHODS

Out of all the 55 pediatric diabetes care centers treating adolescents with T1D in Austria, 28 were randomly selected, 21 agreed to participate and were included in our study. Inclusion criteria for patients were an age between 10 and 22 years (inclusive), T1D duration of more than 1 year, sufficient German language proficiency and absence of an additional severe somatic disease or mental retardation. Patients were contacted by their diabetes centers and written informed consent was obtained from the adolescents and their legal representatives. Participants were asked to complete a set of questionnaires, containing basic sociodemographic and medical data. Those returning the questionnaires were contacted by our study team. Two diagnostic interviews were performed by trained research assistants either face-to-face or via telephone to assess adherence to insulin treatment and prevalence of psychiatric comorbidity. The study was approved by the Ethics Committee of the Medical University of Vienna.

2.1 | Medical data

Medical data including age, HbA1c, and diabetes duration were retrieved from the patients' medical records. A medical questionnaire assessed diabetes complications including the number of events with severe hypoglycemia in the past 12 months (hypoglycemia with coma or seizure and requiring parenteral therapy/assistance of another person), number of hospital admissions due to DKA in the past 12 months

and the number of outpatient visits in the diabetes care centers in the past 12 months.

2.2 | Assessment of adherence to insulin therapy

The Diabetes-Self-Management-Patient-Interview,[60,61] a semi-structured interview was translated into German (by E.S., G.W.& D.G., unpublished) and served to assess insulin-manipulation and adherence to treatment rules via specific questions rated on a five-point Likert-scale. To assess the reasons for insulin-manipulation one extra question was added. We found good reliability for the total score with Cronbach Alpha of 0.799. Criterions validity (correlation of total score with HbA1c) was significant (r = 0.699) (Kunkel, Wagner, Berger et al, unpublished data). Insulin-manipulation was defined as recurrent behavior with intentional under- and/or overdosing of insulin by skipping or reducing insulin amounts, or increasing insulin dosage, or performing additional insulin injections. When patients reported under-and/or overdosing of insulin the interviewer rated if the insulin over- and/or underdosing was unintentional because of an error (ie, wrong estimation of carbohydrates, miscalculation of the insulin dose, and forgetting an insulin injection) or if the over- and/or underdosing was performed as an intentional manipulation for one of the following reasons. In case of overdosing: to facilitate binge eating, to induce feeling "high," suicidal intentions, autoaggressive behavior, or to attract attention. In case of underdosing: to influence shape and weight, denial of diabetes, to hide diabetes in social situations with peers, self-harming behavior, or fear of hypoglycemia.

"Level of adherence"-group assignment: If patients reported to adhere to the prescribed insulin therapy they were assigned to the "Adherent-Group." Patients reporting insulin under-and/or overdosing were - based on the reasons for over- and underdosing—assigned to the following two groups: (a) To the "Error-Group" with unintentional deviations from the insulin dosage and (b) to the "Manipulating-Group" with intentional under- and/or overdosing of insulin.

2.3 | Assessment of psychiatric comorbidity

To assess mental health problems based on Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) and International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) criteria, the Children's Diagnostic Interview for Psychiatric Disorders (CDI-MD, German Version[62]), a semi-structured interview was conducted. This instrument is widely used in German-speaking populations and is the gold standard in diagnosing psychiatric disorders in children and adolescents. Interrater reliability (kappa coefficient) ranges between 0.67 and 0.90 for the classes of lifetime diagnoses in the children version.[62] Content validity can be derived from the classification scheme of the DSM-IV. The clinical interviews were performed with adolescents only. In total, 15 different psychiatric diagnoses were assessed, screening questions for alcohol or drug abuse and for psychosis were included. A psychiatric diagnosis was established when patients fulfilled all specific DSM-IV criteria, including subjective impairment. Functional impairment caused by the mental health problem had to be rated by the interviewer on a four-point Likert-scale. Impairment had to be rated at least with a code of 2 (=severe) in order to be interpreted as clinically relevant. The evaluation was dependent on the individual diagnosis and followed the rules of DSM-IV.[11] A subclinical psychiatric diagnosis was assigned when patients showed significant disabling symptoms of a specific mental health problem with clinical relevance, but did not meet all the corresponding DSM-IV criteria (eg, all but one symptom). Both point and life-time prevalence of psychiatric disorders were assessed.

