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Original Articles

Hypothalamic-Pituitary-Adrenal Axis in Obese Chinese Children

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Abstract

Aims: To evaluate the correlation between hypothalamic-pituitary-adrenal (HPA) axis activity with degree of obesity, severity of obstructive sleep apnoea (OSA) and laboratory parameters in a group of obese Chinese children. ***Methods:*** Consecutive children with primary obesity were recruited from the Obesity & Lipid Disorder Clinic of a university teaching hospital. Degree of obesity was assessed by anthropometric measurements. Those with habitual snoring (snoring for >3 nights per week) underwent overnight sleep study. Laboratory measurements included fasting plasma glucose, lipid profile, and serum insulin. Twenty-four-hour urinary free cortisol (UFC) excretion was used as a surrogate marker of HPA axis activity. ***Results:*** One hundred ninety-six children were studied and their median age and body mass index (BMI) were 12.1 (IQR 9.9-13.9) years and 29.5 (26.2-33.4), respectively. Boys were more obese and had significantly higher UFC than girls (160.0 vs 132.4 nmol/day, p=0.016). Spearman's rank correlation revealed significant positive association between UFC and anthropometric markers of obesity, namely, BMI, waist circumference, and skinfold thickness. There was also negative association between UFC and plasma high-density lipoprotein concentrations. In boys, a positive correlation was demonstrated between UFC and serum insulin concentrations. However, unlike previous publications, only age and male gender were significant independent factors associated with UFC excretion in multivariate analysis. Eighteen children had OSA but no correlation was found between UFC and severity of OSA. ***Conclusion:*** Twenty-four-hour urinary free cortisol is not able to delineate any HPA axis dys-regulation in this cohort, further studies will be required to investigate the relationship between obesity and cortisol pathway in children.

Key words Hypothalamic-Pituitary-Adrenal Axis; Insulin; Obesity; Obstructive Sleep Apnoea; Urinary Free Cortisol Excretion

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Introduction

The problem of obesity and its related complications have become a major health concern globally. In Hong Kong, it was estimated that the prevalence of obesity for children aged 11 years rose from 21% for boys and 10% for girls in 1993 to 34% for boys and 13% for girls in 1998, respectively.[1] According to a recent population study, 12.1% of boys and 10.8% of girls aged 6 to 12 years were obese.[2] Adult complications of obesity may originate from early childhood. Childhood obesity has been independently associated with arterial endothelial dysfunction and thickening, which can predispose events leading to atherosclerosis.[3,4] The prevalence of type 2 diabetes among children, a condition that is strongly associated with obesity, is increasing.[5] Twenty-four percent of a cohort of obese Chinese children had presumed non-alcoholic steatohepatitis (NASH), a condition that can lead to liver fibrosis and later cirrhosis.[6]

Hypothalamic-pituitary-adrenal (HPA) axis dysregulation and cortisol metabolism may play a part in the pathogenesis of obesity. Patients with Cushing syndrome share phenotypic and metabolic consequences that are frequently seen in obese patients. Cortisol affects lipid metabolism by increasing hepatic triglyceride production and visceral fat deposition. It also stimulates appetite and induces insulin resistance.[1,7] In adults, cortisol production rate has been found to increase in parallel with increasing BMI and percentage body fat.[8] Altered sensitivity of the HPA axis in obese adults has also been demonstrated, including an enhanced HPA response to stress,[9] as well as to both stimulation and suppression tests.[10] These changes in response were especially prominent in those with central obesity[11] and insulin resistance.[12] Studies on obese Asians with diabetes or metabolic syndrome have shown elevated serum cortisol concentrations compare to healthy controls.[1,13] Similar data for the paediatric population is however limited. In Germany, a group of investigators demonstrated that in obese, insulin resistant children, their morning serum cortisol concentrations were significantly higher than those obese, non-insulin resistant or normal weight counterparts, irrespective of pubertal stage. Insulin resistance was also found to be correlated with cortisol.[14] A recent study by Barat et al showed that in 45 pre-pubertal obese children there are associations between truncal distribution of fat mass and HPA axis alteration (serum morning cortisol, salivary cortisol response to lunch).[15] However, spot cortisol level may not reliably reflect the status of the HPA axis. With the growing pandemic of childhood obesity and the accumulating evidence to suggest tracking of disease from childhood to adulthood, exploring the role of HPA axis in childhood obesity may provide additional information on the pathogenesis of this important global problem.

