Jcrpe-2018-0055.R2
Original Article
DOI: 10.4274/jcrpe.0055

Insulin Resistance is Related to Psychiatric Disorders Among Obese Children
Özalp Kızılay D et al. Insulin Resistance is Related to Psychiatric Disorders

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Conflict of interest: None declared
Received: 28.03.2018
Accepted: 22.05.2018

What is already known on this topic?
The relationship between childhood adiposity and mental health in the study findings were consistent in relating childhood adiposity with mental health conditions such as depression, behavioral and emotional disorder, anxiety and mood disorder. BeLue and colleagues reeported that adolescents who were obese were 1.6 times more likely to have depression or anxiety. Another research has demonstrated obese children are 3.1 times more likely to have anxiety symptoms and 3.6 times more likely to have depressive symptoms compared to same-age peers.
What this study adds?
Our study reflects, our findings suggest that insulin resistance, rather than obesity-related metabolic co-morbidities, is more predictive of psychiatric illness. The results of our study underline the importance of assessing psychiatricfunctioning among obese children,particularly with insulin resistance. Routine screening of these children is recommended for the identification of psychiatric disorders and the identification of patients who requires clinical intervention.

Abstract
Objctive: The current study aimed to investigate psychiatric consequences of obesity (OBy) and the relationship between metabolic syndrome components and psychiatric disorders in children. Our secondaryaim was to elucidate which of the anthropometric parameters or metabolic components were most strongly associated with psychiatric disorders.
Methods: The study included 88 obese(OB)and overweight (OW) children with a body mass index (BMI) greater than 85th percentile. The patients were evaluated for psychiatric disorders by one child and adolescent psychiatrist. Forty patients who were diagnosed with psychiatric disorders and 48 patients with normal psychiatric evaluation were compared in terms of anthropometric and metabolic parameters. Body mass index (BMI), BMI-Standard deviation score (SDS) and BMI percentile, waist circumference (WC), waist to hip ratio, blood pressure and pubertal stage of all patients were recorded. Fasting serumglucose, insulin,lipid profile and homeostatic model assessments of insulin resistance (HOMA-IR) were measured to evaluate the metabolic parameters. Serum and 24 hour urine cortisol levels were measured.
Results: The presence of insulin resistance in group with psychiatric disorder was found significantly higher than in group without psychiatric disorder. Other anthropometric measurements and metabolic parameters were not significantly different between the two groups.

Conclusıon: An understanding of the relationships between obesity related medical co-morbidities and psychiatric pathologies is important to encourage patients and their families for succesfull healthy lifestyle changes, weight management in terms of appropriate treatment.
Keywords: Child, obesity, insulin resistance, mental disorder

Introductıon

Childhood OByis an important public health problem worldwide. The prevalence of OWand OBy in children has risen dramatically. Childhood OBy has various and considerable adverse consequences for health outcomes. (1) There is an increasing recognition of the relationship between mental illness and OBy. Childhood OW/OBy is negatively associated with psychiatric comorbidities than their healthy-weight peers, such as lower health-related quality of life (HRQOL), lower self-esteem and body image concerns. (2, 3)Moreover, these children are exposed to some difficulties in social life, such as pervasive peer victimization, weight-related teasing, weight stigma and bullying. (4, 5) These may complicate their physical and medical health outcomes. (1, 6)

OBy related psychiatric comorbidities includes a variety of psychiatric illness. (2) In a study by Britz and colleagues, greater than 40% of the obese adolescents study sample met DSM-IV criteria for a psychiatric illness. Increased lifetime rates for mood (42. 6%), anxiety (40. 4%), substance use (36. 2%), somatoform (14. 9%) and eatingdisorders(17. 0%) were reported in obese group compared with the general population.(7)In a large population study sample from US, 43297 children aged between 10-17 years were evaluated; 15% of them were overweight and 16% were obese. In this study obese children compared with children classified as not overweight were more likely to have internalizing and externalizing problems. Attention deficit/hyperactivity disorder, conduct disorder, depression, learning disability and developmental delay were found more common in obese children.(8)

It is still not clear whether psychiatric disorders and psychological problems are causes or consequences of childhood OBy or whether common factors promote both OBy and psychiatric disturbances in children and adolescents. The first aim of this study was to investigate psychiatric consequences of OBy and to evaluate the associations between childhood OBy related co-morbidities and psychiatric disorders in children. The secondaryaimwas to identify which of the anthropometric or metabolicparameters related to OBy has the effect on mental health. For this reason, we compared obese children with and without mental disorders to reveal differences in anthropometric and metabolic parameters.

