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Depressive Symptoms are Associated with Fasting Insulin Resistance in Obese Youth

Tamara S. Hannon, MD, MS[1,3,5], **Zhuokai Li, BS**[2], **Wanzhu Tu, PhD**[2], **Jordan N. Huber, BA**[5], **Aaron E. Carroll, MD, MS**[1,3], **Ann M. Lagges, PhD**[4,6], and **Sandeep Gupta, MD**[1,6]

[1]Department of Pediatrics, Indiana University School of Medicine

[2]Department of Biostatistics, Indiana University School of Medicine

[3]Department of Children's Health Services Research, Indiana University School of Medicine

[4]Department of Psychiatry, Indiana University School of Medicine

[5]Sections of Pediatric Endocrinology & Diabetology, Indiana University School of Medicine

[6]Gastroenterology/POWER Program, Indiana University School of Medicine

Abstract

Background—In adults, depressive symptoms are positively associated with insulin resistance.

Objective—To determine whether an association exists between depressive symptoms and markers of insulin resistance in youth.

Methods—This study used a retrospective review of data from an obesity clinic. We evaluated the association between depressive symptoms (Children's Depression Inventory, CDI) and fasting insulin and homeostatic model assessment–insulin resistance (HOMA-IR) in obese youth (n=207, age 10-18 years). Individuals with lower versus higher CDI T-scores (<65 *vs* ≥65) were compared; this cut-point is accepted as indicating the possibility of clinical depression. Multiple linear regression was used to evaluate relationships between CDI T-scores and insulin resistance.

Results—Fasting insulin and HOMA-IR values were 40% higher in patients with higher CDI T-scores (p=0.04). After accounting for gender, race, age, and BMI, CDI T-score remained associated with HOMA-IR, although the strength of the association was small (b=0.007, p=0.049).

Conclusions—Relationships between depressive symptoms and insulin resistance should be considered when evaluating obese youth.

Keywords

depression; insulin sensitivity; overweight; adolescent; HOMA

Corresponding Author and Contact Information: Tamara S. Hannon, MD, MS, 705 Riley Hospital Drive, Room 5960, Indianapolis, IN 46202-5225, Office: 317-944-3889, Fax: 317-944-3882, tshannon@iu.edu.

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Introduction

In young adults, depressive symptoms are positively associated with insulin resistance (1). Moreover, clinically depressed adults demonstrate insulin resistance, higher fasting glucose, and are known to have greater risk for type 2 diabetes (2). Obese youth have prevalent psychosocial stressors and insulin resistance associated with obesity (3). However, studies evaluating whether depressive symptoms among obese youth are associated with even greater insulin resistance are scarce. This is relevant, as increasing insulin resistance is associated with the development of type 2 diabetes and inferior cardiometabolic risk profiles. The knowledge of this association would aid clinical evaluation, as youth with clinical depression may be at higher risk for developing glucose intolerance or type 2 diabetes. The objective of this study was to determine if an association exists between depressive symptoms and fasting markers of insulin resistance in obese youth. We evaluated relationships between depressive symptoms and biomarkers of insulin resistance in an obese pediatric and adolescent clinic population. We hypothesized that depressive symptoms would be positively associated with fasting insulin levels in obese youth, as has been shown in adults.

Methods

We reviewed clinical data from all patients evaluated in the clinic at the Pediatric Overweight Education and Research (POWER) Program at Riley Hospital for Children at Indiana University Health between January 2009 and November 2011. A waiver of informed consent was obtained from the Indiana University Institutional Review Board prior to initiating the study. For the purposes of the POWER Clinic, obesity was defined as having a body mass index ≥85th percentile for age and gender. The Children's Depression Inventory (CDI) was used as a standard part of the clinical evaluation to assess depressive symptoms (4). The CDI is a widely used measure comprised of 27 items loading on five primary factors: negative mood, interpersonal problems, ineffectiveness, anhedonia, and negative self-esteem. The total raw score from the CDI items is converted to a standardized T-score. CDI T-scores are based on a normative sample of 1266 youths and are calculated based on age and gender. Laboratory evaluation included fasting lipids, liver transaminases, glucose, insulin, and hemoglobin A1c (HbA1c). Plasma glucose was measured using the glucose hexokinase method (CV 2%). Plasma insulin was measured with chemiluminescent sandwich assay (CV 6%). Fasting lipid profile was measured using the Beckman Coulter DXC 800. Liver transaminases were assessed via spectrophotometry. HbA1c was measured with the high-performance liquid chromatography method. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated with fasting glucose and insulin (5).