The aim of this study was to assess the correlation between obesity, obstructive sleep apnoea, insulin resistance and HPA activity in a cohort of obese Chinese children. Based on adult data, we hypothesised that HPA axis activity correlates with degree of obesity in children. The 24-hour urinary cortisol excretion (UFC) was used as a marker of HPA axis activity.

Methods

Subjects

We recruited children aged 7 to 18 years from the Obesity & Lipid Disorder Clinic of a university teaching hospital from 1 January 2000 to 31 December 2004. All subjects were obese with a BMI >95th percentile of local sex and age specific references.[16] They were referred by primary health care physicians for assessment and further management. All of the subjects had primary obesity, confirmed by detailed history taking and physical examination. Children with known endocrine problems, renal insufficiency or depression, and those taking regular corticosteroid were excluded from the study. Informed written consents were obtained from the parents. The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong.

Body Indices Measurement

Parameters of body composition including height, weight, waist circumference, hip circumference and anthropometric measurements were obtained using standard methods. Weight was measured by a calibrated weighing scale to the nearest 0.1 kg. Height was measured by a stadiometer to the nearest 0.5 cm.[17,18] Waist circumference was taken at midway between the lower rib and the superior border of iliac crest. Hip circumference was taken as the largest measurement at buttock protrusion.[19] We used Holtain skinfold caliper to measure skinfolds at biceps, triceps, subscapular and suprailiac areas. Average of 3 measurements at each site was obtained.[18] Body mass index was calculated as kg/m^2. Centile curves for the local paediatric population were used as reference.[16]

Urine and Blood Sampling

Subjects were admitted to hospital for urine and blood collection. Complete collection of 24-hour urine was ensured as it was performed under supervision. If there was any suspicion of incomplete urine saving, the data would not be entered into analysis. After overnight fasting, blood was drawn at 0800h for assay of fasting insulin, glucose and lipid profile (cholesterol [Chol], triglycerides [TAG], high-density lipoprotein cholesterol [HDL-C] and low-density-lipoprotein cholesterol [LDL-C]). Serum insulin was assayed by chemiluminescent immunoassay using Immulite 1000 (Siemens Medical Diagnostic Solutions, Tarry Town, NY, USA). Lipid profile (except LDL-C) were assayed by enzymatic method using DP Modular Analytics (Roche Diagnostic Corp, Indianapolis IN, USA). Coefficient of variation was less than 3%. LDL-C was calculated using Friedewald formula.

Urine samples for cortisol were analysed by electrochemiluminescent immunoassay using E170 Modular Analytics (Roche Diagnostics Corp, Indianapolis IN, USA). Coefficient of variation over the assay range was 5%. Urinary free cortisol excretion rate over 24 hours was then calculated by multiplying the urinary free cortisol concentration in nmol/L and the daily urine output in L/day (nmol/day, reference range 100-379 nmol/day).

Homeostasis model assessment (HOMA), a marker of insulin resistance was calculated as fasting serum insulin x fasting plasma glucose divided by 22.5.[20] There is no sex and age adjusted reference in our locality. We therefore use HOMA > 4 to classify insulin resistance as it has been shown to provide a reliable cut-off between normal healthy children and those at risk of developing type 2 diabetes.[14]