Methods

The study sample and selection of patient group:

This study was conducted in Manisa Celal Bayar University Pediatric Endocrinology and Child Psychiatry Clinics. A total of eighty-eight OBy and OW childrenwith a BMI greater than the 85th percentile for age and sex, according to growth charts from the Center for Disease Control and Prevention (CDC-2000), aged 9 to 17 years, who attended or referred to pediatric endocrinology outpatient clinic for evaluation of obesity and related comorbidities were included in the study. We excluded individuals with developmental delays, chronic diseases, a history of drug use, a previous diagnosis of psychiatric disorders, any disease affecting the endocrine system (e. g. , hypothyroidism and Cushing's disease), or suspected syndromes associated with obesity (e. g. , Prader-Willi and Laurence-Moon-Biedl syndromes).

The study was approved by the local ethics committee of Celal Bayar University, Faculty of Medicine in Manisa (number/date:20478486-382/ 11. 11. 2015), and written informed consent were taken from the primary caregiver and patient, before the study.

Study design

All OW/OBy patients underwent a thorough physical examination, laboratory evaluation and psychiatric assessment. The assessments were all performed by specially trained clinical research staff.

Anthropometric/physical measurements:

Child height was measured by a wall-mounted stadiometer and weight bya calibrated scale. Children did not wear shoes for measurements. The weight of each subject was measured with all clothing removed except undergarments. We calculated the BMI as weight (in kg) divided by square of height (in m^2). BMI-SDS and BMI percentiles were calculated using age and gender specific norms published by the CDC. (9) Obesity was defined as BMI ≥ 95th percentile and OW was defined as BMI ≥ 85th for age and sex. (10)

Waist circumference (WC) was measured with a non-stretchable tape to the nearest 0. 1 cm midway between the lowest rib and the highest point of the iliac crest paralel to the floor, without clothing and during expiration in a standing and relaxed position (Report of a WHO Expert Committee 1995). Hip circumference (HC) was measured around the widest portion of the buttocks. Waist-to-hip ratio (WHpR) was calculated by dividing the WC by the HC.

Findings for pubertal development were recorded according to the classification of Tanner. A testicular volume of ≥4 mL in males, and breast development of stage 2 and over in females, were considered to be findings of puberty.(11)

Medical measurements

Blood samples were taken in the morning after an 10 to 12 h of night fasting (water permitted) for glucose, insulin and lipids including triglycerides (TG), total cholesterol (TC) and high-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol and serum cortisol. 24 hours urine was collected for cortisol measurement. Insulin resistance was evaluated according to the homeostasis model assessment-insulin resistance (HOMA-IR) index. Different cut-off values for prepubertal and pubertal stages were used to determine the status of insulin resistance (prepubertal >2. 5, pubertal > 4. 0). (12)
Blood pressure was taken with the appropriate cuff, systolic and diastolic blood pressure (SBP, DBP) were measured twice in the supine position after a 10-min rest on the right arm by one of the investigators using a calibrated sphygmomanometer and the mean of these two BP values were taken into consideration.
According to the International Diabetes Federation (IDF), metabolic syndrome (MetS) can be diagnosed in children 10 to 16 years old when the following criteria are fulfilled: a WC ≥90th percentile, together with two more risk factors being these ones: fasting blood glucose levels ≥100 mg/dL (5. 6 mmol/L), serum TG levels ≥150 mg/dl (1. 7 mmol/L) or treatment for elevated triglycerides, HDL cholesterol <40 mg/dL (1. 03 mmol/L) or treatment for low HDL and Either SBP≥130 or DBP ≥85, or treatment for hypertension. For children 16 years and older, the adult criteria can be used (ethnic-specific waist circumference percentiles, for Turkish population; ≥94 cm for men, ≥80 cm for women and a sex-specific cut off level for high-density lipoprotein (HDL); <40 mg/dL (1. 03 mmol/L) in men or <50 mg/dL (1. 29 mmol/L) in women). For children younger than 10 years of age, metabolic syndrome cannot be diagnosed, but vigilance is recommended if the WC is ≥90th percentile.(13)