2.4 | Statistical analysis

Age differences between groups were compared using Kruskal-Wallis test. Chi-squared test was used to test for gender differences in clinical characteristics. Bonferroni-Correction was performed for multiple comparisons in prespecified hypotheses. P-values in Tables 1 and 2 were not adjusted for multiple comparisons and should be interpreted as exploratory only. A Poisson regression model was performed to estimate the effect of psychiatric comorbidity, insulin-manipulation, and gender on count data and a linear regression model for the effect on metabolic control. Effects of non-adherence on rates of psychiatric diagnoses and gender effects were calculated by Cochran-Armitage trend test and χ^2 test. Significance was set at a two-tailed $P < 0.05$.

3 | RESULTS

3.1 | Clinical characteristics

Out of 715 patients (mean age 14.68 [SD 2.752] years; 370 male [51.7%]) who were contacted by the diabetes centers, 322 patients (mean age 14.45 [SD 2.67] years; 146 male [45.7%]) participated in the study and completed the set of questionnaires. Three hundred and ninety three patients (mean age 14.88 [SD 2.754] years; 224 male [57.0%]) refused participation, with more males refusing than females ($P < 0.002$). Non-participating patients were older than participating patients ($P = 0.023$) and had a higher HbA1c (8.61% vs 8.16% [70.6 vs 65.68 mmol/mol], $P < 0.000$). For 241 (mean age 14.36 [SD 2.648] years; 103 male; [42.5%]) of the 322 participating patients, diagnostic interviews were successfully conducted. Eighty one participants (mean age 14.73 [SD 2.73] years; 43 male [53.1%]) either refused participation in the interviews or could not be contacted. The ones completing the interviews did not differ in sex ($P = 0.106$) or age ($P = 0.250$).

3.2 | Psychiatric disorders

We found 71 (29.5%) patients to have a current and/or lifetime clinical and/or subclinical psychiatric diagnosis. One-hundred-seventy patients (70.5%) reported no or only minor symptoms. Clinical psychiatric disorders were found in 45 of the patients (18.7%), subclinical psychiatric disorders were found in 44 patients (18.3%). Eighteen patients (7.5%) showed both a clinical and a subclinical disorder. Females (n = 52; 37.7%) were more often diagnosed ($P = 0.001$) with a clinical and/or subclinical psychiatric illness than males (n = 19; 18.4%).

TABLE 1 Distribution of specific psychiatric diagnoses (current and lifetime prevalence) in the adherence groups

Psychiatric disorders	AG n (%)	EG n (%)	MG n (%)	χ^2 *P*-value	*P*-value*
Attention deficit/hyperactivity disorder	2 (1.9)	2 (3.0)	3 (4.2)	0.998	0.974
Conduct disorder	1 (1)	1 (1.5)	2 (2.8)	0.640	0.358
Oppositional defiant disorder	2 (1.9)	0 (0)	4 (5.6)	0.094	0.168
Functional enuresis/encopresis	4 (3.9)	1 (1.5)	2 (2.8)	0.662	0.625
Depression (all subtypes)	**5 (4.9)**	**9 (13.4)**	**13 (18.3)**	**0.017**	**<0.005**
Dysthymia	0 (0)	0 (0)	3 (4.2)	0.026	0.019
Separation anxiety disorder	1 (1)	2 (3.0)	3 (4.2)	0.382	0.168
Agoraphobia	2 (1.9)	3 (4.5)	2 (2.8)	0.629	0.671
Specific (isolated) phobias	**3 (2.9)**	**6 (9.0)**	**15 (21.1)**	**<0.001**	**<0.001**
Social phobia	**0 (0)**	**1 (1.49)**	**5 (7.0)**	**0.011**	**0.004**
Obsessive-compulsive disorder	0 (0)	2 (3.0)	1 (1.4)	0.227	0.333
Clinical/subclinical eating disorders	**2 (1.9)**	**4 (6.0)**	**9 (12.7)**	**0.016**	**0.004**
Generalized anxiety disorder	0 (0)	0 (0)	1 (1.4)	0.301	0.176
Posttraumatic stress disorder	0 (0)	3 (4.5)	1 (1.4)	0.081	0.358
Adjustment disorder	1 (1)	0 (0)	2 (2.8)	0.311	0.333
Alcohol/drug abuse	0 (0)	0 (0)	0 (0)	—	—
Psychosis	0 (0)	0 (0)	0 (0)	—	—
Any psychiatric disorder	**18 (17.5)**	**20 (29.6)**	**33 (46.5)**	**<0.001**	**<0.001**

