

The association between morning cortisol and adiposity in children varies by weight status

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Abstract

Objective: To examine the associations between morning cortisol and adiposity in children at baseline and 9-month follow-up.

Methods: Participants included 649 (301 males, 348 females) children (9.6±0.9 years) for the cross-sectional analysis and 316 (153 males, 163 females) for the longitudinal analysis. Body mass index (BMI, kg/m²) was calculated from measured height and weight and waist circumference (WC, cm) was measured at the superior border of the iliac crest. Cortisol was assessed via saliva samples collected on a single morning. Cross-sectional and longitudinal analyses were conducted to examine the relationships between cortisol and adiposity.

Results: Approximately 31% were overweight (17.7%) or obese (12.8%). The mean cortisol level was 9.36±5.64 nmol/L (0.34±0.20 µg/dL). At baseline, no significant correlations were found between cortisol and BMI or WC ($r < 0.07$). Baseline cortisol did not correlate with change in BMI z-score ($r = -0.03$) or WC ($r < -0.01$) over the follow-up period. When examined by weight status, baseline cortisol was significantly related to changes in WC ($r = 0.32$) and BMI z-score ($r = 0.28$) among overweight subjects.

Conclusions: A positive relationship was found between morning cortisol and change in WC over 9 months in overweight children. Future studies should examine the association between 24-h cortisol patterns and direct measures of trunk fat.

Keywords: hypothalamic-pituitary-adrenal axis; obesity; overweight; stress; visceral fatness.

Introduction

Currently, an estimated 32% of children in the USA are either overweight or obese (1). Overweight/obesity and the

development of the metabolic syndrome (MetS) are two of the most pressing health concerns in this age group (2), given the tracking and relationship of these conditions with adult morbidity and mortality (3–5). Although prevention efforts focus upon physical activity, screen time and diet, an overlooked factor in the development of obesity and MetS is adverse psychosocial stress (6, 7).

Cortisol, the major glucocorticoid produced during hypothalamic–pituitary–adrenal (HPA) axis activity, is commonly used as a biomarker of psychological stress (8, 9). Dysregulation of the HPA axis and excess or altered cortisol secretion is thought to be associated with the accumulation of abdominal adipose tissue. Elevated cortisol levels can promote adipose tissue accumulation, particularly in the viscera, in several ways. Circulating cortisol activates lipoprotein lipase, which reduces lipid mobilization in the presence of insulin ultimately resulting in excess lipid storage in adipose cells. The inhibitory effects of cortisol on the growth hormone axis can also influence fat deposition.

Since the glucocorticoid receptor density is greater in visceral adipose tissue than in other tissues, adipose tissue in the abdominal region is more sensitive to the adipogenic effects of cortisol (10). Indeed, some studies have shown a positive relationship between cortisol and measures of central adiposity in children (11, 12). Studies by Barat et al. (11) and Weigensberg et al. (12), which included only overweight and obese youths, found positive relationships between cortisol and central adiposity measured via dual-energy X-ray absorptiometry (DEXA) and magnetic resonance imaging (MRI), respectively. Conversely, other studies have found no relationship between cortisol and intra-abdominal fat (13), body mass index (BMI) (14), DEXA trunk fat (15) or weight-for-height z-score (16). Although the methodology used in each of these previous studies varied, all except our recent study (15) were cross-sectional analyses. This limits the ability to determine the influence of cortisol on the accumulation of excess abdominal adipose tissue. The current study addresses the limitation of previous research by including a prospective component, in which the relationship between cortisol and change in adiposity was evaluated over a 9-month period.

Given the equivocal results to date, the purpose of this study was to further examine the association between morning cortisol and adiposity in children. Specifically, we examined whether baseline cortisol varies between normal weight, overweight and obese children. Additionally, follow-up data available for a portion of the participants were used to evaluate whether baseline cortisol was correlated with change in BMI percentile over a 9-month time period.

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Methods

Subjects

The participants in this study were 656 elementary school children aged six to 12 years (92% Caucasian, 3% African American) from public elementary schools in two Midwestern communities. Seven subjects were considered statistical outliers with morning cortisol values outside of three standard deviations from the mean and were removed from the analyses, leaving 649 subjects for the cross-sectional analysis. Children were from four public elementary schools in Lakeville, MN (population approximately 50,000) and six public elementary schools in Cedar Rapids, IA (population approximately 125,000). Both communities were involved in a community-, school-, and family-based intervention for the prevention of childhood overweight.

