

Research paper

Internalizing and externalizing problems in obese children and adolescents: associations with daily salivary cortisol concentrations

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ABSTRACT

OBJECTIVE: Pediatric obesity commonly co-exists with emotional and behavioral disorders, while disturbed cortisol concentrations have been reported in both obese and chronically stressed individuals with anxiety and/or depression. We investigated the prevalence of internalizing and externalizing problems, reported by both parents and children, in a clinical population of obese children (OC) compared to normal-weight children. We examined the role of cortisol as a potential mediator between obesity and such problems. **DESIGN:** We compared 110 obese with 31 normal-weight children. The Greek version of the child behavior checklist (CBCL) and the youth self-report (YSR) were used and salivary cortisol was determined serially five times a day. **RESULTS:** T-scores of internalizing problems (anxiety/depression, social withdrawal, somatic complains) reported by both children (49.3 ± 12.3 vs. 43.2 ± 9.1) and mothers (60.6 ± 11.3 vs. 50.6 ± 10.4) were significantly higher ($p=0.03$ and $p<0.001$, respectively) in the obese than in the lean children. Externalizing problems (delinquency, rule-breaking behaviors) reported only by mothers were significantly higher in the OC (57.2 ± 10.5 vs. 48.2 ± 13.3 , $p=0.003$). The cortisol area under the curve (AUC) was significantly smaller ($p=0.03$) in the OC than in the controls; however, a cortisol correlation with internalizing/externalizing symptoms was not observed. **CONCLUSIONS:** There is a high prevalence of internalizing and externalizing problems in a clinical population of OC. A mediation effect of cortisol in the relation between internalizing/externalizing problems and obesity could not be supported.

Key words: Anxiety, Behavior, Children, Cortisol, Obesity, Stress

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INTRODUCTION

Childhood obesity has been recognized as one of the most serious health challenges of the 21st century¹ with a variety of health-related complications, such as metabolic syndrome manifestations (central adiposity, arterial hypertension, insulin resistance,

dyslipidemia) and diabetes mellitus type 2.^{2,3} Recent evidence strongly indicates that both pediatric and adolescent obesity commonly co-exists with anxiety and depression, while a variety of behavioral problems have also been linked to increased weight status in children.⁴⁻⁶ Indeed, in a general population sample of 9-16 year-old children, studied longitudinally, chronic obesity was associated with psychopathology, more specifically, oppositional defiant disorder in both sexes and depressive disorder in males.⁴

Obesity results from an imbalance between energy intake and energy expenditure; however, hyperphagia is commonly a sign of anxiety, depression or impulsivity. In an epidemiologic sample, children and adolescents in the highest quartiles of body mass index (BMI) had a higher prevalence of depression, meaning that associations between these two conditions are more likely to co-exist in individuals with more severe obesity.⁷ In the opposite direction, anxiety disorders and depression in children followed up to adulthood were associated with a higher body weight in girls than controls without such symptomatology, while weights were higher in adolescents and young adults in whom depression was present at an early age.⁸ Furthermore, in a community sample of adolescents, both increased appetite and depressed mood were associated with recurrence of depression in adulthood.⁹

In addition, externalizing behaviors—such as hyperactivity, aggression or delinquency—have also been associated with increased weight status in children as young as 24 months of age.^{5,10,11} Other observational studies produced similar results: in a longitudinal study, a higher percentage of teacher-reported conduct problems was noted in overweight preschool children than in their normal-weight peers.¹² However, an earlier study revealed no association between behavioral problems and obesity at the age of 5 years, while at age 14 overweight girls had over twice the odds of concurrent total behavioral problems, with no such association noted in boys.¹³ Impulsivity was also associated with overweight and weight-loss treatment failure among 9-year-old girls.¹⁴ One study reported that early childhood prevention efforts which targeted parenting practices for child behavior problems reduced these behaviors and lowered rates of obesity.¹⁵

