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Affective Disorders and Self-Injurious Behavior in Children and Young Adults with Carbohydrate Metabolism Disorders

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Abstract

Introduction: Affective disorders and carbohydrate metabolism disorders are problems of increasing importance in the population of children, teenagers and young adults. Much evidence indicates that these problems may co-occur with increased frequency and have much more serious consequences than on their own.

Material and methods: Inclusion criteria were established for the review of studies and comprised participants under 25 years of age diagnosed with carbohydrate metabolism disorders, psychometric measurements of symptoms of affective disorders and self-aggressive tendencies. Review of the MEDLINE database was conducted.

Discussion: The results of 10 out of 12 studies included in the review indicated significantly increased risk of depression and suicidal tendencies in patients with diabetes. In the described publications, the frequency of affective disorders in a specific population ranged from 1.2% to 47.6% and up to 60.4% for unspecified affective disorder, sub-threshold and fully symptomatic, and the HR ranged from 1.33 to 2.0 for fully symptomatic affective disorders and up to 6.49 for unspecified affective disorder, sub-threshold and fully symptomatic. Descriptions of the incidence of self-injurious behavior and suicidal tendencies estimate them in the range from 0.8% to 35.7%, and in the studies comparing to a control group, the risk for a suicide attempt was between HR: 1.7 and 3.25.

Conclusions: The occurrence of affective disorders in children and young adults is significantly more frequent in patients with diabetes compared to patients without carbohydrate metabolism disorders.

Keywords: affective disorder, depression, suicide, diabetes mellitus, children

Streszczenie

Wstęp: Zaburzenia afektu oraz zaburzenia gospodarki węglowodanowej są problemami o rosnącym znaczeniu w populacji dzieci, nastolatków i młodych dorosłych. Wiele dowodów wskazuje na to, iż problemy te mogą ze sobą współwystępować ze zwiększoną częstością i nieść znacznie bardziej poważne konsekwencje niż osobno.

Materiał i metody: Dokonano przeglądu bazy MEDLINE zgodnie z założonymi a priori kryteriami włączenia. Zakwalifikowane badania obejmowały uczestników do 25 roku życia ze zdiagnozowanymi zaburzeniami gospodarki węglowodanowej, a metody badawcze obejmowały pomiary psychometryczne objawów zaburzeń afektu i tendencji autoagresywnych.

Dyskusja: Wyniki 10 z 12 zakwalifikowanych do przeglądu badań potwierdziły zwiększone ryzyko wystąpienia depresji i tendencji samobójczych u pacjentów z cukrzycą. W opisywanych publikacjach częstość zaburzeń afektu w określonej populacji wynosiła od 1.2% do 47.6% oraz do 60.4% dla nieokreślonego zaburzenia afektu o pełno- i niepełnoobjawowym nasileniu, a współczynnik ryzyka HR od 1.33 do 2.0 dla pełnoobjawowych zaburzeń afektu, oraz do 6.49 dla nieokreślonego zaburzenia afektu o pełno- i niepełnoobjawowym nasileniu. Opisy częstości występowania tendencji autoagresywnych i samobójczych

szacują je w zakresie od 0.8% do 35.7%, a w badaniach z porównaniem do grupy kontrolnej współczynnik ryzyka dla próby samobójczej wyniósł między HR: 1.7 a 3.25.

Wnioski: Występowanie zaburzeń afektu u dzieci i młodych dorosłych jest wyraźnie częstsze w przypadku współwystępowania cukrzycy niż w przypadku braku zaburzeń gospodarki węglowodanowej.

