Children and adolescents with obesity and the metabolic syndrome have high circulating cortisol levels

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Abstract

OBJECTIVES: The aim of this study was to investigate the relationship between the varying degrees of obesity and blood glucocorticoid levels in obese children and adolescents with and without metabolic syndrome features.

METHODS: We studied 241 obese children and adolescents aged between 2 and 17.6 years; 127 boys and 114 girls. All children underwent an oral glucose tolerance test. Measurements included blood pressure, cortisol, ACTH, and lipid profiles. The diagnosis of metabolic syndrome was defined according to the criteria adapted from World Health Organisation and National Cholesterol Education Program Adult Treatment Panel-III guidelines.

RESULTS: Blood cortisol and ACTH levels were higher in patients with MS than without MS ($p = 0.02$). ACTH levels increased with weight ($r = 0.13$, $p = 0.02$), systolic blood pressure ($r = 0.21$, $p = 0.002$), diastolic blood pressure ($r = 0.17$, $p = 0.01$), fasting glucose ($r = 0.17$, $p = 0.01$). Cortisol production was only correlated with systolic blood pressure ($r = 0.12$, $p = 0.05$).

CONCLUSIONS: Results from the present study indicates that there may be a link between cortisol production and the metabolic syndrome in obese children and adolescents.

ORIGINAL ARTICLE

Abbreviations:
AGH –Abnormal glucose homoeostasis
BP –Blood pressure
DM –Diabetes mellitus
HDL-C –high-density lipoprotein-cholesterol,
HPA –Hypothalamo-pituitary-adrenal axis
HT –Hypertension
GCs –Glucocorticoids
GI –Glucose intolerance
IFG –Impaired fasting glucose
MS –Metabolic syndrome
OGT –Oral glucose tolerance test
TG –Triglyceride,
LDL-C –Low-density lipoprotein-cholesterol
VLDL-C –Very low-density lipoprotein-cholesterol
WHO –World Health Organisation

INTRODUCTION

Glucocorticoids (GCs) are hormones, involved in the regulation of a variety of physiological functions, essential in all aspects of human health and disease. GCs as their name suggest, are hormones involved in glucose metabolism and play key physiological roles in the regulation of energy homeostasis [16, 20].

Recently, there has been an increasing interest in the role of glucocorticoids in the pathogenesis of metabolic syndrome [5, 11]. Clinical similarity between patients with excess secretion of glucocorticoids, as in Cushing's syndrome, and those with metabolic disease is the major clue for the link between glucocorticoids such as cortisol and the origins of metabolic disease [4, 21]. And now, there is increasing evidence that patients with type 2 diabetes and metabolic syndrome have increased cortisol levels [9] .

Cushing's syndrome is caused by a tumour that stimulates the adrenal glands to produce large quantities of glucocorticoids, and has a clinical presentation (central obesity, hypertension, dyslipidemia, and insulin resistance) that overlaps with the metabolic syndrome [18].

In recent years metabolic syndrome has become increasingly common, in parallel to increasing frequency of childhood obesity and type 2 diabetes mellitus (DM), among children and adults throughout the world [10, 17].

Several studies suggested similarities between the metabolic syndrome and Cushing's syndrome, and hypothalamo-pituitary-adrenal (HPA) axis activity, based on increased cortisol concentration, have been linked to metabolic syndrome development in adults [3, 12, 20].

To our best knowledge such a relation is not evaluated in children. Therefore the aim of this study was to investigate the relationship between the varying degrees of obesity and blood glucocorticoid levels in obese children and adolescents with and without metabolic syndrome features.

SUBJECT AND METHODS

The study protocol was approved by the institutional Committee, and informed permission of parents with children's assent was obtained for enrolment in the study.

The study included 241 obese (BMI ≥ 95th percentile) children and adolescents between the ages of 2.0 and 17.6 years; 127 boys and 114 girls. Patients with secondary obesity due to endocrine or genetic factors, and any other definite cause of hypertension were excluded.

Measurements of height (cm) and weight (kg) were obtained by the same person using the same scale, and without shoes and with light clothing. Patients BMI was calculated, as body weight (in kilograms, to nearest 0.05 kg) divided by height (in meters squared, to the nearest 1 mm), to establish a diagnosis of overweight or obesity.

Appropriate medical history was taken and a thorough physical examination was performed by a paediatric endocrinologist on admission. Blood pressure (BP) measurements were done with an appropriate size cuff manometer from the right arm in a silent room in a comfortable sitting position.