Abbreviations: AG, Adherent-Group; EG, Error-Group; MG, Manipulating-Group.
*Cochran-Armitage trend test, *P*-values not adjusted for multiple testing. Bold letters: p<0.05

3.3 | Insulin-manipulation

We identified 103 (42.7%) patients to be adherent to the prescribed insulin dosages (Adherent-Group), 67 (28.7%) patients to have management problems (Error-Group), and 71 (29.5%) patients to be intentionally manipulating their insulin doses (Manipulating-Group), further details were published elsewhere.[44] A gender effect was seen with the proportion of females significantly increasing with the level of non-adherence (females Adherent-Group n = 47 [45.6%]; Error-Group n = 42 [62.7%]; Manipulating-Group n = 49 [69.0%], *P* = 0.002).

3.4 | Association of insulin-manipulation and psychiatric comorbidity

We explored the distribution of psychiatric disorders among the three adherence groups and found a significant increase of psychiatric comorbidity with the level of non-adherence, ranging between 17.5% and 46.5% (Figure 1). In patients with psychiatric comorbidity, we found 33 (64.7%) to be manipulating their insulin, while in patients without psychiatric disorders 38 (30.9%) patients showed manipulation (*P* = 0.001).

TABLE 2 Association with diabetes complications and frequency of outpatient visits

Association of manipulating behavior with complications and frequency of outpatient visits							
	AG n[a]	CG mean (SD)	EG n[a]	EG mean (SD)	MG n[a]	MG mean (SD)	*P*-value*
DKA with hospital admission[a]	n = 0-5	0.26 (±0.79)	n = 0-1	0.08 (±0.28)	n = 0-7	0.63 (±1.34)	*P* = <0.001 MG vs EG *P* = 0.001 MG vs CG *P* = 0.100
Severe hypoglycemia[a]	n = 0-12	0.52 (±1.450)	n = 0-4	0.32 (±0.748)	n = 0-10	0.79 (±2.042)	*P* = 0.026 MG vs EG *P* = 0.011 MG vs CG *P* = 0.107
Number of outpatient visits[a]	n = 1-10	4.07 (±1.349)	n = 1-9	4.41 (±1.876)	n = 1-12	4.77; ± 2.346	*P* = 0.096 MG vs EG *P* = 0.317 MG vs CG *P* = 0.030
Association of psychiatric comorbidity with complications and frequency of outpatient visits							
	psych. comorbid n[a]		psych. comorbid mean (SD)		no psych. comorbidity n[a]	no psych. comorb. mean (SD)	*P*-value*
DKA with hospital admission[a]	n = 0-7		0.60 (±1.338)		n = 0-4	0.18 (±0.572)	*P* = <0.001
Severe hypoglycemia[a]	n = 0-6		0.50 (±1.098)		n = 0-12	0.56 (±1.654)	*P* = 0.339
Number of outpatient visits[a]	n = 1-12		4.51 (±2.039)		n = 1-12	4.30 (±1.752)	*P* = 0.948

Abbreviations: AG, Adherent-Group; EG, Error-Group; MG, Manipulating-Group.
[a] Number of events in the past year.
**P* values are estimations of a regression model, not adjusted for multiple testing.