Słowa kluczowe: zaburzenia afektu, depresja, samobójstwo, cukrzyca, dzieci

Introduction

Affective disorders are a serious problem of increasing importance in the pediatric population. According to a meta-analysis by Racine et al., symptoms of depression occur with a frequency of 25.2% (95% CI 21.2-29.7%), fully symptomatic depression occurs with a frequency of 0.4% to 8.3% and is one of the most common mental disorders in this group [1,2]. Symptoms of depression, which according to ICD-10 include, among others, apathy, lack of motivation, poor concentration, low mood, low self-esteem and pessimistic thoughts (including suicidal ideation), have a significant negative impact on the quality of life. Much evidence indicates that affect disorders may occur with increased frequency, severity and have more negative consequences in patients with chronic diseases compared to healthy people [2]. This group includes carbohydrate metabolism disorders. According to estimates, in 2021 there were approximately 355,900 new cases of type 1 diabetes (T1DM) globally, of which only 56% (N: 200,400) were diagnosed [3]. In the pediatric population, the dominant type is T1DM, although a disturbing global increasing trend in the incidence of type 2 diabetes (T2DM), which is observed as well [4]. The coincidence of affective disorders with diabetes mellitus (DM) may have extremely dangerous implications, resulting mainly from poor control of carbohydrate metabolism [5], but also from the danger of suicide attempts facilitated by access to insulin [6,7]. Due to the aforementioned facts and the existence of contradictory research results on this topic, we decided to conduct an exhaustive review of the literature on the subject of affective disorders and suicidal tendencies in the course of carbohydrate metabolism disorders in the population of children and adolescents.

Material and Methods

A priori general inclusion criteria were established and comprised participants aged 0 -18, children diagnosed with Type 1 and Type 2 DM, measurements of mood disorders and self-injurious behavior incidence, original articles in English or Polish language. After an initial review of the literature, it was determined that there were too few publications concerning the strictly pediatric population, and therefore, it was determined that publications covering participants no older than 25 years of age would also be included in the review. Due to the inclusion criteria sufficiently specifying the scope of the publications sought, the only exclusion criteria was the lack of availability of the full text and type of articles being review studies or conference proceedings. A MEDLINE database review was carried out. The search query was as follows: ("Self-Injurious Behavior" [MeSH Terms] OR "Mood Disorders" [MeSH Terms]) AND (child* OR adolescent* OR youth OR pediatric) AND ("Glucose Metabolism Disorders" [MeSH Terms] OR "diabetes mellitus" OR "insulin resistance" OR insulin OR glucagon OR hyperglycaemia OR hypoglycaemia OR hyperinsulinism OR glycosuria). The search was carried out on October 31, 2023 and resulted in 693 records found. Articles that matched the inclusion criteria have been extracted by two researchers independently. The questionable cases varying between sets of different researches were examined and approved by a third researcher. The number of 11 records was included in the final review.

Results

Among children and young adults, the most frequent affective disorder is depression, which, according to most sources qualified for the review, is more frequent in the course of DM compared to the healthy population. Butwicka et al. conducted a population-based cohort study involving 17,122 children with T1DM and their 18,847 siblings. In addition, each diabetic patient was assigned 100 healthy children as a control group – in total, medical data of 1,732,580 people with an average age of 9.3±4.5 were analyzed. Affective disorders (defined as diagnoses: ICD-8 codes 296 and 300.4; ICD-9 codes 296, 300E, and 311; ICD-10 codes F30–F39) were diagnosed in 210 (1.2%) study patients, and in the control population group they were found in 10,286 participants (0.6%), which translates into approximately twice the risk of affective disorders in patients diagnosed with DM – hazard (HR): 2.0 (95% CI 1.8 - 2.3). This trend showed variability when analyzed by cohorts differing in year of birth. The incidence of mood disorders and HR compared with control group