Psychiatric measurements

1. Kiddie Schedule for Affective Disorders and Schizophrenia for School Age Children- Present and Lifetime Version (K-SADS-PL) was used. (14) This is a semi-structured interview developed by Kaufman and colleagues (14), to evaluate present and lifetime psychopathology in children and adolescents according to DSM-III-R and DSM-IV criteria. The reliability and validity study of the Turkish translation was conducted by Gokler and colleagues.(15) Psychiatric evaluation of obese patients was performed by the same clinician. The individuals were classified into two pairs as follows: (i) obese group with normal psychiatric evaluation; (ii) obese group with psychiatric disorder.
2. Sociodemographic Form was developed by the study coordinators, and included questions on parental education and vocation, physical/mental illnesses in the family, and information about the patient.

Statistical Analysis

Statistical analysis of the study was performed using Statistical Package for Social Sciences 15. 0 (SPSS 15.0) program. Descriptive data were presented as number ± standard deviation (SD), frequency, and percentage values. Sociodemographic data, medical,anthropometric/physical measurementsfor cases with and without a psychiatric disorder were analysed using the chi-square test for categorical variables, t-test for those that were normally distributed and Mann- Whitney test for data that were not normally distributed.

RESULTS

In this study, 88 children and adolescents diagnosed with obesity were evaluated. The mean age of the participants was 13. 20 ± 2. 44 years (min: 9, max: 17); 59 (67%) were female and 29 (33%) were male. The mean weightand height of the subjects were 73. 94 kg(SD=16. 93 kg) and 155. 93 cm (SD=11. 56 cm),respectively. The number of subjects attendingschoolwere 84 (95. 5%).
Psychiatric disorder was found in 40 (45. 5%) of the children and 5 of them had multiple psychopathologies. Distribution of patients's diagnoses were 31 anxiety disorders (% 35. 2), 2 depressive disorders (%2. 3), 2 oppositional defiant disorders (%2. 3) and 5 comorbid anxiety and depressive disorders (%5. 7).
Demographic, clinical and metabolic parameters were compared in children with and without mental disorder, and the results are presented in tables 1, 2 and 3. The group with mental disorders was not statistically different from the group without mental disorder in terms of age, sex, family history of psychiatric and chronic disorders, parents employment status, pubertal status, the degree of obesity and metabolic syndrome components. Insulin resistance was significantly higher in children diagnosed with psychiatric disorder and school attendance was found to be significantly lower (p=0,035).

Discussion

The worldwide rates of OW and OBy in children has increased rapidly among all age groups and both sexes over the past few decades. (16) Childhood OBy is associated with several short- and long-term consequences (cardiovascular diseases, hypertension, hypercholesterolemia, insulin-resistance, type 2 diabetes, ,pulmonary and liver disease etc. in addition to mental disorders). (6, 17, 18, 19, 20)

In this study, we evaluated psychiatric disorders in children who were obese and overweight, and compared the characteristics of anthropometric measurements and biochemical data in individuals with and without psychiatric impairment. We also assessed whether there is a metabolic or anthropometric difference that may related

psychopathology among obese children and investigated the association of psychiatric disorders with MetS, diagnosed according to the IDF.