Patients treated for depression or other psychiatric conditions (n=45) or who had diabetes (n=8) were excluded. This was a retrospective review of clinical data where Tanner stage data was inconsistently available. Thus, we restricted the analysis to youth between the ages of 10-18 years with complete data (n=207) to minimize the number of prepubertal children in the analysis. Individuals with lower versus higher CDI T-scores (<65 *vs* ≥65) were compared. This cut-point is accepted as useful for indicating the potential of clinical

depression (4). The chi-square test for independence or the Fisher's exact probability test was used to compare categorical variables. The Welch t-test, suitable for two groups with unequal sample sizes and unequal variances, was used to compare continuous variables. We evaluated whether CDI T-scores as a continuous variable were associated with markers of insulin resistance while controlling for gender, race, age, and BMI Z-score with multiple linear regression. R software was used to perform analyses. P-values <0.05 were considered significant. This study was approved by the Indiana University Institutional Review Board.

Results

The characteristics of the patients are summarized in Table 1. The mean CDI T-score for the study population was 48±11; median=46; range 34-100. CDI T-scores did not vary by gender, race, or age. Markers of cardiometabolic risk and insulin sensitivity according to CDI T-score group are shown in Table 2. There were no differences in anthropometric measures, blood pressure, lipids, liver transaminases, HbA1c, or fasting glucose among the groups. The mean fasting insulin and HOMA-IR values were 40% higher in the group with higher CDI T-scores (p=0.03 and p=0.04) reflecting greater insulin resistance.

After controlling for the effects of gender, race, age, and BMI Z-score, CDI T-score measured as a continuous variable remained associated with HOMA-IR (b=0.007, 95% CI (0.00001, 0.014), adjusted R^2=0.12, p=0.049). Hispanic race (b=0.438, p=0.007), female sex (b=0.170, p=0.044), and BMI Z-score (b=0.560, p<0.001) were significantly associated with greater insulin resistance.

Discussion

Currently, approximately 17% of U.S. adolescents are obese, as defined by having a BMI greater than or equal to the 95th percentile for age and sex (6). Of this population, a significant percentage has a combination of unfavorable risk factors for the development of type 2 diabetes, including insulin resistance, which poses enormous public health implications. In this study of a clinic population of 10-18 year-old obese youth, patients meeting the CDI T-score cut-point indicating increased risk for depression had 40% higher fasting insulin and HOMA-IR values than patients with CDI T-scores in the normal range. After adjusting for gender, race, age, and BMI, CDI T-scores remained positively associated with HOMA-IR values, although the strength of the association was small. These findings suggest that obese youth with more depressive symptoms are insulin resistant compared with those without depressive symptoms, independent of BMI. The relationships between depressive symptoms and metabolic risk factors in obese youth are likely to be highly relevant and potentially modifiable, which holds the promise of facilitating improvement in the health care of obese youth and improving clinical outcomes. The findings here imply that there is a need to implement systems to screen obese youth for depressive symptoms, in addition to risk for type 2 diabetes, during routine clinical care. Moreover, additional research is needed to determine the effectiveness of addressing depressive symptoms (medically and/or via social support) to reduce risk factors for type 2 diabetes.

Some studies have found depressive symptoms to be correlated with the degree of obesity (7), while others have found an association between depressive symptoms and insulin resistance after controlling for obesity in adolescents (8, 9). A prospective pediatric study evaluated depressive symptoms and HOMA-IR at a baseline visit and again approximately 6 years later (10). Depressive symptoms at baseline predicted follow-up HOMA-IR, independent of BMI. While the directionality of these relationships remains unclear, results of this previous study suggest that the pathophysiology related to depressive symptoms precedes the increase in fasting insulin. This implies that treating depressive symptoms in youth might improve insulin sensitivity, which deserves further investigation.