were as follows: in the cohort born in 1973-1986 0.2% (95%CI 0.0-0.5), 2.2 (95%CI 1.0-5.2); in the years 1987-1996 0.7% (95%CI 0.5-1.1), 2.0 (95%CI 1.6-2.6); in 1997-2009 3.4% (95%CI 2.7-4.3), 2.0 (95%CI 1.7-2.4), respectively [8]. Perry et al. examined cross-sectionally and longitudinally the data of 3208 participants aged 18 for the cross-sectional analysis and 9 and 18 years for the longitudinal study. Indicators of carbohydrate metabolism disorders, such as insulin resistance or impaired glucose tolerance, and depression measured with the Clinical Interview Schedule-Revised (CIS-R) tool were taken into consideration. The result of the cross-sectional analysis was the fulfilment of the diagnostic criteria for a depressive episode in 9% of participants, and the discovery of a weak positive correlation of depressive symptoms with HOMA2 score (an updated mathematical model of HOMA - Homeostasis Model Assessment – which is a marker of insulin resistance) and fasting insulin levels: β= 0.04 (95% CI 0.02-0.30) for HOMA2; β=0.05 (95% CI 0.03-0.33) for fasting insulin. There was also a weak inverse correlation with fasting glucose levels: β=-0.05 (95% CI -0.36 to -0.02). A statistically significant odds ratio (OR) of 1.16 (95% CI 1.01 – 1.33) was also found for a depressive episode, with fasting insulin level being the predictor. In a longitudinal study, correlations between indicators of carbohydrate homeostasis disturbances and symptoms of depression did not reach statistical significance [9]. Sinnamon et al. used the Physiological Hyperarousal and Positive And Negative Affect Schedule for Children (PH-PANAS-C) tool to determine the severity of affect disorders in a group of 107 study participants aged 7-18 years, divided into a study group – 53 patients diagnosed with T1DM, and a control group – 54 healthy counterparts. Unspecified disturbed affect with full and subthreshold intensity was found in as many as 60.4% of participants in the study group, compared to 9.3% of participants in the control group. However, after differentiating into anxiety-related, depressive and mixed disorders, only the difference in the frequency of anxiety-related disorders between the groups reached statistical significance – 37.7% in the study group vs 1.9% in the control group [10]. Helgeson et al. recruited a group of 263 children in their early adolescence (10.7 – 14.2 years old) for the purposes of their study – 132 children with T1DM and 131 healthy children for the control group, who were then interviewed using CDI. There were no statistically significant differences between the groups in terms of the severity of depressive symptoms or anxiety disorders. However, a greater decrease in social acceptance and a higher rate of eating disorders were found in the DM group [11].

The review identified only two publications exploring the issue of suicidal tendencies in pediatric patients with DM that met the established eligibility criteria. Butwicka et al. during the previously mentioned population analysis determined the risk of suicide attempts in the group of participants suffering from T1DM – out of 17,122 participants in the study group, 129 attempted suicide, which accounts for 0.8% - twice the percentage of the control group – 0.4% (N: 7,427), HR: 1.7 (95% CI: 1.4 – 2.0) [8]. Efe and Erdem studied differences in the self-injurious behavior in adolescents aged 15-18 years, the study group included 60 patients with T1DM, as well as 319 healthy counterparts. Exam using the Aggression Questionnaire and Inventory of Statements About Self-injury tools did not reveal statistically significant differences in suicidal and auto-aggressive tendencies between the groups [12].

The publications described up to this point concerned the strictly pediatric population. The following studies included children and young adults up to 25 years of age.

Vila et al. are the authors of one of the early reports on the increased risk of affective disorders in young (13-19 years old) female patients with T1DM and obesity – an increased incidence of dysthymia was found in patients with T1DM with obesity (N:15), and without obesity (N:37), 47% and 16%, respectively, and in obese patients without DM (N:22) – 18%, compared to healthy, non-obese girls from the control group (N:24), among whom dysthymia occurred in 8% of cases. Authors utilised Beck Depression Inventory (BDI) for evaluation of affective disorders [13]. Kovacs et al. conducted their study with a study group of a similar size – 92 children diagnosed with T1DM aged 8 to 13 were subject to regular psychiatric observations. The study was conducted without the participation of the control group. After 10 years from the diagnosis (average age – 20 years), 47.6% of the participants were diagnosed with a mental disorder or disease, the most common of which was depression, with which 27.5% of patients were diagnosed. Depression was most often diagnosed in the first year after the diagnosis of DM. An important risk factor turned out to be a history of depression in the participants' mothers and a psychiatric history in the participants themselves [14]. Similar trends, but in a much larger group, were presented in a population-based cohort study by Robinson et al. When comparing 3,544 participants with T1DM with a control group of 1,388,397 participants (aged 15-25 years), DM patients had a 1.33 times higher risk of developing affective disorders diagnosed in the emergency department or during hospital treatment – HR 1.33 (95% CI 1.19 – 1.50), they had a higher risk of developing any other psychiatric condition as well – HR 1.29 (95% CI 1.21 – 1.37) [15]. T2DM may carry the risk of affect disorders in a manner analogous to T1DM – Roberts et al. in a group of T2DM patients aged 13-21 determined the incidence of high-grade depressive symptoms at 22% - Patient Health