The baseline data included in this paper were collected in the fall of 2005, prior to randomization into the control or treatment arms of the study. Thus, these data represent a cross-sectional, observational research design. Prospective analyses included subjects from the control group only ($n=316$).

Parental consent and child assent were obtained prior to data collection. The study protocol was approved by the University of Minnesota Human Subjects Review Board.

Salivary cortisol

Salivary cortisol accurately reflects serum unbound cortisol concentrations and is an effective, easily obtainable measure of the physiological manifestations of psychosocial stress (17). In this study salivary cortisol, as opposed to serum, serves as a better measure of stress hormone by eliminating the additional undue stress caused by venipuncture in children.

Subjects were given sterile saliva collection tubes (Salimetrics, State College, PA) and instructed to collect a 0.5 mL sample in their own home on a typical day, immediately upon waking. Instructions on proper sample collection (e.g., do not brush teeth, avoid cough medicine or mouth wash for 24 h before collection, rinse mouth with water prior to collection, etc.) were given to the participants and their parents.

Samples were collected by research staff and shipped to our laboratory. The samples were then centrifuged at $100\times g$ for 2 min at 20°C and stored at -80°C until assayed. Salivary cortisol concentrations were measured using an enzyme-linked immunoabsorbent assay (ELISA; Salimetrics, State College, PA). The intra-assay coefficient of variability, determined on duplicate samples, was $<5\%$.

Anthropometry

Standing height, body mass and waist circumference (WC) were measured by a school nurse according to standard procedures (18). Standing height was measured using a portable stadiometer (Seca Road Rod).

Body mass was measured using a strain gauge scale (Lifesource MD). The body mass index (BMI in kg/m^2) was calculated from standing height and body mass. Overweight

and obesity were determined based on age- and sex-specific reference values defined by the Centers for Disease Control (CDC) (19). Children with BMIs between the 85th and 95th percentile were classified as overweight and those with BMIs ≥ 95 th percentile were classified as obese.

WC was measured to the nearest 0.1 cm above the superior border of the iliac crest. Previous studies in children have found WC to be moderately associated with visceral adipose tissue determined by magnetic resonance imaging (MRI) (20) and computed tomography (CT) (21).

Prior to data collection, the nurses were trained by one of the lead researchers (JCE) and intra- and inter-observer measurement error was determined at the completion of training. In addition, measurement error was also determined during data collection for this study by duplicate measures of every 25th subject. Overall, measurement error was small [standard error of measurement (SEM)=0.3 cm standing height; 0.1 kg body mass; 0.2 cm WC].

Statistical analysis

Descriptive statistics were calculated for anthropometric variables and morning cortisol for the total sample and by sex. Analysis of covariance was used to determine differences in morning cortisol between normal weight, overweight and obese participants. Partial correlations were used to examine the relationship between morning cortisol and both BMI and WC. Sex was controlled in all correlation analyses, and BMI was also controlled in some analyses of WC. Change in BMI z-score and WC were calculated for the 316 (49% of sample) participants in the control group by subtracting the value at baseline from that at follow-up. These changes over time were examined using partial correlation first controlling for age, and then for age and baseline BMI. Data analyses were carried out using SPSS version 18.0.

Results

Physical characteristics of the sample at baseline are shown in Table 1. The mean BMI percentile for the total sample was $62.8\pm 28.0\%$ (boys, 64.6% and girls, 61.3%). Approximately 31% were classified as overweight (17.7%) or obese (12.8%) according to CDC reference values. The mean morning cortisol level was 9.36 ± 5.64 nmol/L. No significant differences were found between boys and girls in any of the anthropometric measures or morning cortisol.

Mean morning cortisol did not differ across weight categories (i.e., normal weight, overweight and obese) in males or females (see Table 2). When examining the full sample, weak correlations approaching zero were found between cortisol and baseline BMI and WC ($r<0.07$). The results for the longitudinal analysis also indicated a lack of a relationship between morning cortisol and change in BMI z-score ($r=-0.01$; Table 3) in girls and change in WC ($r=-0.05$ to 0.09) between both sexes. In boys, however, a low positive correlation was found between morning cortisol and change in BMI z-score ($r=0.15$, $p<0.05$).

Table 1 Descriptive characteristics of the sample.