Both emotional-behavioral and biological path-

ways may mediate associations between childhood obesity and internalizing/externalizing problems.¹⁶ Lifestyle and behavioral parameters include poor adherence to self-care activities, sedentary habits and lack of physical exercise.¹⁷ Biologic mechanisms are mainly related to dysregulation of the stress system in which primarily the hypothalamic-pituitary-adrenal axis (HPA axis) and the sympathetic nervous system are involved. There is abundant evidence suggesting that children with symptoms of anxiety/depression are in most cases characterized by increased secretion of the stress hormones CRH and cortisol and the catecholamines norepinephrine and epinephrine.¹⁶ This hormonal state, when present on a chronic basis, could lead to central adiposity and the metabolic syndrome and also affect timing of puberty, physical growth and cognitive development.^{17,18}

In this study we aimed to investigate the prevalence of internalizing (depression/anxiety, somatic complaints and withdrawal) and externalizing (delinquent and aggressive) problems reported by both parents and children in a clinical population of obese children (OC) compared to normal-weight children. In addition, we examined the role of cortisol, as measured by five daily salivary samples, as a potential mediator between stress-related symptoms and obesity. We hypothesized a greater prevalence of internalizing and externalizing problems in obese than normal-weight children. Moreover, we hypothesized associations between these symptoms and daily salivary cortisol concentrations and a potential mediating role of cortisol.

METHODS

The study was approved by both the Scientific and the Ethics Committee of the “Aghia Sophia” Children’s Hospital. Written informed consent was obtained from the participants and their parents. The study group consisted of children and adolescents evaluated at the Childhood Obesity Clinic of our Pediatrics Department. The comparison group consisted of normal-weight children recruited from the community by research advertisement. The recruitment was conducted according to the Helsinki Declaration.¹⁹ The study protocol was described and published previously,²⁰ while a number of the children of the obese group (OG) had also participated in our previously published study.²⁰

Clinical evaluation and anthropometry

BMI calculation: The children's BMI was calculated as their weight in kilograms divided by the square of their height in meters. Weight and height were measured during the physical examination. The status of obesity or overweight was defined based on Cole's international criteria.²¹ BMI standard deviations (SD) and z-scores were calculated based on the Greek growth charts for age and gender.²² A full clinical examination was performed by a certified pediatrician.

Pubertal assessment: Participants' pubertal development was determined via physical examination by a certified pediatrician based on the 5 Tanner Stages of pubic hair and genital development in boys and pubic hair and breast development in girls.²³ Children with a Tanner Stage (for genital development in boys and breast development in girls) 2-4 were characterized as mid-pubertal and those with stage 5 as post-pubertal.

Exclusion criteria were: 1) underlying chronic illnesses, such as cardiac, hepatic and renal diseases; 2) chronic use of medications; 3) syndromic obesity; 4) mental disorders or pre-existing psychopathology; and 5) chromosomal disorders affecting puberty and/or body weight.

Psychometric instruments

The Greek version of the child behavior checklist (CBCL) and the youth self-report (YSR) were used to assess internalizing and externalizing symptoms in children.^{24,25} As conceived by Achenbach in 1991,²⁶ internalizing symptoms refer to problems of withdrawal, somatic complaints and anxiety/depression, while externalizing symptoms manifest in delinquent and aggressive behaviors. Cronbach's alpha for internalizing and externalizing problems in the Greek version of the CBCL is 0.90 and 0.94, respectively, whereas for both internalizing and externalizing problems in the Greek version of the YSR it is 0.90. The data obtained through these two questionnaires were inserted into the ASEBA (Achenbach System of Empirically Based Assessment) computerized system²⁷ and T-scores and percentiles of symptoms, based on Greek norms, were calculated. In addition, anxiety and depressive symptomatology were assessed using the Greek versions of the state-trait anxiety inventory

for children (STAIC) and the children's depression inventory (CDI). The analysis of these two questionnaires is presented and discussed in our previous article with the same general cohort of children.²⁰