Questionnaire – 9 (PHQ-9) was utilised. When it comes to 23% of participants, they reported high levels of disease-related distress, especially patients treated with insulin and covered by public health insurance. The authors did not include a control group in the study design [16].

On the base of their study of 126 patients diagnosed with T1DM and their comparison to a control group of 499 subjects (participants aged 14-19 years), Radobuljac et al. assessed the frequency of suicidal thoughts and self-harm at 35.7% and 12.9% in the study group vs 38.3% and 19.7%, respectively in the control group. It was found that girls with T1DM were at the highest risk of suicidal ideation, but not of self-harm. The lowest incidence of suicidal ideation and self-harm tendencies was found in boys with T1DM – both the difference between boys and girls with T1DM and boys with T1DM and the control group were statistically significant. In total, more patients with T1DM sought psychological help compared with controls [17]. Cooper et al. conducted a population-based study involving data regarding 1,309 children with T1DM and 6,451 controls, then compared to data from the Cause of Death Register appropriate for the location of the statistical office (mean follow-up age: 25.6 years). Standardized mortality ratio for death from any cause compared to the group control ratio was 1.7 for males and 10.1 for females in the group of patients with T1DM, however, for suicide, it did not reach statistical significance [18]. The remaining publications maintain a similar trend of results indicating the negative impact of DM on mental health. In the study by Majidi et al. participated 550 teenagers and young adults (10-24 years old) – during evaluation with PHQ-9, 9% (N:49) of them expressed suicidal thoughts during their life, and among them, 83.4% showed symptoms of depression, 16% had a history of suicide attempts. None of the participants reported a suicide plan at the time of the study, although 5 people admitted that they had previously considered the possibility of using insulin for suicidal purposes. Three participants used insulin in a suicide attempt [19]. The publication by Robinson et al. mentioned earlier in the context of disordered affect – the authors created a cohort containing 3,544 participants with DM (at the age of 15, follow-up at the age of 25). Participants with DM had a more than three-fold higher suicide risk compared to healthy controls – HR for suicide attempt 3.25 (95% CI 1.79 – 5.88) [15].

Table 1. Summary of articles included in the review.

Study	Country of Origin	Sample size (n)	Age (years)	Type of study	Measurement	Results	Additional findings
Butwicka et al. [8]	Sweden	1,732,580	mean 9.3±4.5; median follow-up after 5.8 (interquartile range 2.8-9.4)	Population-based, cohort	Affective disorders (defined as diagnoses: ICD-8 codes 296 and 300.4; ICD-9 codes 296, 300E, and 311; ICD-10 codes F30–F39) registered in Swedish National Patient Register	Affective disorders: 1.2% in study group vs 0.6% in control group HR: 2.0 (95% CI 1.8 - 2.3)	The incidence of mood disorders and HR compared with control group were as follows: in the cohort born in 1973-1986 0.2% (95%CI 0.0-0.5), 2.2 (95%CI 1.0-5.2); in the years 1987-1996 0.7% (95%CI 0.5-1.1), 2.0 (95%CI 1.6-2.6); in 1997-2009 3.4% (95%CI 2.7-4.3), 2.0 (95%CI 1.7-2.4), respectively
					Suicide attempts	0.8% of the study study group attempted suicide - twice the percentage of the control group –0.4%; HR: 1.7 (95% CI: 1.4 –2.0)	