In our study, psychiatric disorder was detected in 40 patients (approximately 45% of all) with the psychiatric evaluation of 88 OB and OW patients. We consider that this is a very high percentage of patients who are diagnosed during screening. Anxiety disorder was found the most common psychiatric disorder among our study sample. According to the data obtained from the examination of nine previous studies about the relationship between childhood adiposity and mental health in the rewiev of Ross H and Sanders et al. , study findings were consistent in relating childhood adiposity with mental health conditions such as depression, behavioral and emotional disorder, anxiety and mood disorder. (1) BeLue and colleagues (2009) reeported that adolescents who were obese were 1.6 times more likely to have depression or anxiety. (21) Another research has demonstrated obese children are 3.1 times more likely to have anxiety symptoms and 3.6 times more likely to havedepressivesymptoms compared to same-age peers. (22) In a study by Fox et al, 102 adolescents were evaluated and in the overall sample, 34% endorsed symptoms consistent with depression and 32% endorsed symptoms of anxiety. (23) Similar results have been found in studies of Turkey. In the study by Taner et al, 54 obese children were evaluated and psychopathology was detected in 50% of these children.(24) In the study of Topçu et al, There were significant differences among obese and control groups in terms of the total score of state-trait anxiety inventory(STAI-C) and child depression inventory (CDI).(25) Our study results are consistent with studies in both Turkey and other countries.

There are many articles evaluating the relationship between ADHD and obesity in the literature.In Erermiş et al.'s study, obese cases admitted to the endocrine clinic were evaluated and 13.3% of them were diagnosed with ADHD (26).Cortese et al. analyzed 42 studies including a total of 48.161 ADHD and 679.975 control subjects,and found a significant relationship between obesity and ADHD in children. (27) In another review, Cortese and Tessari presented seven studies evaluating the prevalence of ADHD in individuals referred for obesity treatment. All these studies, except one, have confirmed significantly higher rates of ADHD in individuals with obesity compared to normal weight controls. (28) Conversely, there were no cases diagnosed with ADHD in our study. In children, ADHD affects academic achievement and social adjustment negatively in the school setting, and is mostly recognized and diagnosed during primary school period. In this study, a known mental illness or drug use were the exclusion criteria and the mean age of the children was 13.2 and most of themwere in the secondary school period. In this age group, children have high rates of previous ADHD diagnosis, thereforepresumablythey were not included. We thought that was the reason why we could not find any ADHD diagnosis in the study group.

It has been reported that when the obesity is accompanied by psychiatric disorder, children are disoriented to obesity treatment and their school performance decrease, body sense is more negative and quality of life is more distorted. (24, 29) With the diagnosis and treatment of the existing psychiatric disorder and improved self-esteem or other factors associated with mental health in obese individuals may be a more successful way for increasing motivation. (30) As a result, due to the high prevalence of psychiatric issues among obese children, the present study emphasizes the importance of mental health assessment prior to treatment in order to not miss diagnoses that may affect the outcome of the treatment. Establishment of multidisciplinary teams and psychiatric evaluation are important in the effective treatment of obesity.

The relationship between obesity and mental disorder has not been clearly elucidated yet, such as which one is trigger or if they co-occur. Compared to the relatively well-documented the association of psychiatric disorders such as depression and anxiety disorders with MetS in adults. (31) There ara limited data about the nature of the association between obesity related metabolic syndrome and other comorbidities and psychiatric disorders in children.

A number of studies have documented the association of depressive symptoms or disorders with MetS. (32, 33, 34, 35) The metabolic syndrome in childhood predicted higher levels of depressive symptoms in adulthood.(36) The association of MetS with anxiety disorder has received significantly less attention and the results of the studies on this issue remain different. Some authors have reported greater anxiety symptoms severityand more anxiety disordersin MetS patients, while other researchers have not confirmed the association between anxiety disorders and MetS. (37- 40)