Overnight Sleep Study

Subjects with habitual snoring (snoring >3 nights per week) underwent overnight polysomnographic study (PSG). PSG was performed using Siesta ProFusion II PSG machine (Compumedics Telemed PTY Ltd. Abbotsford, Australia). Parameters included electroencephalogram from four leads (C_3/A_2, C_4/A_1), bilateral electrooculogram, electromyogram of mentalis activity and bilateral anterior tibialis were recorded. Pneumatic effort belt was used to detect respiratory movements of the rib cage and abdomen. Body position was monitored via a body position sensor. Electrocardiogram and heart rate were continuously recorded from two anterior chest leads. Arterial oxyhaemoglobin saturation (SaO_2) was measured by an oximeter (Ohmeda Biox 3900 Pulse Oximeter) with finger probe. Respiratory airflow pressure signals were measured at the anterior nares. Snoring was measured by a snoring microphone placed near the throat. Further details of the methodology used have been published.[21] Oxygen saturation nadir, obstructive aponea index (OAI), apnoea hyponea index (AHI) and percentage of total sleep time with desaturation less than 90% were obtained, and OSA was defined as OAI >1. OSA were classified as mild if OAI ≤5. For those with an OAI >5, they were considered to have moderate to severe disease.

Statistical Analysis

Baseline variables were expressed as medians and ranges of gender. Comparison of variables was tested by Mann-Whitney U and *Chi*-square tests, where appropriate. Univariate analysis using Spearman's rank correlation coefficients was used to assess the association between urinary cortisol levels and measurements for obesity (BMI z-score, waist circumference, waist hip ratio, anthropometric measurement), insulin level, insulin resistance (HOMA) and demographic characteristics (sex, age). Those variables found to be significant in the univariate analysis will then be entered into multiple linear regression with forward stepwise strategy to assess the significant factors that were associated with UFC simultaneously. All statistical tests were performed with SPSS for Windows (Release 14.0; SPSS, Chicago, IL, USA). The level of significance was set at 5% in all comparisons.

Results

A total of 196 patients were recruited during the study period. Median age and BMI of the group were 12.1 (IQR 9.9-13.9) years and 29.5 (IQR 26.2-33.4) kg/m^2, respectively. Demographic data, laboratory measurements and sleep study results of the participants are shown in Table 1. One hundred and ninety-three children completed 24-hour urine collection for UFC analysis. Results from three patients were excluded for analysis. One was found to be taking regular corticosteroids. Another was suspected to have pituitary problem. The third subject misplaced some of the urine sample during the collection period.

There were more boys in this cohort than girls. The boys had higher 24-hour urinary cortisol output when compared to the girls (160.0 nmol/day vs. 132.4 nmol/day, p=0.016). On the other hand, girls were found to have significantly higher insulin concentrations (22.5 mIU/l vs 16.2 mIU/l,

Table 1 Demographic characteristics of the study population

	Female (n=58)	Male (n=138)	P	All subjects
Age (years)	12.6 (10.8, 14.7)	11.9 (9.8, 13.8)	0.25	12.1 (9.9, 13.9)
% <90%	0.50 (0.2, 1.7)	1 (0.1, 2.9)	0.47	0.7 (0.1,2.6)
SaO_2 nadir (%)	80 (72, 90)	81 (72, 88)	0.83	81 (72, 88.5)
OAI (per hour)	0.4 (0, 0.9)	0.2 (0, 1)	0.8	0.3 (0, 1)
AHI (per hour)	1.4 (0.3, 2.6)	1.7 (0.8,4.7)	0.2	1.6 (0.8, 4.3)
Weight (kg)	73.1 (56.7, 87.8)	69.4 (55.6, 85.8)	0.7	70.5 (55.9, 86.1)
Height (cm)	155 (144.6, 161)	150.5 (143, 164)	0.8	152 (143.5, 162.8)
Body mass index (kg/m^2)	29.3 (26.6, 34)	29.5 (26.2, 33.3)	0.9	29.5 (26.2, 33.4)
Body mass index z-score	2.9 (2.6, 3.4)	3.1 (2.7, 3.4)	0.1	3 (2.7, 3.4)
Waist (cm)	88.3 (78.4, 93.3)	89 (81.5, 97.5)	0.4	88.8 (81, 96)
Hip (cm)	104.5 (90.3, 115)	99 (89.5,108)	0.06	100 (89.5, 109)
Biceps (mm)	19 (15.4, 24.3)	18.8 (14.5,23.9)	0.9	19 (14.9, 24)
Triceps (mm)	28.7 (26.2, 33)	28 (22.6,33.4)	0.3	28.4 (23.9, 33)
Subscapular (mm)	34.4 (31, 40)	34 (29, 38)	0.1	34.3 (29.7, 39)
Suprailiac (mm)	33.4 (30.5, 37.5)	34.5 (30.2, 38.4)	0.5	34 (30.5, 38)
Insulin (mIU/l)	22.5 (14.8, 34.4)	16.2 (12.4, 23.3)	0.011*	17.8 (12.7, 28.9)
Glucose (mmol/l)	5.1 (4.8, 5.5)	5.1 (4.9, 5.5)	0.27	5.1 (4.9, 5.5)
HOMA index	5.2 (3.5, 7.8)	3.8 (2.9, 5.7)	0.018*	4.1 (2.9, 6.5)
Cholesterol (mmol/l)	4.6 (4.2, 5.1)	4.6 (4.1, 5.2)	0.8	4.6 (4.1, 5.1)
TAG (mmol/l)	1.3 (1, 1.8)	1.29 (1, 1.7)	0.5	1.3 (1, 1.8)
HDL-C (mmol/l)	1.2 (1.1, 1.4)	1.3 (1.1, 1.4)	0.9	1.3 (1.1, 1.4)
LDL-C (mmol/l)	2.7 (2.3, 3.2)	2.7 (2.2, 3.2)	0.8	2.7 (2.2, 3.2)
Urine cortisol (nmol/24h)	132.4 (95.3,172.5)	160 (122.5, 219.5)	0.016*	156.3 (112.8, 206.5)

