Clinical Nutrition 31 (2012) 359–363

Contents lists available at SciVerse ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Anthropometric measures and fasting insulin levels in children before and after cure of Cushing syndrome☆

Margaret F. Keil [a,b,*], Jennifer Graf [c], Nirmal Gokarn [a], Constantine A. Stratakis [a,b]

[a] Section on Endocrinology Genetics, Program on Developmental Endocrinology Genetics (PDEGEN), Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892, USA
[b] Pediatric Endocrinology Inter-Institute Training Program (PEITP), National Institutes of Health, Bethesda, MD 20892, USA
[c] Department of Clinical Nutrition, Clinical Center, National Institutes of Health, Bethesda, MD 20892, USA

ARTICLE INFO

Article history:
Received 17 June 2011
Accepted 15 November 2011

Keywords:
Cushing
Pediatric
Obesity
Insulin resistance
Waist circumference
Anthropometrics

SUMMARY

Background & aims: Children with Cushing syndrome present with growth delay and excess adiposity that tends to be generalized rather than centripetal. There are no prospective studies of this phenotype as it evolves before and after treatment in children. The aims of this study were to evaluate children prior to and one-year after surgical cure compared to controls and to determine fasting insulin levels and their possible association with waist circumference and waist-height ratio, pre- and post-cure of Cushing syndrome.
Methods: 30 children with Cushing syndrome were evaluated prior to and one-year post-treatment and compared to 14 age and body mass index-matched controls.
Results: Only triceps skin fold z- score showed a significant difference between patients with active Cushing syndrome and controls. A positive correlation between fasting insulin levels and waist circumference z- score was found for children with Cushing syndrome; this association persisted one-year following cure.
Conclusions: Unlike adults affected with Cushing syndrome, upper arm muscle area of children with Cushing syndrome did not differ from obese children without Cushing syndrome. The persistence of a positive correlation between waist circumference and fasting insulin despite remission of Cushing syndrome suggests that children with a history of Cushing syndrome may have an increased risk for adverse long-term effects of increased abdominal fat mass.
Clinical Trial numbers: NCT00001595, NCT00001452, NCT00005927.

1. Introduction

Children with Cushing syndrome (CS) typically present with growth delay and excess adiposity, which tends to be generalized rather than centripetal. Studies of adults with CS report a phenotype of higher abdominal and truncal fat percentages (as measured by dual-energy X-ray absorptiometry), intra-abdominal fat deposit (as measured by computed tomography) and reduced lean mass percentage compared with body mass index (BMI)- and age-comparable controls.[1,2] In addition, studies with adult patients report that CS is associated with increased intra-abdominal fat stores compared to subcutaneous fat.[3–5] However the effect of CS on the phenotype of children and adolescents remains largely unknown.

Glucocorticoid effects on glucose metabolism include impaired peripheral glucose uptake and hepatic insulin resistance. An increase in visceral fat is associated with insulin resistance and cardiovascular morbidity. We recently reported what appears to be an 'East Asian' phenotype of patients with CS, which is characterized by lower BMI and less significant abdominal obesity. In addition, compared to age-matched Caucasian patients with CS, East Asian CS patients had lower morning cortisol levels with no difference in urine free cortisol excretion (UFC).[6] No prospective studies have been performed with a large group of children to determine the effect of CS on body habitus. One study reported an increase in visceral and subcutaneous fat that persisted after cure in an adolescent girl with CS.[7] A prospective study of 14 children and

☆ Initial data presented as abstract at The Endocrine Society's 88th Annual Meeting, 2006, Boston, MA.

* Corresponding author. Section on Endocrinology Genetics, Program on Developmental Endocrinology Genetics (PDEGEN), Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, 10 Center Drive, Bldg 10 Room 1E 3330, Bethesda, MD 20892, USA. Tel.: +1 301 435 3391; fax: +1 301 402 0574.
E-mail address: keilm@mail.nih.gov (M.F. Keil).

0261-5614/$ – see front matter © 2011 Elsevier Ltd and European Society for Clinical Nutrition and Metabolism. All rights reserved.
doi:10.1016/j.clnu.2011.11.007

adolescents with successfully treated (surgical) CS, reported significant alterations in body composition resulting in small but significant decrease in bone mass and an increase in visceral adiposity, suggesting that these patients are at increased risk of the metabolic syndrome.[8]

Since both elevated cortisol and insulin contribute to visceral adiposity, the aim of this study was to evaluate the CS-related phenotype (i.e. anthropometric measurements) and the relationship between body fat distribution and fasting insulin levels in children with CS prior to and one-year after surgical cure compared to controls. The second aim of this study was to determine whether fasting insulin was associated with waist circumference and waist-height ratio, pre- and post-cure of CS. Our hypothesis was that children with CS may have increased insulin levels compared to age and BMI-z-score- matched controls, and that insulin levels in patients with CS may be positively associated with waist circumference even after cure of their disease.