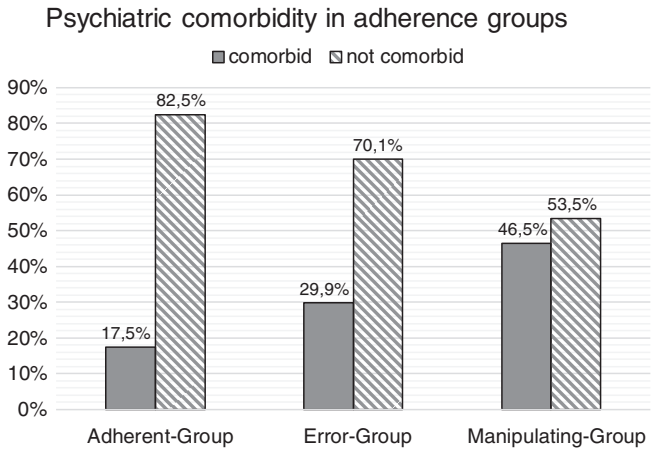

FIGURE 1 Percentage of psychiatric comorbidity in the adherence groups ([*P* = 0.001] Cochran-Armitage trend test)

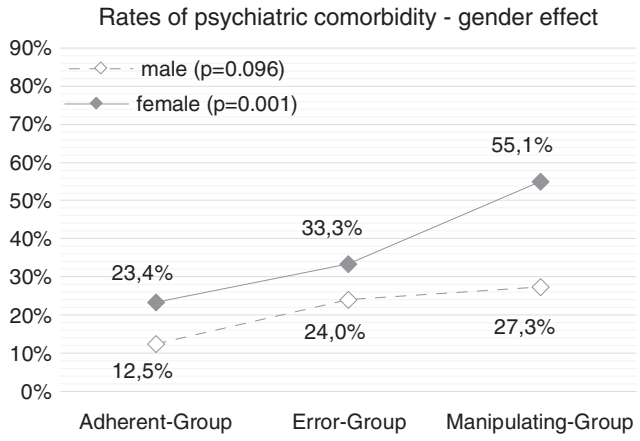

FIGURE 2 Gender effect on psychiatric comorbidity (Cochran-Armitage trend test)

3.5 | Specific psychiatric diagnoses

We found elevated rates of specific phobia, social phobia, depression, and eating disorders in the Manipulating-Group. For all other diagnoses, no significant differences were found between adherence groups (Table 1). Both under- and overdosing were performed in the majority of the diagnoses (Table 3).

3.6 | Gender effect

In the female sample, the percentage of psychiatric comorbidity significantly increased with the level of non-adherence (*P* = 0.001), while in male patients this effect was not significant (*P* = 0.096) (Figure 2).

3.7 | Association with metabolic control

The participants of the study showed a mean HbA1c of 8.13% (±1.514) (65.36 mmol/mol). The regression model revealed no influence of psychiatric comorbidity on HbA1c: in patients with psychiatric comorbidity HbA1c was 8.16% (65.68 mmol/mol), in patients without psychiatric comorbidity HbA1c was 8.12% (65.25 mmol/mol) (*P* = 0.427). However, insulin-manipulation had a significant association with metabolic control (*P* = 0.001) with higher values in patients less adherent to insulin therapy. The estimated difference (adjusted for psychiatric comorbidity) was a higher HbA1c of plus 0.89% in the Manipulating-Group compared to the Adherent-Group (*P* = <0.001) and a higher HbA1c of plus 0.60% in the Error-Group compared to the Adherent-Group (*P* = 0.0186, n.s. after Bonferroni correction), details published elsewhere.[44]