All children underwent oral glucose tolerance test (OGT). An oral load of 1.75 g/kg body weight (max. 75 g) glucose solution was given in the morning following a 12-hour fasting period, and simultaneous venous blood glucose and insulin levels were measured in blood samples taken 0, 30, 60, 90 and 120th minutes after oral glucose ingestion. Lipid profile (triglyceride (TG), total cholesterol (C), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), very low-density lipoprotein-cholesterol (VLDL-C), cortisol and ACTH was determined in the first blood samples obtained at 08^{00} h (a.m). Glucose levels were determined promptly with glucose oxidase analytical method, while insulin levels were measured with radioimmunoassay (Immunotech kit) method after storage of serum samples at –20°C for at least a week. Serum lipid profiles were examined using modular analytical system (Roche/Hitachi). Serum fasting cortisol was assessed using a radioimmunoassay and plasma ACTH was quantified with a commercial immunoradiometric assay (Nichols Institute Diagnostics, San Clemente, CA) with an interassay CV of 6.8% to 7.8% between 36 and 358 pg/mL ACTH.

Glucose tolerance was defined according to the World Health Organisation (WHO) criteria for glucose tolerance status [19]. Hyperinsulinism (HI) was defined from norms for pubertal stage: prepubertal ≥15 mIU/L, mid-puberty (stage 2–4) ≥30 mIU/L, post-puberty ≥20 mIU/L [2, 15].

Table 1. Demographic and clinical data of the study population, divided into two subgroups, with and without metabolic syndrome

Variable	MS (-) (n = 135)	MS (+) (n = 106)	Total (n = 241)	*P* value
Gender (Male/female)	64/71	63/43	127/114	NS
Age (years)	10.8 ± 3.3	12.2 ± 2.5	11.4 ± 3.0	0.001
BW (gram)	3398.5 ± 6	3528.7 ± 573.0	3455.8 ± 573.2	NS
Weight (kg)	57.33 ± 18.11	74.48 ± 19.57	64.87 ± 20.6	0.001
Height (cm)	143.71 ± 16.45	155.12 ± 13.39	148.73 ± 16.2	0.001
Body mass index (kg/m^2)	26.98 ± 3.82	30.47 ± 4.37	28.52 ± 4.4	0.001
Systolic blood pressure (mmHg)	109.20 ± 12.26	120.96 ± 14.50	114.4 ± 14.5	0.001
Diastolic blood pressure (mmHg)	69.94 ± 8.88	78.63 ± 11	73.810.8	0.001
Duration of obesity	5.57 ± 2.55	6.15 ± 2.66		NS

Values are mean and standard deviation (SD); M: male; F: female; BW: Birth weight; NS: non significant, MS: metabolic syndrome

Definition of Metabolic Syndrome:

Metabolic syndrome was diagnosed based on the criteria modified from WHO and National Cholesterol Education Program Adult Treatment Panel-III (NCEP ATP III). The diagnostic criteria for metabolic syndrome can be grouped under 4 headings [1, 7, 8, 17]:

1. Obesity: BMI ≥95th percentile for age and gender
2. Abnormal glucose homoeostasis (AGH): The presence of one of the following:
   a. Hyperinsulinemia (with fasting blood or oral glucose tolerance test)
   b. Impaired fasting glucose (IFG)
   c. Glucose intolerance (GI)
3. Hypertension (HT): age and gender adjusted systolic/diastolic blood pressure within ≥95th percentile
4. Dyslipidemia: presence of one of the following values adjusted for age and gender:
   a. High triglycerides (TG) (≥95th percentile)
   b. Low HDL-cholesterol levels (<5th percentile)
   c. High total or LDL-cholesterol (≥95th percentile)

Metabolic syndrome was established by the coexistence of at least three of the clinical criteria established for clinical diagnosis of metabolic syndrome.

Statistical analyses

All statistical analyses were performed using SPSS, version 10. Data are expressed as means ± S.D. Intergroup differences of means were examined with Student's *t*-test. Associations between baseline pituitary-adrenal activity and the components of the metabolic syndrome were assessed using Pearson correlation analysis. $p < 0.05$ was considered as statistically significant.

RESULTS

Metabolic syndrome was diagnosed in 43.9% of the children involved. A summary of characteristics including physical and metabolic profiles of the children and adolescents involved in this study are presented in Table 1.

Chronologic age, weight, height, BMI, average systolic and diastolic pressure values were higher in patients with metabolic syndrome than the corresponding values in patients without metabolic syndrome ($p = 0.001$) (Table 1). Mean values of birth weight did not differ between the groups.

Table 2 shows laboratory findings including plasma ACTH, cortisol, lipid, insulin, and glucose. Blood cortisol and ACTH levels were higher in patients with MS ($p = 0.023$, $p = 0.042$, respectively). Furthermore, fasting levels of blood glucose, insulin, and lipids (TG and total C) were found to be higher in cases with metabolic syndrome (Table 2).

Correlation analysis revealed that ACTH levels increased with weight ($r = 0.13$, $p = 0.02$), increased systolic blood pressure ($r = 0.21$, $p = 0.002$), diastolic blood pressure ($r = 0.17$, $p = 0.01$), and fasting glucose ($r = 0.17$, $p = 0.01$) levels. Increased cortisol levels were only weakly correlated with systolic blood pressure ($r = 0.12$, $p = 0.05$, data not shown in tables).