2. Methods

2.1. Study design

Thirty children (16 females, mean age 12 ± 2.8 years, range 8–18 years) with CS were evaluated prior to and one-year post-surgical treatment: twenty-six children were diagnosed with pituitary tumors (Cushing disease- CD) and underwent transsphenoidal surgery (TSS), 4 were diagnosed with adrenal tumor(s) and underwent adrenalectomy (3 bilateral, 1 unilateral). Fourteen patients (9 females, 13.3 ± 3.6 years) referred for evaluation of CS, who had biochemical data not consistent with a diagnosis of CS, were included as controls. All children were enrolled in protocols (95CH0059, 97CH0076, and 00CH0160) approved by the institutional review board of the *Eunice Kenney Shriver* National Institute of Child Health and Human Development for evaluation and treatment of suspected CS. The cause of CS was confirmed by histology. All children were enrolled in protocols (95CH0059, 97CH0076, and 00CH0160) approved by the institutional review board of the *Eunice Kenney Shriver* National Institute of Child Health and Human Development.

Endocrine and anthropometric assessments were done prior to and one-year post-TSS or adrenalectomy for patients in the CS treatment group. Evaluation and confirmation of CS was performed as described by Batista et al. 2007.[9] Only CS patients with biochemical evidence consistent with cure were included in the final analysis. CS patients who did not complete baseline and one-year follow-up anthropometric measurements were not included; the design of the study was such that each patient served as his/her own control. Blood samples for glucose, insulin, and lipid panel were collected after an overnight fast.

A total of 64 children were referred for evaluation of CS from June 2004 to July 2007. Of the 64 children, 47 were confirmed to have CS and underwent surgery; of those 47 patients, 30 children (16 females, 11.8 ± 2.8 years) completed pre- and post- anthropometric measurements and had biochemical data consistent with cure of CS, and were included in the study. Seventeen patients with confirmed CS who either did not return for one-year follow-up (10), or due to scheduling limitations did not complete 1-year follow-up anthropometric measurements (5); or had biochemical data not consistent with a cure of CS (2), were not included in this study. Fourteen patients (9 females, 13.5 ± 3.4 years) referred for evaluation of their weight gain with biochemical data not consistent with a diagnosis of CS, were included as controls. Two patients referred for evaluation of CS that was not confirmed by biochemical testing, were diagnosed with an underlying genetic condition; they were excluded from the analysis. One patient did not complete anthropometric measurements and was not included in control group.

Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. BMI (kilogram per meter squared) and BMI −for −age *z* scores were calculated from the CDC growth charts. The average of at least 3 measurements was recorded. Anthropometric measurements were obtained by one dietitian (JG) in triplicate to the nearest 0.1 cm for circumference, and to the nearest 0.5 mm for skin folds (using Lange calipers for skin folds); the average of the measurements was used for analysis. Mid-upper arm circumference (MAC) and triceps skin fold (TS) were measured at the midpoint between the acromion and olecranon processes as described by Lohman et al.[10] TS and MAC were used to calculate upper arm muscle areas (AMA) and upper arm fat area (AFA), using the following equations: $AMA = [MAC\text{-} (TS \times \pi)]^2/(4 \times \pi)$; $AFA = [MAC^2/(4 \times \pi)] - AMA$.[11] The subscapular skin fold (SS) site was measured just inferior to the inferior angle of the scapula and was measured at a ~45° infero-lateral angle.[10] Waist circumference was measured immediately superior to the iliac crest. Hip circumference was measured at the level of maximum extension of the buttocks with subjects wearing only underwear.[12]

2.2. Statistical analysis

Descriptive statistics were calculated for continuous variables. Only patients who had anthropometric measurements both pre- and post-operatively and had biochemical evidence of cure of CS were included in the analysis. Anthropometric measurement *z* scores (height, BMI, waist circumference, hip circumference, skin folds (subscapular and triceps), upper- arm fat and muscle area, and mid-arm circumference) were determined using anthropometric data for US children.[11,13] Anthropometric and laboratory data are reported as means, standard deviations (SD), and/or *z* scores. Paired Student's *t*-test, or its non-parametric parallel (Wilcoxon signed-rank test) were used to compare continuous data. Pearson correlation coefficients were used for correlation analysis. Data were analyzed using SPSS system software. Statistical significance was accepted for *p* values equal to or below 0.05.

3. Results

3.1. Clinical evaluations pre- and post-operatively

At baseline, CS was confirmed by biochemical testing, as described by Batista et al. 2007,[9] including the confirmation of elevated UFC (385 ± 487 μg/24 h), and lack of diurnal variation in serum cortisol levels (midnight cortisol 16.6 ± 8.2 μg/dL; 8AM cortisol 20.4 ± 8.8 μg/dL). The estimated duration of CS based on clinical symptoms and/or decreased growth velocity was 2.4 ± 1 years. Patients in the control group had normal UFC (21 ± 23 μg/24 h); normal diurnal serum cortisol levels (midnight cortisol 1.4 ± 0.5 μg/dL; 8AM cortisol 10.1 ± 4.7 μg/dL). There was no significant difference between the CS and the control group of patients for age (12.8 ± 2.8 vs. 13.5 ± 3.4 yrs; $p. > 0.05$) or BMI standard deviation unit (SDU) (2.2 ± 0.5 vs. 1.9 ± 0.6; $p > 0.05$) at baseline evaluation. Physical

Table 1
Clinical features for patients with CS and controls.

	Cushings	Controls
Systolic hypertension	26.6%	23%
Diastolic hypertension	30%	7.6%
Striae	66.7%	50%
Acne	70%	50%
Hirsutism	73.3%	28.5%
Facial plethora	73.3%	7%
Easy bruising	16.6%	7%