Perry et al. [9]	England	3,208	9; follow-up at 18	Cross-sectional, longitudinal (cohort)	CIS-R	Cross-sectional: depressive episode in 9% of participants; positive correlation of depressive symptoms with HOMA2 and fasting insulin levels: β= 0.04 (95% CI 0.02-0.30) for HOMA2; β=0.05 (95% CI 0.03-0.33) for fasting insulin; odds ratio (OR) of 1.16 (95% CI 1.01 –1.33) for a depressive episode, with fasting insulin level being the predictor	In a longitudinal study, correlations between indicators of carbohydrate homeostasis disturbances and symptoms of depression did not reach statistical significance
Sinnamon et al. [10]	Australia	107	mean 12.53±3.53; range 7-18	Cross-sectional, case-control	PH-PANAS-C	Unspecified disturbed affect with full and subthreshold intensity in 60.4% in study group vs 9.3% in the control group	After differentiating into anxiety-related, depressive and mixed disorders, anxiety-related disorders –37.7% in the study group vs 1.9% in the control group; depressive and mixed disorders did not reach statistical significance
Helgeson et al.[11]	United States of America	263	mean 12.08±0.73; range 10.7-14.2	Case-control	CDI	No statistically significant differences in depressive symptoms or anxiety disorders between study and control group	Greater decrease in social acceptance and a higher rate of eating disorders were found in the DM group
Efe and Erdem [12]	Turkey	379	mean 16.49±1.11; range 15-18	Case-control	Aggression Questionnaire and Inventory of Statements About Self-injury	No statistically significant differences in suicidal and auto-aggressive tendencies between study and control group	

Vila et al. [13]	France	98	mean 15.6±1.9; range 13-19	Case-control	BDI	47% rate of dysthymia in T1DM obese patients vs and 16% in T1DM without obesity vs obese patients without DM 18% vs 8% in non-obese non DM girls	
Kovacs et al. [14]	United States of America	92	mean 11.0±1.5; range 8-13; follow-up at 20	Cross-sectional, longitudinal	ISCA	27.5% depression rate at follow-up	History of depression in the participants' mothers and a psychiatric history in the participants themselves turned out to be risk factors.
Robinson et al. [15]	Canada	1,391,941	mean (at diagnosis) 10.68 ± 3.52; range 1-15; mean follow up after 6.67 ± 2.97 (range 1-10)	Population-based, cohort	1) mood disorders diagnosed in the emergency department (ED) or hospital; secondarily 1) mood disorders diagnosed exclusively in the outpatient clinic and 2) any visit to a psychiatrist	HR of 1.33 (95% CI 1.19 –1.50) for developing affective disorders diagnosed in the emergency department or during hospital treatment for DM patients, HR 1.29 (95% CI 1.21 –1.37) for developing any other psychiatric condition as well	
					1) hospitalization for a suicide attempt, 2) deaths by suicide	HR 3.25 (95% CI 1.79 –5.88) for suicide attempt in DM group	
Roberts et al. [16]	United States of America	64	mean 15.8±2.0; range 13-21	Cross-sectional	PHQ-9	High-grade depressive symptoms in 22% of participants; high levels of disease-related distress in 23% of participants	