Values are presented as median and interquartile range

OAI=obstructive apnoea index; AHI=apnoea hyponoea index; % <90=% sleep time with saturation less than 90%; HOMA=homeostasis model assessment; TAG=triglycerides; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density-lipoprotein cholesterol

*statistical significant with p-value <0.05

p=0.011) and HOMA index (5.2 vs 3.8, p=0.018) compared to boys.

Eighty five patients underwent PSG and 18 were confirmed to have sleep apnoea. Nine of the children had mild disease while the other nine had moderate to severe OSA. The median OAI and AHI were 0.27 (IQR 0.0-1.0) and 1.6 (IQR 0.8-4.3) episodes per hour, respectively. The median saturation nadir was 81% (IQR 72-89%). Percentage of sleep time of oxygen below 90 was 0.7%. Analysis was performed with subjects stratified according to the severity of OSA. Those with more severe OSA were older, heavier, with greater waist and hip circumference and greater subscapular and suprailiac skinfold thickness. However there were no significant differences in urinary cortisol levels between the two groups (Table 2).

Significant correlations with urinary cortisol were found for age, weight, height, waist circumference, hip circumference, and skinfold thickness (Table 3). UFC did not correlate with BMI z-score nor HOMA index. Negative correlation with urinary cortisol was found for HDL-C (-0.2, p at 0.01 level). However if boys and girls were separately analysed, UFC correlated positively with insulin level and HOMA in boys, in addition to the above body indices.

Logarithmic transformation was applied to urinary cortisol as the data were skewed. In multiple regression analysis, UFC was only positively associated with male gender and age (Table 4).

Discussion

There were more boys than girls in this large group of obese patients, reflecting the higher prevalence of obesity in boys in our population. In adults, male have a higher production rate of cortisol.[8] We also found that boys have higher UFC when compare to girls. Therefore it is important

Table 2 Demographic characteristics of children who underwent polysomnographic study

