

## Association between the Metabolic Syndrome and Serum Cortisol in Overweight Latino Youth

Marc J. Weigensberg, Claudia M. Toledo-Corral, and Michael I. Goran

Departments of Pediatrics, Preventive Medicine, and Physiology and Biophysics, University of Southern California, Los Angeles, California 90089

**Objective:** The purpose of this report is to investigate the associations between metabolic syndrome (MS) and levels of morning serum cortisol in a cohort of overweight Latino youth.

**Design:** Subjects were 205 overweight, Latino youth (age 8–13 yr, body mass index percentile > 85, family history positive for type 2 diabetes). Measures included body composition by dual-energy x-ray absorptiometry, intraabdominal adipose tissue (IAAT) by magnetic resonance imaging, insulin sensitivity by frequently sampled iv glucose tolerance test/minimal model, fasting lipids, and serum cortisol.

**Results:** Children with MS had higher body mass index percentile, total body fat mass, and IAAT and lower insulin sensitivity than those without MS. Children with MS had higher morning serum cortisol levels, whether unadjusted ( $10.1 \pm 3.7$  vs.  $9.0 \pm 2.8$   $\mu\text{g/dl}$ ,  $P < 0.05$ ) or after adjusting for age, gender, total body fat and lean tissue mass, and insulin sensitivity ( $10.4 \pm 0.4$  vs.  $8.9 \pm 0.3$   $\mu\text{g/dl}$ ,  $P < 0.01$ ). Increasing number of features of MS was associated with higher cortisol levels, after adjusting for covariates ( $P = 0.001$ ). Among individual features of MS, systolic blood pressure had the strongest relationship with adjusted cortisol level ( $r = 0.34$ ;  $P < 0.001$ ), followed by diastolic blood pressure and fasting plasma glucose (both  $r = 0.23$ ;  $P < 0.01$ ). IAAT was associated with cortisol ( $r = 0.16$ ;  $P < 0.05$ ), whereas high-density lipoprotein, triglycerides, and waist circumference were not.

**Conclusions:** In overweight, Latino youth, MS is associated with higher morning serum cortisol levels, independent of body fat and insulin sensitivity. More studies are needed to investigate the role of relative hypercortisolism and chronic stress in obesity-related metabolic disorders in children. (*J Clin Endocrinol Metab* 93: 1372–1378, 2008)

In the past decade, there has been a marked increase in the prevalence of obesity in children and adolescents, especially among Latino youth (1). Along with this increased prevalence of obesity comes an increased risk of type 2 diabetes as well as other comorbidities of obesity including metabolic syndrome (MS), the clustering of risk factors for cardiovascular disease. Although MS is present in approximately 4% of North American adolescents aged 12–19 yr of all ethnicities and weights, the prevalence of MS is about 5.6% specifically among Mexican-American adolescents (2). We have previously shown that approximately 30% of overweight or at-risk-for-overweight Latino youth with a family history of type

2 diabetes have MS and that the number of features of MS is related to the degree of insulin resistance, independent of total body fat (3).

In adults, MS has been linked to chronic stress and abnormalities in the activity of the hypothalamic-pituitary-adrenal axis (HPA) leading to the suggestion that subjects with MS may have a mild form of hypercortisolism (4, 5). Evidence supporting this hypothesis includes the findings that increased stress-related cortisol secretion is associated with features of the MS in both men and women (6, 7), and men with MS have increased urinary cortisol metabolite secretion (8). Because cortisol is a well-known counter-regulator of insulin action, it

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Abbreviations: BMI, Body mass index; BP, blood pressure; CV, coefficient of variation; GCRC, General Clinical Research Center; HDL, high-density lipoprotein; HOMA-IRI, homeostatic model insulin resistance index; HPA, hypothalamic-pituitary-adrenal axis; IAAT, intraabdominal adipose tissue; MS, metabolic syndrome; OGTT, oral glucose tolerance test.

has been proposed that the relationship between MS and cortisol is likely due to the increased insulin resistance seen in the relative hypercortisolemic state (9). Although increased levels of serum cortisol have been linked to insulin resistance in overweight children (10), the associations between MS and measures of HPA activity in children or adolescents remain unknown.