Neuroendocrine evaluation: Salivary samples of the children were collected by their parents at home on the nearest Sunday to the physical and psychological examination day and were returned to the investigators within two days. The samples were collected five times a day (8.00 pre-breakfast, 12.00, 15.00, 18.00 and 21.00 hrs pre-bed). The time of awakening was scheduled for 7.30 a.m. Detailed instructions were given to parents and children in order that they would collect the saliva samples correctly, using a Salivette device (Sarstedt, Nuembrecht, Germany). Participants were not receiving any medications. The children were told not to eat, drink, brush their teeth or exercise for at least half an hour prior to sample collection. Each of the samples was collected by having the participant place a cotton swab in his or her mouth for 2 min or by his/her chewing it for 1 min. The cotton swab was then placed inside a plastic tube and kept in the refrigerator at 0-4 °C. Within two days from collection, the samples were given to the investigator for further processing. Salivary cortisol was extracted from the cotton swab by centrifuging the plastic tubes and cotton at 1000 g for 8 min to separate off the saliva into the outer tube. The cotton swab was then removed and all samples were stored at -85 °C. In addition, morning fasting blood samples were obtained for the measurement of serum cortisol. These samples were collected during a scheduled second visit to the Obesity Clinic, between 8 and 9 a.m. The blood samples were centrifuged and the serum obtained was stored at -85 °C. Samples were processed using the Elecsys Cortisol reagent kit produced by ROCHE Co (Basel, Switzerland). Serum and salivary cortisol concentrations were measured using an electrochemiluminescence immunoassay (Roche Co., Basel, Switzerland). The intra- and inter-assay precision coefficients of variation for serum cortisol concentrations were 1.1-1.3 and <8%, while for salivary cortisol concentrations they ranged from 1.5-6.1 and 4.1-8%, respectively. The analytical sensitivity (lower detection limit) for salivary cortisol concentrations was <0.036 µg/dl.

STATISTICAL ANALYSIS

Continuous data are presented as mean \pm SD, whereas categorical variables are presented as absolute (n) and relative (%) frequencies. Comparisons of means were performed with the Student t-test. Relations between nominal variables were assessed by the Fisher exact test and correlations between continuous variables were estimated by Pearson's *r*. Non-parametric procedures (Kruskal-Wallis, Mann-Whitney and Spearman rho) were used whenever sample sizes were small (<30). Linear regression analysis was used to adjust for the potential confounding effect of age and gender on the relation between cortisol and obesity. All statistical procedures were run in the Stata 11.0 statistical software (StataCorp, 4905 Lakeway Drive College Station, Texas, 77845, USA).

RESULTS

Clinical characteristics (age, gender, BMI z-scores and pubertal status) of the study population are presented in Table 1. The children of the OG were younger than the comparison (normal-weight) Group (NWG).

T-scores of internalizing and externalizing symptoms were provided by the ASEBA based on the Greek norms. OC had a greater percentage of self-reported and mother-reported symptoms of internalizing symptoms categorized in the clinical range, as shown in Table 2. T-scores of internalizing symptoms expressed by the children themselves (using the YSR questionnaire) were significantly higher in the obese than the normal-weight children ($p=0.03$). The same was noted ($p<0.001$) for internalizing symptoms as assessed by mothers (using the CBCL). No significant differences were noted in externalizing symptoms

as assessed by the children themselves. However, externalizing symptoms assessed by mothers were significantly higher in the obese than in the NWG ($p=0.003$). These results are presented in Table 2.

Cortisol area under the curve (AUC), as calculated by the five serial salivary samples for cortisol, was significantly higher ($p=0.03$) in the normal-weight than in the OG (Table 3). However, Pearson's correlation between cortisol AUC and age was significant ($r=0.3$, $p=0.005$). When gender was examined, differences in AUC between females (0.625 ± 0.485) and males (0.536 ± 0.292), as examined by the T-test, were not significant ($p=0.3$). In order to examine possible confounding effects of age and gender in the relation between cortisol and obesity, a linear regression analysis of cortisol AUC including age, gender and obesity was performed. The results, which are presented in Table 4, reveal that the significance of the relation between obesity and AUC was lost. In our data, this relation was probably due to the confounding effects of age and gender.

Lastly, associations between the children's AUC and internalizing-externalizing symptoms, expressed by both children and mothers, were not significant. Additional comparisons of AUC between children with high and low symptoms, expressed by both children and mothers, did not reveal significant results. Therefore, a mediation effect of cortisol in the relation of internalizing/externalizing disorders with obesity could not be supported by our data.