	OAI		
	≤1	**>1**	**P**
Number	67	18	
Age	11.75 (9.14, 13.31)	12.44 (11.18, 13.89)	0.123
% <90%	0.45 (0.00, 1.30)	6.40 (1.40, 11.45)	<0.001*
SaO_2 nadir (%)	83 (75, 90)	72 (62, 82)	0.001*
OAI (per hour)	0.14 (0.00, 0.50)	5.70 (1.75, 15.95)	<0.001*
AHI (per hour)	1.20 (0.40, 2.19)	17.53 (5.90, 30.20)	<0.001*
Weight (kg)	59.70 (49.60, 75.30)	73.70 (59.80, 91.45)	0.011*
Height (cm)	148.00 (137.00, 158.50)	155.50 (147.00, 165.75)	0.054
Body mass index (kg/m^2)	28.46 (25.58, 30.34)	32.12 (27.37, 35.12)	0.019*
Body mass index z-score	2.91 (2.57, 3.19)	3.15 (2.96, 3.51)	0.037*
Waist (cm)	84.50 (76.50, 90.00)	94.00 (87.50, 102.50)	0.001*
Hip (cm)	95.00 (86.00, 103.25)	105.00 (91.50, 114.50)	0.025*
Biceps (mm)	17.50 (14.00, 21.56)	20.00 (15.75, 24.50)	0.138
Triceps (mm)	26.13 (22.38, 30.00)	28.00 (26.00, 33.25)	0.092
Subscapular (mm)	34.00 (27.88, 38.00)	35.00 (31.75, 39.25)	0.278
Suprailiac (mm)	32.00 (29.06, 36.00)	36.00 (34.25, 39.63)	0.004*
Insulin (mIU/l)	16.35 (12.03, 21.88)	15.80 (12.20, 29.50)	0.827
Glucose (mmol/l)	5.10 (4.90, 5.50)	5.30 (4.85, 5.70)	0.246
HOMA index	3.85 (2.69, 5.12)	3.23 (2.68, 7.60)	0.854
Cholesterol (mmol/l)	4.55 (4.00, 5.10)	4.70 (4.30, 5.50)	0.314
TAG (mmol/l)	1.17 (0.89, 1.65)	1.42 (1.16, 1.88)	0.049*
HDL-C (mmol/l)	1.27 (1.10, 1.50)	1.10 (0.95, 1.50)	0.158
LDL-C (mmol/l)	2.70 (2.10, 3.00)	2.90 (2.50, 3.25)	0.281
Urine cortisol (nmol/24h)	159.20 (109.25, 203.26)	130.00 (75.65, 194.75)	0.243

Values are presented as median and interquartile range

OAI=obstructive apnoea index; AHI=apnoea hyponoea index; % <90=% sleep time with saturation less than 90%; HOMA=homeostasis model assessment; TAG=triglycerides; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density-lipoprotein cholesterol

*statistical significant with p-value <0.05

to assess the HPA axis according to gender as there are intrinsic differences between boys and girls.

However in this study we did not demonstrate correlation between UFC and insulin resistance or degree of obesity, unlike results published by Reinehr et al.[14] It may be due to the fact that we used different method to assess the HPA axis. Daily urinary free cortisol (UFC) represents the level of free cortisol in blood during the examined period. It reflects better in terms of the activity of the HPA axis than an isolated serum cortisol level, which is highly variable even for the same individual.[22] It is a sensitive test for hypercortisolism and is the recommended first-line test for screening Cushing syndrome with a cutoff of 4 times the upper normal limit.[23] It has been demonstrated to be elevated in centrally obese women and is positively correlated with truncal fat distribution.[24] The test is non-invasive, making it suitable for the paediatric population. It is particularly important in obese children as venous access is usually difficult and serial blood taking may be too stressful to them. In this study complete urine collection was ensured by supervision of our subjects. However as paediatric reference ranges for UFC are not available it was not possible to determine the extent to which our subjects had hyperactive HPA activity. Studies had shown total UFC to be within normal range in obese adults.[25,26] In Barat's study, they also could not demonstrate association between fat distribution and UFC. In obese adults, they are shown to have elevated overnight urinary cortisol excretion but not 24-hour urinary cortisol excretion.[27] Some researchers found the overnight UFC excretion rate was higher in patients with central fat distribution.[28] It was speculated that an increased overnight urinary cortisol excretion may reflect better the flattening of diurnal cortisol secretion, which could identify subtle alteration of the HPA axis. UFC therefore may not be

Table 3 Spearman's rank correlation between urinary free cortisol and anthropometric and laboratory parameters