3.8 | Association with diabetes complications and frequency of outpatient visits

DKA, number of severe hypoglycemia and frequency of outpatient visits in a diabetes care center (typical frequency is four visits per year)

TABLE 3 Number of patients with psychiatric diagnoses performing intentional insulin-manipulation (Manipulating-Group)

Psychiatric disorder	only under-dosing	only over-dosing	Under- and overdosing
ADHD	1	1	1
Conduct disorder	1	–	1
Oppositional defiant disorder	2	1	1
Funct. enuresis/encopresis	–	1	2
Depression (all subtypes)	–	4	9
Dysthymia	–	–	3
Separation anxiety disorder	2	–	1
Agoraphobia	2	–	–
Specific (isolated) phobias	5	4	6
Social phobia	2	2	2
Generalized anxiety disorder	–	–	1
OCD	0	0	1
Anorexia nervosa	–	–	1
Bulimia nervosa	1	–	1
EDNOS	–	–	5
Subclinical eating disorder	–	1	–
PTSD	–	–	1
Adjustment disorder	–	–	2

Abbreviations: ADHD, attention deficit/hyperactivity disorder, OCD, obsessive-compulsive disorder, EDNOS, eating disorders not otherwise specified, PTSD, posttraumatic stress disorder.

were highest in the Manipulating-Group. Patients with psychiatric comorbidity had more hospital admissions with DKA than patients without. There was no significant gender effect on DKA (P = 0.485), severe hypoglycemia (P = 0.0568) or frequency of outpatient visits (P = 0.713) (Table 2).

4 | DISCUSSION

In our interview based cross sectional study, we interviewed 241 young patients with T1D performing two diagnostic interviews to assess psychiatric comorbidity and adherence to insulin therapy. We found a strong association of insulin-manipulation and internalizing psychiatric comorbidity, especially in female patients. To our knowledge, this is the first study using a systematic approach to assess the prevalence of psychiatric disorders in patients who intentionally do or do not manipulate their insulin dosage.

4.1 | Rates of psychiatric comorbidity

Elevated rates of psychiatric comorbidities in patients with diabetes were detected in several studies.[8,13–15] We found a prevalence of 29.3% and therefore, a comparable rate with Butwicka et al[63] who found a prevalence rate of 26.6% in youth with T1D. The lower rate of psychiatric comorbidity in the Adherent-Group (17.5%) was comparable with the rates in children and adolescents without a chronic disease.[10] The increased rate up to 46.5% in the Manipulating-Group indicates that insulin-manipulation might be a risk factor for or a symptom of psychiatric disorders.

Internalizing disorders are suspected to be pronounced among young patients with T1D.[8,14] Accordingly, we found internalizing disorders elevated—but only in association with insulin-manipulation. In these patients the depression rates were four times higher, the rate of specific phobia three times higher and the rate of social phobia doubled compared to patients who were adherent to insulin therapy. The latter even had prevalence rates below the general rates. In eating disorders, we also found elevated rates associated with insulin-manipulation—which is already known from numerous previous studies.[20–22] What our study adds is that for the first time we could reveal that patients with T1D and eating disorders not only with underdose insulin for weight control purposes— but also overdose it to enable uncontrolled eating and binge eating. Interestingly, we did not find under- or overdosing associated to specific psychiatric disorders. Both behaviors were found in the majority of the diagnoses and almost two thirds of the patients performed both underdosing and overdosing of insulin.

4.2 | Gender aspects

We found female patients to be at higher risk for both psychiatric disorders and insulin-manipulation. This result corresponds to many epidemiological studies finding internalizing psychiatric disorders to be pronounced in female gender[10,64] and therefore might reflect a general pattern in psychiatry.

4.3 | Insulin-manipulation as a symptom of internalizing psychiatric comorbidity?