Therefore, the purpose of this report is to investigate the associations between MS and levels of morning serum cortisol in a cohort of overweight Latino children and adolescents. We hypothesized that children with MS would demonstrate higher levels of serum cortisol and that insulin resistance would mediate this relationship. Because the MS consists of several diverse features that may not share the same pathophysiology, our second objective was to explore the extent to which the individual features of the MS may be related to serum cortisol levels in this overweight adolescent population.

## Subjects and Methods

### Subjects

Participants (n = 205, 118 males and 87 females) were recruited from Los Angeles County through medical clinics, advertisements, and local schools. The current analyses include participants from the first annual visit of the University of Southern California SOLAR (Study of Latino Adolescents at Risk) Diabetes Project, a longitudinal study exploring metabolic risk factors for type 2 diabetes. We have previously reported findings from this cohort relating to MS and diabetes risk (3, 11, 12). Study participants satisfied the following criteria for inclusion: 8–13 yr of age, body mass index (BMI) at or higher than 85th percentile, Hispanic ethnicity (*i.e.* parents and grandparents of Hispanic descent), and positive family history for type 2 diabetes in a parent, grandparent, or sibling. Participants were excluded if they were using a medication or diagnosed with a condition known to influence body composition or insulin/glucose metabolism or if they were diagnosed with diabetes by oral glucose tolerance test (OGTT) at time of entry to the study. Before any testing procedure, informed written consent from parents and assent from the children was obtained. The study was approved by the Institutional Review Board of the University of Southern California.

### Outpatient screening visit

Participants arrived at the University of Southern California General Clinical Research Center (GCRC) at approximately 0800 h after an overnight fast. A comprehensive medical history and physical examination was performed by a licensed pediatric health care provider. After the exam, OGTT was performed to determine eligibility. Subjects ingested 1.75 g oral glucose solution/kg body weight (to a maximum 75 g). Blood was sampled and assayed for glucose and insulin at –5 min (fasting) and 120 min (2 h).

### Inpatient visit

Approximately 7–14 d after the outpatient visit, participants were readmitted to the GCRC at approximately 1300 h for their inpatient hospital visit. Body composition (total fat mass and total lean tissue mass) was determined by whole-body dual-energy x-ray absorptiometry scan using a Hologic QDR 4500W (Bedford, MA). Central fat distribution was measured directly by magnetic resonance imaging using a General Electric 1.5 Signa LX-Echospeed device with a General Electric 1.5-T magnet (Waukesha, WI). A single-slice axial TR 400/16 view of the abdomen at the level of the umbilicus was analyzed for cross-sectional area of intraabdominal adipose tissue (IAAT) (13).

After body composition measurements, participants were served dinner and a snack before 2000 h, which marked the beginning of an overnight fast. Water alone was permitted during this period. At 0630 h the following morning, an insulin-modified frequently sampled iv glucose tolerance test was performed as follows. Intravenous catheters were placed in the antecubital fossae of both arms. After two fasting blood samples were taken at –15 and –5 min, glucose (0.3 g/kg body weight) was administered iv at time 0 over a 1-min period. Subsequent blood samples were collected at 2, 4, 8, and 19 min. Insulin (0.02 U/kg body weight, Humulin R; Eli Lilly, Indianapolis, IN) was administered iv at 20 min, followed by blood sample collection at 22, 30, 40, 50, 70, 100, and 180 min. Plasma was analyzed for glucose and insulin concentration, and results were then entered into MINMOD MILLENNIUM 2003 software (version 5.16; RN Bergman, Los Angeles, CA) for calculation of insulin sensitivity. Aliquots of the –15 min fasting draw were sent for measurement of serum cortisol and lipids.