	Male	Female	All subjects
Age (years)	0.330**	0.469**	0.330**
% <90%	-0.118	-0.594**	-0.213
SaO_2 nadir (%)	0.173	0.265	0.199
OAI (per hour)	-0.131	-0.328	-0.175
AHI (per hour)	-0.092	-0.354	-0.140
Weight (kg)	0.374**	0.322*	0.344**
Height (cm)	0.351**	0.299*	0.320**
Body mass index (kg/m^2)	0.279**	0.269	0.260**
Body mass index z-score	0.135	0.022	0.123
Waist (cm)	0.352**	0.273	0.333**
Hip (cm)	0.352**	0.453**	0.346**
Biceps (mm)	0.183*	0.117	0.165*
Triceps (mm)	0.185*	0.265	0.189*
Subscapular (mm)	0.256**	0.137	0.202**
Suprailiac (mm)	0.211*	-0.035	0.154*
Insulin (mIU/l)	0.191*	0.112	0.124
Glucose (mmol/l)	0.066	0.230	0.131
HOMA index	0.212*	0.144	0.156
Cholesterol (mmol/l)	-0.061	-0.093	-0.057
TAG (mmol/l)	-0.132	-0.053	-0.113
HDL-C (mmol/l)	-0.218*	-0.174	-0.204**
LDL-C (mmol/l)	0.074	0.012	0.061

OAI=obstructive apnoea index; AHI=apnoea hyponoea index; % <90=% sleep time with saturation less than 90%; HOMA=homeostasis model assessment; TAG=triglycerides; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density-lipoprotein cholesterol

*Correlation is significant at the 0.05 level (2-tailed); **Correlation is significant at the 0.01 level (2-tailed)

Table 4 Multiple regression results for 24-hour urinary free cortisol

	Unstandardised coefficients (SE)	Standardised coefficients	P-value
Female	-0.208 (0.074)	-0.201	0.006
Age (years)	0.053 (0.012)	0.308	0.000

sensitive enough to detect mild HPA axis dys-regulation in our subjects.[11,24,29] We did not measure the ratio of different cortisol metabolites, which has been shown to be altered in obese adult subjects.[25] Therefore a "normal" 24-hour UFC value alone does not exclude the presence of mild or early HPA axis dys-regulation. On the other hand, we included patients of a wide range of age. So the group is heterogeneous with different pubertal states. Therefore, we cannot directly compare with other study populations on the degree of obesity even with the BMI z-score, which may hinder the difference in terms of the degree of HPA axis alteration. It would be better if we could stratify them according to pubertal states and perform separate analysis.

The stress of hypoxia may alter HPA axis function in humans with untreated OSA, as demonstrated by studies involving adult OSA patients.[30-32] Lanfranco et al demonstrated that obese OSA patients had enhanced ACTH response to CRH stimulation test when compared to simple obese and normal weight subjects. The mechanism was still unclear and the authors postulated possible change in neurotransmitter control of ACTH secretion. Hypoxia may also serve as a chronic stress factor which may trigger the HPA axis activity. However, in the same study, the authors were not able to establish significant differences in 24-hour UFC excretion between OSA and non-OSA subjects, similar to our findings. Our negative result may also be related to the mild disease severity in our cohort of OSA children. In addition, the duration of disease in children is much shorter

compared to adults, hence a shorter period of stimulation for the HPA axis.

There are certain limitations to our study. The lack of paediatric references for UFC, or of a control group for our study, makes it difficult to determine whether the values obtained in our subjects lie outside the normal range. The fact that subjects were all hospitalised may affect the HPA axis due to the stress associated with the unfamiliar environment. The result may be more valid if we could analyse patients according to different pubertal stages. Similarly, we could analyse according to age if the study sample is big enough. The design of this report was cross-sectional, longitudinal data would have provided much stronger evidence for the causal relationship between HPA axis and obesity.

Conclusion

By using UFC, there was no evidence of HPA axis dysregulation in this large sample of obese Chinese children. Future longitudinal studies with age, sex and pubertal states matched controls would be better to further delineate the possible mechanisms of HPA dysfunction in the pathogenesis of obesity.

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