This study was not designed to evaluate the mechanisms of this relationship, but the results indicate need for studies examining factors linking depression and insulin resistance. Previously proposed mechanistic pathways linking anxiety, emotional stress, and depressive symptoms to adverse cardiometabolic risk factors include poor sleep (11), activation or dysregulation of the hypothalamic–pituitary–adrenal axis leading to chronically increased levels of catecholamines (12), and systemic inflammation and oxidative stress (13). Advances in the understanding of insulin resistance and depression provide evidence that shared inflammatory mechanisms may link these conditions biologically (14).

There were limitations associated with this retrospective review of clinical data. Socioeconomic status data was not available for analysis. Most patients were insured but we cannot rule-out an effect of socioeconomic status on the results. Moreover, these results are not generalizable to non-obese individuals or to youth with previously diagnosed depression. We had relatively few youth with CDI-T-scores ≥ 65, limiting the power to detect differences between the two groups, and the study did not include repeated CDI measurements over time. Finally, we did not adjust for the effect of puberty on insulin sensitivity because Tanner stage data was inconsistently available. Age, BMI, and BMI Z-score were remarkably similar between the two groups, which would be unlikely to occur if the pubertal stage was significantly different in one of the two groups. Future studies should also address race/ethnicity, as others have reported that depressed mood may be most problematic among adolescent girls in the white racial/ethnic group (15).

In conclusion, youth referred for treatment of obesity who endorse more depressive symptoms have markers indicating greater insulin resistance. Obese youth should be screened for depression, along with diabetes risk factors (family history, acanthosis nigricans, minority race/ethnicity, etc) to direct clinical care (16).

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Table 1

Patient Characteristics (n = 207)

	CDI T-score < 65 (n = 192) 46 ± 8	CDI T-score ≥ 65 (n = 15) 76 ± 12	p-value
Gender, n (%)			
Male	68 (35%)	5 (33%)	0.91
Female	124 (65%)	10 (67%)	
Race, n (%)*			
White	97 (51%)	8 (53%)	
Black	75 (39%)	5 (33%)	0.66
Hispanic	12 (6%)	1 (7%)	
Other	6 (3%)	1 (7%)	
Age, y	13.5 ± 2.2	13.5 ± 1.9	0.93
BMI, kg/m^2	38.3 ± 8.3	37.7 ± 6.7	0.78
BMI Z-score	2.49 ± 0.32	2.45 ± 0.20	0.63

Data are expressed as mean ± standard deviation unless otherwise indicated.

*Race information was missing for 2 (1%) of patients.

Table 2

Markers of Cardiometabolic Risk and Insulin Sensitivity According to Children's Depressive Inventory T-Score Group

	CDI T-score < 65 (n = 192) 46 ± 8	CDI T-score ≥ 65 (n = 15) 76 ± 12	p-value
Blood pressure, mmHg			
Systolic	114.1 ± 12.8	107.5 ± 14.6	0.07
Diastolic	70.3 ± 11.0	72.8 ± 9.3	0.41
Blood pressure, %ile			
Systolic	58.52 ± 30.56	42.05 ± 30.72	0.05
Diastolic	64.98 ± 25.22	71.54 ± 22.28	0.35
Cholesterol, mg/dL	156.38 ± 31.33	164.93 ± 39.51	0.34
HDL cholesterol, mg/dL	37.8 ± 9.4	39.0 ± 8.8	0.63
LDL cholesterol, mg/dL	96.3 ± 25.1	100.4 ± 32.8	0.56
Non-HDL cholesterol, mg/dL	118.5 ± 30.0	125.6 ± 36.3	0.41
Triglycerides, mg/dL	112.8 ± 74.9	112.2 ± 56.7	0.97
ALT, U/L	24.3 ± 14.2	25.6 ± 9.8	0.72
AST, U/L	25.1 ± 16.1	24.2 ± 6.0	0.83
HbA_1c, %	5.60 ± 0.43	5.57 ± 0.27	0.78
Fasting glucose, mg/dL	95.3 ± 12.0	94.0 ± 7.4	0.68
Fasting insulin, μU/mL	24.8 ± 15.5	34.9 ± 32.6	0.03
HOMA-IR	5.89 ± 4.01	8.28 ± 7.80	0.04

Data are expressed as mean ± standard deviation.