DISCUSSION

We have studied a sample of obese children and adolescents to determine whether MS is associated with increased HPAA activity, as measured by accurately timed fasting morning plasma cortisol concentrations, and whether cortisol and ACTH concentrations were correlated with weight, blood pressure, and glucose tolerance. And, we found higher levels of blood glucose,

Table 2. Laboratory findings of study population, divided in the two subgroups with and without metabolic syndrome

Variable	MS (-) (n = 135)	MS (+) (n = 106)	Total (n = 241)	*P* value
ACTH (ng/L)	24.37 ± 15.99	29.15 ± 18.10	26.52 ± 17.10	0.042
Cortisol (µg/dl)	11.97 ± 4.87	13.61 ± 6.23	12.69 ± 5.56	0.023
TG (mg/dl)	92.80 ± 43.56	151.08 ± 66.53	118.43 ± 61.94	0.001
LDL cholesterol (mg/dl)	94.22 ± 27.538	98.26 ± 31.36	96.00 ± 29.29	NS
HDL cholesterol (mg/dl)	52.66 ± 16.48	45.2 ± 11.78	49.38 ± 15.04	0.001
Total cholesterol (mg/dl)	164.21 ± 33.30	173.33 ± 36.06	168.22 ± 34.76	0.043
Fasting blood glucose (mg/dl)	85.97 ± 7.61	89.02 ± 10.04	87.31 ± 8.88	0.008
Fasting blood insulin (mIU/L)	15.78 ± 10.39	23.37 ± 10.59	19.12 ± 11.12	0.001
120th min blood glucose (mg/dl)	109.00 ± 25.61	119.20 ± 24.80	114.82 ± 25.58	0.01
120th min blood insulin (mIU/L)	77.76 ± 55.85	133.50 ± 79.78	109.56 ± 75.56	0.001

Values are mean and standard deviation (SD). ACTH: adrenocorticotrophic hormone; TG: triglyceride; MS: metabolic syndrome; LDL-C: Low-density lipoprotein; HDL-C: high-density lipoprotein-cholesterol; NS: not significant.

blood cortisol, ACTH, insulin, and lipids in cases with metabolic syndrome.

The elevation of ACTH was significantly correlated with body weight, systolic and diastolic blood pressure and glucose levels. The elevation of cortisol concentrations was weakly correlated with systolic blood pressure. These results are consistent with the related findings in adult obese patients [13]. It is known for long time that obese subjects have increased cortisol production rate but normal circulating plasma cortisol concentration which is due to accelerated degradation of cortisol [14].

The frequency of metabolic syndrome among obese children ranges between 30–50 percent [10, 23]. In our study, the frequency of MS was found to be 43.9 %. This results reflect that in our country the frequency of MS is somewhat lower than developed world but reached to a serious proportions among obese children and adolescents [6].

In adults, previous studies have shown an association between adrenal steroid hormones and the metabolic syndrome development [3, 12, 22].

But there is no study investigating any associations between cortisol concentration and cardiovascular risk factors in children and adolescents. Our study revealed relationship between MS and plasma cortisol, ACTH in children and adolescents. To our knowledge this is the first study demonstrating that increased glucocorticoid action may be contributing to development of the metabolic syndrome in children and adolescents with a high body mass index. These results also indicates that fasting morning cortisol concentration likely to represent individuals may go on to develop cardiovascular risk factors, and monitoring these factors may be of importance in obese children and adolescents with regard to the development of metabolic syndrome

In Andrew's study [3], specifically total glucocorticoid production had increased with increasing systolic blood pressure, fasting glucose and insulin. In our study, ACTH levels increased with weight, systolic blood pressure, diastolic blood pressure, fasting glucose (respectively r = 0.13, $p = 0.02$, r = 0.21, p = 0.002, r = 0.17, $p = 0.01$, r = 0.17, p = 0.01). Cortisol production increased only with systolic blood pressure (weakly correlated r = 0.12, $p = 0.05$. We have shown that 08^{00} h fasting plasma cortisol concentrations were related to systolic blood pressure in child and adolescent. Furthermore, raised fasting plasma ACTH concentrations were significantly associated with higher blood pressure, plasma fasting glucose concentrations, and weight. These observations are consistent with the hypothesis that resetting of the HPA axis may explain developing of MS. We showed that the metabolic syndrome is associated with subtle dysregulation of the hypothalamic-pituitary-adrenal axis leading to raised circulating cortisol concentrations (as there were associations between the components of the metabolic syndrome and higher morning cortisol, ACTH concentrations).

In conclusion, this study suggests an association between plasma cortisol concentration and the metabolic syndrome in obese children and adolescents. Because the associations observed were relatively weak, although of potential etiological relevance, quantification of circulating cortisol, further studies of the relationship between the circulating cortisol profile and risk of development of metabolic syndrome is required for a more conclusive statement.

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