### Definition of the MS

Because there is no consensus definition of the MS in children, we defined MS as we had in our previous report (3) by the presence of at least three of the following features: abdominal obesity (waist circumference  $\geq$  90th percentile for age and gender) (14), hypertriglyceridemia (triglycerides  $\geq$  90th percentile for age and gender) (15), low high-density lipoprotein (HDL) cholesterol ( $\leq$ 10th percentile for age and gender) (15), high blood pressure (either systolic or diastolic blood pressure  $>$  90th percentile adjusted for height, age, and gender) (16), and impaired glucose tolerance (OGTT 2-h glucose  $\geq$  140 mg/dl) (17).

### Assays

OGTT glucose was analyzed immediately by the *in vitro* hexokinase method (Dimension clinical chemistry system; Dade Behring, Deerfield, IL). Blood samples collected during the frequently sampled iv glucose tolerance test were centrifuged immediately for 10 min at 2500 rpm to obtain plasma aliquots, which were then frozen at –80 C until assayed. Glucose was assayed using a Yellow Springs Instruments analyzer (YSI Inc., Yellow Springs, OH) that uses a membrane-bound glucose oxidase technique. Insulin was assayed using a specific human insulin ELISA kit from Linco [St. Charles, MO; intraassay coefficient of variation (CV) 4.7–7.0%, interassay CV 9.1–11.4%, and cross-reaction with human proinsulin 0%]. Homeostatic model insulin resistance index (HOMA-IRI) was calculated according to the equation [fasting glucose (millimolar)  $\times$  fasting insulin (micro-units per milliliter)]/22.5. Morning serum cortisol concentrations were determined by RIA kit [Siemens, Deerfield, IL; intraassay CV 4.69%, interassay CV 6.28%, and minimal detection limits (90% bound) for cortisol 0.47  $\mu$ g/dl]. Fasting lipids were assessed using Vitros Chemistry DT slides (Johnson and Johnson Clinical Diagnostics, Inc., Rochester, NY).

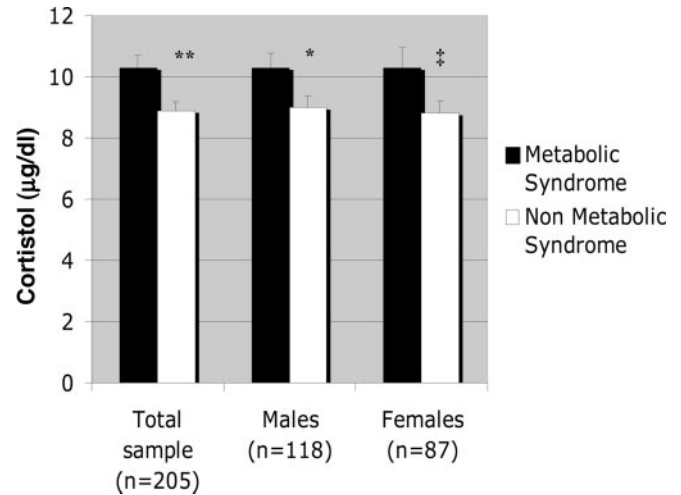
### Statistics

A total sample size of 205 participants, unless otherwise indicated in data tables, was used for descriptive analysis. Mean variable differences by MS or non-MS were analyzed by a general linear model. Analysis of covariance was used to determine estimated marginal mean cortisol differences in those with and without MS with covariates of age, gender, total lean tissue mass, total fat mass, insulin sensitivity, and IAAT. These analyses were then repeated using each category of number of MS features (zero through five features). Determination of a linear trend of cortisol levels by increasing number of metabolic risk factors (ordinal numeration) was accomplished via linear regression. Adjusted partial correlation analysis was used to examine the relationships of cortisol with each individual feature of the MS while controlling for age, gender, total lean tissue mass, total fat mass, insulin sensitivity, and IAAT. Data were analyzed using SPSS for Windows version 13.0 (SPSS Inc., Chicago, IL), with an *a priori*

significance level set at  $P < 0.05$ . Data reported are mean  $\pm$  SD unless otherwise indicated.

