The 24-Hour Average Concentration of Cortisol is Elevated in Obese African-American Youth with Type 2 Diabetes

Pinar Gumus Balikcioglu, MD,MHSc[1], Metin Balikcioglu, PhD[2], Arlette Ariane Soros, MD[3], Stuart Alan Chalew, MD[4]

[1]Division of Endocrinology ,Duke University, Durham NC, [2]SAS Institute Inc, Advanced Analytics Division, Cary, NC, [3]Boston Medical Center, Department of Pediatrics, Boston, MA, [4]Division of Endocrinology, LSU Health Sciences Center and Children's Hospital of New Orleans, LA

Introduction

Factors that facilitate the progression from simple obesity to clinical type 2 diabetes (T2D) in pediatric patients are not well understood. During this progression, the patient loses the ability to overcome insulin resistance with further increases in circulating insulin. previously reported that 24 hour average (IC) plasma concentrations of cortisol and growth hormone are lower in obese youth and adults without diabetes compared to lean subjects(1,2). We hypothesized that loss of suppression of growth hormone (GH) and cortisol might also be part of this diabetes diathesis. In order to test this hypothesis, we compared 24-hour integrated plasma GH and cortisol levels in obese African-American youth with and without T2D. We hypothesized that obese pediatric patients with T2D would have increased levels of cortisol and GH compared to those without T2D.

As cortisol and GH both have pulsatile secretion and diurnal variation, measuring the average or integrated concentrations (IC) of hormones over the course of a day has been recommended as the most accurate estimate of tissue exposure (3-5). Besides secretory changes in cortisol, its concentration may be influenced by the activity of a pair of 11βOH hydroxysteroid dehydrogenase (HSD) enzymes(6). Type 2 11βOH-HSD inactivates cortisol by converting it to cortisone, while type 1 11βOH-HSD regenerates cortisol from cortisone. The relationship between circulating IC-cortisol and IC-cortisone might indicate the balance of inter-conversion of cortisol and cortisone by the two 11βOH HSD isoforms in patients with pediatric diabetes (7).

Methods

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Enrollment was limited to AA children since more than 90% of our patients with T2DM are AA. Exclusion criteria included T1DM, abnormal liver and renal function tests, anemia, decompensated hypothyroidism, taking medications other than metformin, insulin or levo-thyroxine, pregnancy, genetic syndrome, BMI<2SD, urine free cortisol >2SD. Patients had indwelling venous catheters placed and blood was withdrawn half-hourly for 24 hours. A 24-hour IC was made by pooling a small aliquot from each half-hourly sample

Methods

Between group comparisons were performed by t-test (2-tailled) if the variable was normally distributed or by Wilcoxon rank sum test (Mann Whitney U test) when not normally distributed.
The ratio of insulin to C-peptide was performed after conversion to SI units. Statistics were performed using SAS version 9.4. Aggregate results in tables are reported as mean±1SD. Statistical significance was accepted by conventional at P=0.05 level or less.

Results

A total of 17 obese subjects completed full studies, 8 patients with diabetes and 9 patients without diabetes. Please refer to *Table 1* for a comparison of participant characteristics between the two groups. The groups were similar in age, height and gender distribution. All subjects had BMI percent ≥ 94%, (BMIz similarly elevated) and would be considered extremely obese.

Table 1: Characteristics of Participants, mean(1SD)

Characteristics	Without T2D (n=9)	With T2D (n=8)	P-Value
Age, years	14.77 (2.09)	15.04 (3.09)	0.8304
Sex, F/M	7/2	5/3	0.6199
Weight, kg	116.37 (17.99)	98.41 (14.63)	0.0751
Height, cm	166.33 (12.67)	166.01 (7.70)	0.9514
BMI (kg/m^2)	41.94 (3.87)	35.86 (5.60)	0.0189
BMI z-score	2.58 (0.16)	2.25 (0.36)	0.0429
Duration Diabetes (yrs)		3.3(3.5)	
HbA1c (%)	-	7.7(2.8)	
Pre-Breakfast Glucose (mg/dL)	90(11)	132(63)	0.052

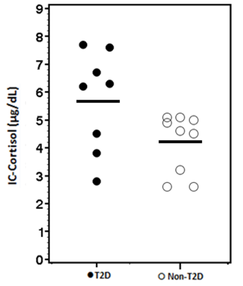
Table 2: Blood metabolites of obese subjects with and without T2D

Integrated Concentrations	Without T2D (n=9)	With T2D (n=8)	P-Value
IC-Cortisol (µg/dL)	4.18 (1.07)	5.70 (1.80)	**0.0481**
IC-Cortisone (µg/dL)	0.87 (0.39)	1.15 (0.34)	0.1311
IC-CBG (mg/dL)	2.59 (0.50)	2.69 (0.36)	0.6486
IC-cortisone/IC-Cortisol ratio	0.23 (0.16)	0.20 (0.05)	0.7363
IC-GH (ng/mL)	1.46 (0.81)	1.75 (0.79)	0.4606
IC-Insulin (µU/mL)	41.11 (17.12)	26.37 (25.65) n=6	0.2019
IC-C-peptide (ng/mL)	4.36 (1.12)	2.33 (0.89)	**0.0010**
IC-Insulin/IC-C-peptide	0.21(0.09)	0.19(0.16) n=6	0.7940

Results

IC-F was higher in patients with T2D than individuals without diabetes (p=0.0481). IC-E, IC-CBG, the ratio of IC-E/IC-F, and IC-GH were not statistically different between the groups *(Table 2)*. IC-F was correlated with IC-E (r=0.46, p=0.0471) but not with IC-CBG, IC-GH, or IC-CP. IC-CP was higher in patients without diabetes (p=0.001) compared with the T2D group. There were two fewer samples for IC-insulin (IC-I) in the T2D group (n=6), and although mean IC-I was also higher in individuals without T2D this relationship did not achieve statistical significance. The ratio of IC-insulin/IC-C-peptide was similar between the groups.

Figure 1: IC-Cortisol (IC-F) of study participants with and without T2D. IC-Cortisol was higher in patients with T2D, p=0.0481. The majority of patients with T2D have IC-cortisol over the range of individuals without diabetes. Horizontal black line is mean for the group



IC-F and IC-GH levels for obese participants in the current study without diabetes were very similar to levels we previously reported using continuous withdrawal technology. *Figure 1* depicts the range of IC-cortisol for the individual participants. None of the participants without diabetes had an IC-F over the mean IC-F=5.7 µg/dL of the patients with T2D, (or over +2SD of the reported mean of the historic reference group of obese individuals without diabetes. Five of the participants with T2D had IC-Fs over the upper range of the obese youth without diabetes in this study.

Conclusions

1) IC- cortisol levels are higher and IC-C-peptide lower in obese African-American youth with T2D.
2) Higher levels of IC-cortisol in obese youth with T2D may indicate a change in hypothalamic-pituitary-adrenal regulation which may exacerbate hyperglycemia and other metabolic complications of obesity.
3) A longitudinal study would be required to deduce the relationship of cortisol level, insulin secretion and resistance over time in obese youth predisposed to developing diabetes.

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