	Male (n=301)	Female (n=348)	Total (n=649)	Range (n=649)
Age, years	9.6±0.9	9.6±0.9	9.6±0.9	6.1–12.0
Height, cm	138.8±7.4	138.3±7.9	138.6±7.7	117.5–166.3
Weight, kg	35.9±9.2	35.7±9.4	35.8±9.3	19.3–80.8
BMI, kg/m ²	18.4±3.4	18.4±3.4	18.4±3.4	12.4–35.4
Overweight, %	19.9	15.8	17.7	–
Obese, %	12.6	12.9	12.8	–
Waist circumference, cm	63.7±9.4	63.4±9.5	63.5±9.4	46.0–108.6
Morning cortisol, nmol/L	9.28±5.40	9.43±5.85	9.36±5.64	0.06–29.88
Morning cortisol, µg/dL	0.34±0.20	0.34±0.21	0.34±0.20	0.00–1.08

Values are mean±standard deviation. Range of values is included for the total sample.

In a sub-analysis of overweight and obese subjects only, the lack of relationship between cortisol and both current BMI ($r < -0.01$) and WC ($r < 0.01$) remained. When examining the longitudinal relationships in overweight and obese subjects, however, a stronger relationship was found for both change in BMI z-score ($r = 0.18$) and change in WC ($r = 0.06$), though these results did not reach statistical significance ($p > 0.05$). When overweight and obese subjects were analyzed separately, stronger and statistically significant relationships were found between baseline cortisol and change in both BMI z-score ($r = 0.28$, $p = 0.04$) and WC ($r = 0.33$, $p = 0.01$) in the overweight subjects, while correlation coefficients for the obese subjects approached zero ($r = 0.04$ and $r = -0.05$, respectively).

Discussion

The lack of relationship between cortisol and both BMI and WC is in agreement with other studies (13–16). To date, two studies have shown a positive relationship between cortisol and adiposity (11, 12). However, these studies included only overweight and obese youths. In a sub-analysis of overweight and obese subjects only, we found the correlation between cortisol and both BMI and WC approached zero ($r < -0.01$ and $r < 0.01$, respectively).

Discordance between our results and those of others may be explained by the use of WC as a surrogate for visceral adiposity. Although WC has been established as a moderately reliable indicator of visceral adiposity (20, 21), MRI

Table 2 Adjusted means for morning cortisol [nmol/L; (µg/dL)] by BMI category, controlling for age.

	Normal	Overweight	Obese
Male	9.38±0.28 (0.34±0.01)	8.28±0.55 (0.30±0.02)	9.93±0.83 (0.36±0.03)
Female	9.38±0.28 (0.34±0.01)	8.83±0.83 (0.32±0.03)	9.93±0.83 (0.36±0.03)
Total	9.38±0.28 (0.34±0.01)	8.55±0.55 (0.31±0.02)	9.93±0.55 (0.36±0.02)

Values are mean±standard error.

and CT-determined visceral adiposity provide a greater precision of assessment. DEXA can also be used as a measure of regional fat distribution (total trunk or abdominal region). Previous studies including MRI or DEXA measures have, however, shown mixed results (11–13). Another study from our laboratory in which DEXA was used also failed to indicate a relationship between cortisol and trunk fat, both cross-sectionally and over a one- and 2-year follow-up period (15).

It is possible that the mixed results in this area are due to ethnic differences. The study by Weigensberg et al. (12) included only Latino boys, for instance, while Syme et al. (13) examined French-Canadian adolescents.

The differential findings between overweight and obese subjects are interesting and important to consider. Although baseline cortisol was positively correlated with changes in BMI z-score ($r = 0.28$, $p = 0.04$) and WC in overweight youths ($r = 0.33$, $p = 0.01$), this relationship was not observed in the obese. These results may suggest that elevated cortisol levels are associated with increased adipose tissue accumulation up to a certain level of adiposity at which time the effects are lessened (i.e., a “ceiling or threshold effect”). It has been suggested that suppression of cortisol production or reduced sensitivity to cortisol in obese youths may be an adaptive response that protects obese children from insulin resistance and progression to type 2 diabetes (22).

Two studies (23, 24) have also shown altered 11β-HSD1 activity in obese individuals, such that excretion of cortisol metabolites in urine is increased while salivary cortisol levels are not altered. Wiegand and colleagues (24) suggested that this altered cortisol metabolism in obese individuals may be protective; thus preventing an increase in circulating cortisol levels and thereby avoiding the increased insulin resistance and adipogenesis that has been associated with

Table 3 Partial correlations between morning cortisol and change in BMI z-score (r^1) and controlling for baseline BMI (r^2).

	r^1	r^2
Male (n=153)	0.160 ($p = 0.007$)	0.150 ($p = 0.009$)
Female (n=163)	-0.012	-0.015

hypercortisolemia in Cushing's syndrome. This altered 11 β -HSD1 activity in visceral adipose tissue previously mentioned may, however, result in greater exposure to active cortisol in the viscera, where reactivation of cortisone to cortisol may be increased (7).