## Results

Table 1 shows the characteristics of our subjects with and without MS. There were no significant differences between children with and without MS in terms of age, Tanner stage, height, or gender, although there was a trend toward a higher percentage of boys overall ( $P = 0.07$ ) as well as prepubertal boys ( $P = 0.052$ ) in the MS vs. non-MS group. Children with MS had greater weight, BMI, and BMI percentile (all  $P < 0.01$ ) as well as greater total fat mass ( $P < 0.05$ ), total lean tissue mass ( $P < 0.01$ ), and IAAT ( $P < 0.01$ ). As expected, all individual features of MS were different between the groups, with significantly higher waist circumference, systolic blood pressure (BP), diastolic BP, triglycerides, and 2-h glucose in the MS group (all  $P$  values  $\leq 0.001$ ). HDL cholesterol was lower in MS subjects ( $P < 0.001$ ). There was no difference in fasting glucose levels between the two groups. Assessment of insulin dynamics showed that the MS group was more insulin resistant, with significantly higher fasting and 2-h insulin levels, higher HOMA-IRI (all  $P < 0.01$ ), and lower insulin sensitivity ( $P < 0.001$ ).



**FIG. 1.** Morning serum cortisol in overweight boys and girls with and without MS. Data represent estimated marginal means  $\pm$  SEM, after adjustment for covariates of age, sex, total body fat, and lean tissue mass. \*\*,  $P < 0.01$ ; \*,  $P < 0.05$ ; †,  $P = 0.09$ .

The unadjusted level of morning serum cortisol, although well within the normal physiological range, was significantly higher in the MS vs. non-MS group (Table 1,  $P < 0.05$ ). Figure 1 shows the values for morning serum cortisol after adjustment for age, gender, body fat, and lean tissue mass. Morning cortisol after adjustment

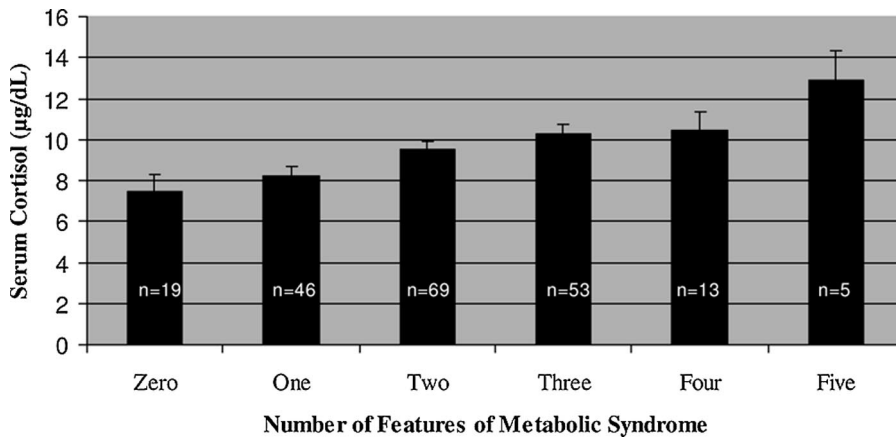
**TABLE 1.** Characteristics of subjects with and without MS