DISCUSSION

Our study revealed an increased prevalence of internalizing (withdrawal, somatic complaints and

Table 1. Characteristics of the Study Population

	Total (n=141)	Obesity Status (according to Cole et al, 2000)		p-value
		Normal Weight Group [NWG] (n=31)	Obese Group [OG] (n=110)	
Age (years, mean \pm SD)	11.3 \pm 2.2	13.0 \pm 1.5	10.9 \pm 2.2	<0.001
Gender, females, %	51.8%	58.6%	50.0%	0.5
BMI z-score (mean \pm SD)	2.47 \pm 1.81	-0.13 \pm 0.60	3.17 \pm 1.32	<0.001
Pubertal status, pre-/mid-/postpubertal, n (%)	41.3%/40.6%/18.1%	3.5%/51.7%/44.8%	51.4%/37.6%/11.0%	<0.001

***Fisher's exact test

Table 2. Internalizing and Externalizing Problems, in T-scores and classification, reported by both child and mother, in obese and normal weight children (Obesity Status according to Cole et al)

	Total	Obesity Status		p-value
		Normal Weight Group	Obese Group	
Internalizing, child				
T-score	48.3 ± 11.9	43.2 ± 9.1	49.3 ± 12.3	0.03
classification:				
normal, borderline, clinical (%)	80.3%, 8.2%, 11.5%	96.2%/3.8%/0%	76.0%, 9.4%, 14.6%	0.048
Internalizing, mother				
T-score	58.8 ± 11.4	50.6 ± 10.4	60.6 ± 11.3	<0.001
classification:				
normal, borderline, clinical (%)	54.2%, 11.7%, 34.1%	83.3%, 4.2%, 12.5%	46.9%, 13.5%, 39.6%	0.006
Externalizing, child				
T-score	47.2 ± 11.0	45.0 ± 10.4	47.8 ± 11.5	0.28
classification:				
normal, borderline, clinical (%)	85.3%, 4.9%, 9.8%	88.5%, 7.7%, 3.8%	84.4%/4.2%/11.4%	0.38
Externalizing, mother				
T-score	55.2 ± 11.1	48.2 ± 13.3	57.2 ± 10.5	0.003
classification:				
normal, borderline, clinical (%)	64.2%, 14.2%, 21.7%	75.0%, 16.7%, 8.3%	61.5%, 13.5%, 25.0%	0.18

Table 3. Cortisol distribution in the study population according to Obesity Status (Cole et al, 2000)

	Total	Obesity Status		p-value
		Normal Weight Group	Obese Group	
Cortisol AUC	0.581 ± 0.402	0.696 ± 0.251	0.558 ± 0.424	0.03

Table 4. Linear regression of Cortisol AUC, including age, gender and Obesity Status (Cole et al., 2000) as covariates

	β -coefficient (95% ci)	p-value
Age	0.062 (0.021, 0.103)	0.003
Gender (males vs. females)	-0.161 (-0.335, 0.011)	0.067
Obesity Status (obese vs. Normal weight)	-0.004 (-0.241, 0.233)	0.972

anxiety/depression) and externalizing (delinquent and aggressive behaviors) problems in a clinical population of OC, in comparison to normal weight children. Increased T-scores of internalizing problems in our sample were expressed by both mothers and children, whereas increased T-scores of externalizing problems were reported only by mothers. Daily salivary cortisol concentrations were lower in the obese than in the control group; however, the significance was lost when age and gender were inserted in the

analysis. No associations were found between cortisol and internalizing-externalizing problems.

Our study is in accordance with epidemiological studies showing an increased prevalence of mental health problems in OC.^{4,5,7,28} The OC in our study are derived from a Childhood Obesity Clinic, supporting previous evidence that treatment seekers (clinical samples) are more likely to have disturbed eating behaviors than overweight youngsters from community samples.²⁹ Several mechanisms link internalizing problems and obesity in children: poor adherence to self-care activities and sedentary habits such as excessive television viewing and internet use.¹⁷ Disturbed eating behaviors, such as emotional and external eating patterns, are potential mediators of this association.³⁰ In addition, low self-esteem and feelings of guilt and personal failure characterize both obesity and internalizing problems.^{31,32} Furthermore, the obesogenic effect of reduced sleep is thought to