Phillips et al. compared depressionand anxiety symptoms among metabolically healthy and unhealthy obese and non-obeseindividuals. The risk of anxiety and depressive symptoms were found greater among the metabolically unhealthy obese subjects than the metabolically healthy non-obese individuals. Increased risk of these conditions was not observed among the metabolically healthy obese subjects. (31)Hamer et al. , investigated whether the association between obesity and depressive symptoms is dependent on an individual's metabolic health and report that metabolically unhealthy obese had increased risk of depressive symptoms after a 2 year follow-up, but this relationship was not found in metabolically healthy obese individuals.(41)Furthermore, the data obtained from a recent analysis of eight studies by Jokela et al., demonstrate that obese individuals with a favorable metabolic profile have a slightly increased risk of depressive symptoms compared with non-obese, but the risk is greater when obesity is combined with an adverse metabolic profile. (42) Phillipset al. investigated

associations between the metabolic risk factors and depressive symptoms and anxiety among the metabolic unhealty obese subjects. Insulin resistance and abdominal obesity were associated with depressive symptoms, only insulin resistance remained significant in adjusted models for both depressive symptoms and anxiety. (31) We expected that accompanying obesity-related comorbidities ormetabolic syndrome components, rather than obesity alone, would relate to impaired psychiatric functioning and greater psychiatric distress. In view of the metabolic syndrome and related components, we only found thatchildren in the OV/OBy with psychiatric disorders have higher rates of insulin resistance. We know that, obesity related cardiometabolic co-morbidities are less common in children and which tend to occur later in life. Insulin resistance, which is the most common and early onset obesity related co-morbidity, is significantly associated with an increase in the frequency of mental disorders, even other metabolic changes have not begun yet. We think that is an important outcome for this study.

Obesity and mental disorders share some behavioral factors and adverse dietary habits but also have related of different stress systems like disturbances in the hypothalamic – pituitary-adrenal axis, dysregulation of the central serotonin norepinephrine and dopamine neurotransmitter systems may contribute to change in body composition and metabolic parameters.(43-47)Endocrinologic abnormalities may play a role in the association between psychiatric disorders and insulin resistance. It has been shown that the fluoxetine, a SSRI, improves insulin-mediated glucose utilization independently by its action on body weight. (48) These facts show that the serotonergic system plays a role in both pathogenesis of the mental disorders and insulin resistance and may link these two pathogeneses. In current study, our findings may suggest that psychiatric disorders might affect peripheral insulin sensitivity, possibly via the behavioral and/or neuroendocrinologic pathway.

Comorbid psychiatric disordersand related lifestyle factors affect the presence of insulin resistance in obese patients. It may be predicted that adequate treatment of psychiatric disorders and following improvement of psychopathology related factors such as an increase in daily physical activity, improvement in sleep disturbances, or changes in eating behavior willimprovethe insulin resistance. Therefore, early diagnosis and successful treatment of underlying psychiatric disorder in obese children are very important for the improvement of impaired insulin sensitivity and decreasing the risk of developing diabetes, hypertension, and cardiovascular disease in future.

Study Limitations

This study has some limitations. First, it is unclear from this study whether obesity worsens psychosocial factors or, rather psychosocial factors worsen obesity. Also, there may be other factors affecting these relationships, which are not included in the present study (e. g. , Personal characteristics of the patient, duration of psychiatric illness, family stressors). The lack of evaluation of mental disorders severity isanother limitation of this study. Longitudinal data is needed in understanding the nature of the relationship, as well as documenting any changes in psychosocial functioning with reduction in BMI due to successful clinical treatment. Further research will help to determine the most appropriate strategies.

Conclusion

Our findings suggest that insulin resistance, rather than obesity-related metabolic co-morbidities, is more predictive of psychiatric illness. The results of our study underline the importance of assessing psychiatric functioning among obese children, particularly with insulin resistance. Routine screening of these children is recommended for the identification of psychiatric disorders and the identification of patients who requires clinical intervention. In the absence of such screening and treatment when indicated, it is unlikely that lifestyle recommendations will be successful in weight management of obese patients. Furthermore,screening for MetS in individuals with psychiatric disorder may help to reduce the risk of cardiovascular disease and diabetes mellitus type 2 onset.