	MS (n = 71)	Non-MS (n = 134)	P value
Age (yr)	11.1 $\pm$ 1.7	11.1 $\pm$ 1.7	0.75
Gender (male/female)	47/24	71/63	0.07
Tanner stage			0.62
1	30/5	34/16	0.052
2	9/6	27/15	0.50
3	2/0	5/9	0.18
4	4/10	2/14	0.26
5	2/3	3/9	0.47
Height (cm)	151.0 $\pm$ 12.1	148.3 $\pm$ 11.1	0.10
Weight (kg)	69.7 $\pm$ 19.0	61.9 $\pm$ 19.2	0.006
BMI (kg/m <sup>2</sup> )	29.9 $\pm$ 4.5	27.6 $\pm$ 5.7	0.004
BMI percentile	98.6 $\pm$ 1.1	96.5 $\pm$ 3.4	<0.001
Total fat mass (kg)	27.3 $\pm$ 8.9	24.0 $\pm$ 10.6	0.026
Total lean tissue mass (kg)	39.7 $\pm$ 10.7	35.7 $\pm$ 9.6	0.007
IAAT (cm <sup>2</sup> ) <sup>a</sup>	54.3 $\pm$ 17.6	45.2 $\pm$ 21.4	0.005
Waist circumference (cm)	92.8 $\pm$ 11.7	86.4 $\pm$ 13.7	0.001
Systolic BP (mm Hg)	115.3 $\pm$ 10.9	107.6 $\pm$ 8.4	<0.001
Diastolic BP (mm Hg)	65.6 $\pm$ 6.3	62.0 $\pm$ 5.4	<0.001
HDL cholesterol (mg/dl)	32.4 $\pm$ 5.1	39.6 $\pm$ 8.6	<0.001
Triglycerides (mg/dl)	142.8 $\pm$ 62.9	89.7 $\pm$ 41.0	<0.001
Fasting glucose (mg/dl)	91.9 $\pm$ 6.3	91.3 $\pm$ 6.9	0.96
2-h glucose (mg/dl)	133.9 $\pm$ 20.1	123.3 $\pm$ 15.0	<0.001
Cortisol (µg/dl)	10.1 $\pm$ 3.7	9.0 $\pm$ 2.8	0.02
Fasting insulin (µU/ml)	19.0 $\pm$ 10.2	15.0 $\pm$ 9.8	<0.01
2-h insulin (µU/ml)	193.8 $\pm$ 150.1	140.5 $\pm$ 122.3	<0.01
HOMA-IRI	4.34 $\pm$ 2.45	3.41 $\pm$ 2.30	<0.01
Insulin sensitivity ( $\times 10^{-4}/\text{min}^{-1}$ )/(µU/ml) <sup>b</sup>	1.6 $\pm$ 1.1	2.3 $\pm$ 1.5	<0.001

Data values are mean  $\pm$  SD.  $\chi^2$  was used to compare differences in MS by gender. General linear model analyses were used to compare means between MS and non-MS subjects. Total sample size = 205, except as indicated below.

<sup>a</sup> Sample size = 176 (60 with MS).

<sup>b</sup> Sample size = 203 (71 with MS).



**FIG. 2.** Morning serum cortisol vs. number of features of MS. Bars illustrate estimated marginal means  $\pm$  SEM for morning cortisol levels as determined by analysis of covariance after adjustment for age, sex, total body fat, total body lean tissue mass, and insulin sensitivity.  $P = 0.001$  for overall trend of cortisol vs. number of features.