be mediated by both behavioral and hormonal factors. Children have more time to eat, and sleep deprivation reduces leptin and raises ghrelin levels, which increase appetite.³³ Externalizing problems in children are by definition assessed by parents' and teachers' reports and not by the reports of children themselves, which is consistent with our findings. Attention deficit hyperactivity disorder, the most prevalent behavioral disorder in childhood, is highly comorbid with other externalizing problems and has been linked to obesity in children.³⁴⁻³⁷ Underlying mechanisms linking externalizing problems with pediatric obesity include: impulsive behaviors related to uncontrolled eating,³⁷ elevated sensitivity to immediate reward³⁸ and impaired executive functions (neurocognitive skills that are necessary for planning, monitoring and executing goal-directed actions) that might foster dysregulated eating behaviors, such as binge eating, emotional eating or eating in the absence of hunger.³⁹ Children with externalizing behaviors may also be at greater risk of food addictions. Lastly, externalizing problems and obesity may share common genetic and neurobiologic dysfunctions, involving the dopaminergic and possibly other systems.⁴⁰

The HPA axis, in addition to other biologic mechanisms, may mediate both internalizing and externalizing behaviors in childhood obesity, since anxiety disorders and depression have been linked to HPA axis dysregulation in adults and children.⁴¹⁻⁴⁴ However, relatively few studies have examined associations between anxiety/depression, the HPA axis and obesity.^{20,45-47} Our previous study, carried out in a clinical population of OC,²⁰ revealed that overall salivary cortisol concentrations were increased in children with anxiety or depressive symptomatology, as assessed by the STAIC and the CDI questionnaires^{48,49} compared to OC without any affective morbidity and to those with anxiety and depression comorbidity. Disturbed cortisol concentrations in these children might be associated with further morbidity. In the present study, we did not find any differences in daily cortisol concentrations between children with and without internalizing problems. This finding may be due to the fact that "internalizing problems" of CBCL involve a wider range of symptoms compared to those of STAIC and CDI. The HPA axis has also recently been investigated in children with externalizing prob-

lems.⁵⁰⁻⁵⁵ There is a body of evidence demonstrating an association between altered HPA axis reactivity and aggressive behavior. Several studies have shown reduced cortisol concentrations and a blunted HPA axis reactivity to stress.⁵⁶⁻⁵⁹ No evidence has so far linked childhood obesity, externalizing symptoms and cortisol concentrations. In our study, we investigated but did not establish such associations, possibly due to the fact that only problem-scales, and not clinical psychiatric disorders, were investigated. In addition, basal cortisol concentrations, relative to stress-induced cortisol concentrations, are a weaker measure of HPA activity in children.⁶⁰

Finally, we found that OC, in general, had a lower cortisol AUC compared to normal-weight children. This finding is consistent with a recent school-based study showing lower daily basal cortisol concentrations in obese than in normal-weight children.⁶¹ In this study, cortisol levels did not vary significantly with age or sex. A small number of other studies⁶²⁻⁶⁴ examining either basal cortisol levels or cortisol responses to stress confirm these results; however, other studies do not.^{65,66} In our sample, although OC had a significantly lower AUC compared to controls, this difference was lost after inserting the effect of age. A larger sample size of normal weight children could provide better evidence.

The main strength of the study is the fact that, in contrast to school-based or epidemiological studies, all children were examined in a clinical setting by pediatricians specialized in pediatric obesity. Limitations of our study are the cross-sectional design and the mild age difference in our groups. However, T-scores (for age and gender), and not absolute numbers, of internalizing/externalizing problems were used; thus, age and gender were incorporated in T-score values allowing comparisons between the two groups. Furthermore, the possible confounding effect of age and gender on the relation between obesity and cortisol was taken into account by inserting age and gender as co-variables in the multivariate regression analysis. Thus, differences in age and gender between the two groups, the obese and the normal weight, did not affect the interpretation of the results. Not all scales of the CBCL and the YSR were analyzed. In order to avoid repetitions and overlaps between symptom-scales, we chose to

analyze only the two wide scales of internalizing and externalizing problems. Lastly, no behavioral-emotional mechanisms, such as emotional and/or external eating, were taken into account. Future research carried out in clinical populations of OC are likely to overcome these limitations thus providing more insight into the biologic and behavioral mechanisms linking obesity to psychosocial and mental health.

DISCLOSURE STATEMENT

The authors have nothing to disclose. There is no conflict of interest.

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