Additionally, it is interesting that no relationships were found between cortisol and any measure of adiposity among normal weight youths, even though there was not a mean difference in baseline cortisol levels between any of the weight categories. The reason for this finding is unclear. Possible differences in glucocorticoid receptor density and cortisol metabolism at the tissue level may explain the differential findings between normal weight and overweight/obese youths in this study. Glucocorticoid receptor density is higher in visceral adipose tissue; thus, individuals with more adipose tissue around the abdomen may be more sensitive to cortisol than their normal weight counterparts (7). To better elucidate a causal relationship between cortisol and adiposity, future studies should examine cortisol levels earlier in life and extend longitudinal analyses over several years to capture these relationships more clearly.

Two previous studies (11, 12) examining the relationships between cortisol levels and adiposity among overweight and/or obese youth have also found positive relationships. In each of these studies, only abdominal adiposity was associated with morning cortisol. In contrast, we report positive longitudinal associations between change in both BMI z-score and WC and morning cortisol among overweight youths, but did not find any relationship between these variables in the cross-sectional analysis or in any other weight group. When adjusting for baseline WC, the strength of the relationship between cortisol and change in BMI z-score in the present study was unchanged. This difference between our study and previous studies may be partially explained by differences in the assessment of adiposity (WC vs. imaging techniques) and the distribution of overweight and obese children within each sample. Overweight and obese children were not classified separately in the study by Weigensberg and colleagues (12); however, the mean BMI percentile reported in that study was above the 95th percentile suggesting that most of the sample would be classified as obese. Additionally, Barat and colleagues (11) included only obese children from hospital-based obesity clinics. Therefore, comparisons between these studies and the present study are limited.

This study includes several limitations. First, we did not include an assessment of biological maturity status. Salivary cortisol levels have been reported to vary by pubertal stage (25–27); thus, any potential findings may be obscured by the inability to account for differences according to pubertal status. Another important consideration and limitation when examining this topic is the use of a single cortisol sample obtained immediately upon or shortly after waking. Although subjects in this study were directed to obtain saliva samples immediately upon waking, we cannot be certain that all subjects followed these instructions. Cortisol levels change rapidly in the first hour upon waking, so any deviation from the prescribed sampling time would obscure any relationships that may exist.

Additionally, although we would expect altered HPA axis activity to produce elevated cortisol, it is important to consider the daily pattern as some individuals may show “normal” morning cortisol yet abnormal peaks that remain elevated throughout the day rather than the typical diurnal variation. Indeed, morning cortisol is not a good predictor of cortisol area under the curve (28). Thus, examination of the total daily cortisol profile would provide a more comprehensive assessment of HPA axis function than a single value and perhaps more accurate results to this question.

In a study of the relationships between cortisol and obesity in adults, Bjorntorp and Rosmond (10) found that cortisol levels were associated with both waist-to-hip ratio and BMI. In their study, men who were particularly sensitive to stress had higher total daily cortisol levels and were more likely to exhibit components of the metabolic syndrome, even though morning cortisol levels in this group were lower than those in the healthy control group. These results in adults indicate that it may be more important to study the full daily pattern than just a single morning measure, and may help to explain the variability found among previous studies in children as well.

Another potential explanation for the null findings in this study and others is that some obese individuals may experience HPA axis “burnout”, in which case HPA axis activity actually decreases in response to prolonged activation and chronic stress (29). Future studies should consider the duration of stressful events among obese children.

In spite of these limitations, the present study included several strengths. First, this study included a large number of participants (n=649) in which the prevalence of overweight and obesity approximated that among youth in the USA. Additionally, the 9-month follow-up period allows for prospective analysis of the relationships between baseline cortisol and changes in adiposity, which has not been studied extensively to date.

In summary, the results of this study showed a lack of relationship between morning cortisol and adiposity in children. A positive relationship was found, however, between morning cortisol and change in WC over 9 months in overweight children. Future studies examining the relationships of cortisol secretion and metabolism with adiposity in children should include multiple samples across a given day as well as analysis of urinary cortisol metabolites.

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