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Tablo 1. Demographic and clinical characteristics of Obese patients with and without psychiatric disorders

Sociodemographic characteristics:	**Obese patients with psychiatric disorders (n= 40)**	**Obese patients without psychiatric disorders (n= 48)**	**P**
Age (years)	13. 7±2. 48	12. 38±2. 36	0. 083
Gender Male Female	 11 29	 18 30	0. 368
Family history of psychiatric disorder Positive Negative	 15 25	 10 38	0. 100
Family history of chronic			

disorder Positive Negative	 18 22	 28 20	 0. 284
Mother's occupation status Working Unemployed	 8 30	 15 33	 0. 334
Father'soccupation status Working Unemployed	 31 6	 46 2	 0. 073
School attendance Positive Negative	 36 4	 48 0	 0. 039
Clinical characteristics			
Tanner stage: n (%) Prepubertal(1) Pubertal(2-5)	 3 37	 1 47	 0. 326
Weight status: n (%) Overweight Obesity Morbide obesity	 8 26 6	 9 26 13	 0. 382

*****There is a lack of information about the parent's occupation status(2 related to the mother / 3 related to the father)

Tablo 2. Comparison of metabolic characteristics between obese patients with and without psychiatric disorders

Metabolic syndrome components	**Obese patients with psychiatric disorders (n= 40)**	**Obese patients without psychiatric disorders (n= 48)**	**P**
Waist circumference (cm)	99. 10±11. 20	94. 67±10. 20	0. 056
Increased WC - n (%)	40(%100)	47(%97. 9)	0. 361
Fasting blood glucose (mg/dL)	84. 07±7. 68	86. 75±7. 52	0. 104
High fasting blood glucose (≥100 mg/dL) - n (%)	1(%2. 5)	3(%6. 3)	0. 623
Triglycerides (mg/dL)	135. 37±70. 61	139. 34±118. 80	0. 853
High triglycerides (≥150 mg/dl)- n (%)	11(%27. 5)	11(%22. 9)	0. 631
HDL cholesterol (mg/dL)	47. 12±7. 86	46. 77±8. 64	0. 843
Low HDLcholesterol (<40 mg/dL)- n (%)	6(%15)	12(%25)	0. 296
Systolic blood pressure (mmHg)	120. 66±11. 17	115. 77±13. 30	0. 070
High systolic blood pressure (SBP ≥130)-n (%)	10(%25. 0)	8(%16. 7)	0. 425
Diastolic blood pressure (mmHg)	77. 89±10. 95	75. 20±11. 52	0. 272

High diastolic blood pressure-(DBP ≥85)-n (%)	9(%22. 5)	7(%14. 6)	0. 406

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Tablo 3. Comparison of metabolic syndrome related components between obese patients with and without psychiatric disorders

Metabolic syndrome related components	**Obese patients with psychiatric disorders (n= 40)**	**Obese patients without psychiatric disorders (n= 48)**	**P**
BMI (kg/m2)	30. 74±4. 51	29. 41±4. 50	0. 173
BMI (kg/m2)SDS	2. 02±0. 37	2. 00±0. 38	0. 849
BMI (kg/m2)persantil	97. 04±2. 77	96. 91±2. 86	0. 832
Hip circumference (cm)	108. 63±11. 38	105. 67±10. 29	0. 225
Waist/hip ratio	0. 91±0. 062	0. 89±0. 051	0. 186
Total cholesterol, mg/Dl	162. 40±30. 29	161. 20±31. 75	0. 858
LDL cholesterol (mg/dL)	86. 09±28. 45	41. 74±22. 72	0. 303
Two-hour 75-g OGTT glucose (mg/dL)	123. 35±23. 21	123. 45±24. 15	0. 983
İnsulin (mU/L)	29. 46±13. 23	24. 31±11. 79	0. 057
HOMA-IR	**6. 59±3. 36**	**5. 21±2. 67**	**0. 035**
Serum cortisol	11. 34±5. 01	11. 98±5. 30	0. 569
24-hour urine cortisol	119. 07±76. 08	104. 63±49. 53	0. 290