So far, an association between insulin-manipulation and psychiatric disorders was only established for "insulin-purging."[50] Patients in our study reported to skip insulin because of weight loss intentions, but also because of denial of diabetes, to hide diabetes from peers, or because of self-destructive behavior or fear of hypoglycemia. Additional insulin was given to enable uncontrolled binge eating, because of self-destructive behavior or because of suicidal intentions.[44] This is in line with known symptoms of anxiety and depression: Reduced energy, lacking self-care and being self-destructive, even suicidal, by using less insulin, or by applying hazardous extra doses of insulin would be a diabetes specific symptom in depressive disorders. In anxiety disorders avoiding insulin by skipping or reducing insulin could be classified as an avoidance behavior in fear of hypoglycemia or in social phobia, when diabetes is hidden from the peers. Therefore, insulin-manipulation could be a diabetes specific symptom also in anxiety and depression.

4.4 | Association with metabolic control and diabetes complications

The strong association of insulin-manipulation with metabolic control and diabetes complications in our study underlines the role of behavior and adherence problems as mediating factors in metabolic deterioration and diabetes complications.[43]

4.5 | Strength and limitations

Psychiatric comorbidities, especially internalizing disorders, often are overlooked in the course of routine clinical care in T1D. Recent observational studies based on the "German-Diabetes-Database (Diabetes-Patienten-Verlaufsdokumentation—DPV)" derived psychiatric diagnoses from patients' medical records and not from diagnostic interviews. They showed rates of depression and eating disorders far below the general prevalence rates, confirming this problem of underdiagnosing.[32,65] Diagnostic interviews are regarded to be the most accurate way to diagnose internalizing disorders.[37] The strength of our study is the systematic approach and the use of standardized diagnostic interviews to establish psychiatric comorbidity and therapy adherence.

One limitation of our study is that out of 715 contacted patients 393 refused to participate. The refusing patients were more often males, were older, and had a higher HbA1c. One can hypothesize that these patients are the less adherent. If so, however, our study might even underestimate the rate of non-adherence with insulin therapy, probably in male patients. Furthermore, data on insulin administration is based on self-reports from the adolescent patients. There is no way to assess the actual applied amount of insulin. Electronic pump records document boluses, but some of the patients in the Manipulating-Group reported to disconnect the pump before giving a bolus or to use the "catheter priming program" for secret boluses, so those records are not always valid.[55] As patients knew their answers were treated strictly confidential, we are confident that most patients reported truthfully. Still, we might have missed some patients who

manipulate insulin but were not willing to share their secret behavior, or reported to have unintentionally taken the incorrect dose which would have led to a misclassification to the Error-Group. Therefore, this group might be biased by some patients manipulating insulin. This is supported by the linear increase in diabetes complications according to level of non-adherence in the group comparisons. A further limitation refers to the low number of cases for each of the psychiatric disorders and for diabetes complications in the different groups. Results should be regarded as exploratory, however, a tendency for increasing prevalence of internalizing psychiatric disorders with the level of non-adherence can be shown.

4.6 | Implications

Diabetes teams should be aware of this secret behavior and prompt a systematic evaluation of patients with either insulin-manipulation, psychiatric symptoms or deteriorated metabolic control. Most psychiatric problems start at young age and tend to persist into adulthood.[12,66] So, early detection of psychiatric comorbidity and insulin-manipulation is essential and may be of long-term value. Studies assessing the persistence and diabetes outcome of insulin-manipulation and underlying psychiatric comorbidities should be performed to lay grounds for the development and evaluation of specific therapeutic interventions.

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G.B. initiated the study, developed the protocol, and wrote the manuscript. G.W. coordinated the data analysis and developed the study protocol, T.W. performed the statistical analysis and wrote the statistical analysis paragraph. E.S., B.R., and A.K. provided clinical expertise and reviewed the drafts. I.B. contributed to the data management and performed the diagnostic interviews. D.G. contributed to the data management. All authors commented on drafts of the manuscript. G.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. M.T. and L.P. contributed with English language editing.

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APPENDIX

Multicenter study: Contributing diabetes care centers

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