Radobuljac et al. [17]	Slovenia	525	mean 16.9±1.7; range 14-19	Cross-sectional	Self-reported questionnaire by Kienhorst et al.	Frequency of suicidal thoughts and self-harm at 35.7% and 12.9%, respectively in the study group vs 38.3% and 19.7%, respectively in the control group.	T1DM were at the highest risk of suicidal ideation, but not of self-harm. The lowest incidence of suicidal ideation and self-harm tendencies was found in boys with T1DM. In total, more patients with T1DM sought psychological help compared with controls.
Cooper et al. [18]	Australia	7760	mean (at diagnosis) 9.5; range 0.8-17.9; follow up at mean 25.6	Population-based, cohort	Australian Cause of Death Register	Standardized mortality ratio for death from any cause compared to the group control ratio was 1.7 (95% CI 0.7–.3) for males and 10.1 (95% CI 5.2–7.7) for females in the group of patients with T1DM.	Differences in suicide rate between groups did not reach statistical
Majidi et al. [19]	United States of America	550	mean 15.2±3.1; range 10.0 - 23.9	Cross-sectional	PHQ-9	9% expressed suicidal thoughts during their life, and among them, 83.4% showed symptoms of depression, 16% had a history of suicide attempts	5 participants admitted that they had previously considered the possibility of using insulin for suicidal purposes. 3 participants used insulin in a suicide attempt

CIS-R – Clinical Interview Schedule-Revised; PH-PANAS-C - Physiological Hyperarousal and Positive And Negative Affect Schedule for Children; CDI – Children's Depression Inventory; BDI - Beck Depression Inventory; ISCA – Interview Schedule for Children and Adolescents; PHQ-9 – Patient Health Questionnaire-9

Discussion

We conducted a comprehensive review of the literature regarding the frequency of symptoms of affective disorders and suicidal tendencies in the population of children, adolescents and young adults up to 25 years of age with DM. Results of the reviewed research papers ranged from 1.2% to 47.6% for full-symptom affect disorders, or even 60.4% for unspecified affect disorders, sub-threshold and fully symptomatic. In studies involving a control group, the risk for the development of affective disorders was found to range from HR of 1.33 to 2.0, or even 6.49 for an unspecified affective disorder, sub-threshold and fully symptomatic. One publication was identified that did not describe any statistically significant difference in the risk of affective disorders between the study and control groups, and one paper describes this difference only in the case of joint diagnosis of depressive and anxiety disorders, without statistical significance with those disorders analyzed separately. Authors of descriptions of the incidence of self-injuring behaviors and suicidal tendencies estimated them in the range of 0.8% to 35.7%. Studies that compared

the risk for suicide attempts resulted in estimated HR between 1.7 and 3.25. Buchberger et al. conducted a meta-analysis, the results of which support the results of the review. The meta-analysis consisted of data from 12 studies involving 3,100 children and adolescents with diabetes, with a mean age ranging from 13.4 to 17.7 years, mean duration of DM at the time of study of 3.23 to 7.7 years, and mean HbA1c values between 7.1% and 9.68%. A high level of depressive and anxiety symptoms was found among children and adolescents with T1DM, which in the meta-analysis amounted to 30.04% (95% CI 16.33 - 43.74). The studies included in the meta-analysis determined the level of prevalence of those symptoms to be ranging from 17.2 to 63%. However, it should be noted that all studies subjected to the meta-analysis were assessed by its authors as low-quality evidence due to the study groups being unrepresentative of the population, small group size and single- or two-center studies, as well as the use of self-report tools such as the Children's Depression Inventory (CDI) [19]. A high fraction of the publications included in our review demonstrate similar problems, which may be the cause for a large spread of results. It is worth emphasizing the need for population-based studies on the pediatric population as well – the deficiency of studies concerning populations aged no more than 18 years makes it impossible to effectively synthesize information regarding the strictly pediatric population. Depressive symptoms, which – according to the evidence above - occurs with increased frequency in patients with carbohydrate metabolism disorders, should be reduced using standard interventions, but there is evidence that better glycemic control may also be effective. In a meta-analysis by Zhang et al. antidiabetic treatment resulted in a greater reduction in depressive symptoms than placebo [20], which may indicate a bidirectional relationship between carbohydrate metabolism disorders and affect disorders.

Conclusions

The vast majority of research results indicate an increased risk of symptoms of depression and suicidal tendencies among children and young adults suffering from DM. This highlights the need to seek and implement appropriate screening tools for affective disorders in pediatric diabetes care, both for patients' mental health and for DM treatment outcome improvement.

Conflict of interest

The authors have declared no conflict of interest.

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