was significantly higher in MS children when looking at the whole study group (estimated marginal mean  $\pm$  SEM =  $10.3 \pm 0.4$  vs.  $8.9 \pm 0.3$   $\mu\text{g/dl}$ ;  $P < 0.01$ ) as well as among boys ( $10.3 \pm 0.5$  vs.  $9.0 \pm 0.4$   $\mu\text{g/dl}$ ,  $P < 0.05$ ), whereas girls showed a trend toward the same relationship ( $10.3 \pm 0.7$  vs.  $8.8 \pm 0.4$   $\mu\text{g/dl}$ ,  $P = 0.06$ ). Adjusting for insulin sensitivity did not change the relationship between cortisol and MS, as cortisol remained significantly higher in the MS group ( $10.4 \pm 0.4$  vs.  $8.9 \pm 0.3$   $\mu\text{g/dl}$ ,  $P < 0.01$ ). After adjusting for IAAT, the difference in morning cortisol between MS and non-MS groups was no longer significant (estimated marginal mean  $\pm$  SEM =  $9.7 \pm 0.4$  vs.  $9.0 \pm 0.3$   $\mu\text{g/dl}$ ;  $P = 0.14$ ). Adjusting for Tanner stage in addition to other covariates did not change the results of any analyses. Inclusion of impaired fasting glucose in the definition of MS, as recommended by the the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (18), did not appreciably change the relationships between cortisol and MS [estimated marginal mean  $\pm$  SEM =  $10.4 \pm 0.4$  vs.  $8.7 \pm 0.3$   $\mu\text{g/dl}$  for MS group ( $n = 77$ ) vs. non-MS group ( $n = 128$ );  $P = 0.001$ ].

Figure 2 demonstrates the adjusted cortisol levels vs. number of individual features of MS. There was a clear and significant increase in cortisol with increasing number of MS features ( $P < 0.01$  for overall trend). This trend of increasing cortisol with increasing number of features was similar for both boys and girls (data not shown,  $P < 0.01$  for trend within each gender group).

Adjusting for insulin sensitivity did not change these relationships, as the overall trend between cortisol and number of MS features remained significant (Fig. 2,  $P = 0.001$ ). Similarly, the relationship remained significant after adjustment for IAAT ( $P < 0.05$ ). Repeated analyses including impaired fasting glucose in the definition of MS did not appreciably change the results (data not shown).

We next investigated correlations between morning cortisol level and each of the individual features of MS, both unadjusted and after adjusting for age, gender, total body fat, total body lean tissue mass, and last, insulin sensitivity. As shown in Table 2, unadjusted correlations demonstrated that cortisol was associated significantly with systolic BP, diastolic BP, and fasting glucose. These relationships held when adjusted for body composition as well as after adjusting for insulin sensitivity. The strongest relationship was between cortisol and systolic BP. The adjusted partial correlation between cortisol and 2-h OGTT glucose approached significance ( $P = 0.09$ ). There were no significant associations between cortisol and triglycerides, HDL, or waist circumference. However, after adjustment for age, gender, total fat, and lean tissue mass, cortisol was positively related to IAAT ( $r = 0.15$ ;  $P < 0.05$ ), and this relationship was not changed when further adjusted for insulin sensitivity ( $r = 0.16$ ;  $P < 0.05$ ). There was no relationship between cortisol and total body fat measured by dual-energy x-ray absorptiometry ( $r = -0.07$ ;  $P = 0.3$  adjusting for age, gender, and lean tissue mass).

### Discussion

We have demonstrated significantly higher serum cortisol levels in overweight Latino youth with MS compared with those without MS. This remained true after adjusting for relevant covariates including age, gender, and body composition. Furthermore, insulin resistance did not explain this association, as cortisol levels were higher in MS youth even after adjusting for insulin sensitivity. The relationship between increasing cortisol and in-

**TABLE 2.** Correlations between morning serum cortisol and individual features of MS

MS feature	Cortisol (Pearson correlation)	Cortisol (partial correlation) <sup>a</sup>	Cortisol (partial correlation) <sup>b</sup>
Systolic BP	0.23*	0.32†	0.34†
Diastolic BP	0.21*	0.23*	0.23*
Fasting glucose	0.23*	0.23*	0.23*
2-h glucose	0.12‡	0.12‡	0.12
Triglycerides	0.03	0.05	0.07
HDL cholesterol	0.07	0.03	0.02
Waist circumference	-0.11	0.01	0.02

<sup>a</sup> Adjusted for age, gender, total fat mass, and total lean tissue mass.

<sup>b</sup> Adjusted for age, gender, total fat mass, total lean tissue mass, and insulin sensitivity.

\*,  $P < 0.01$ ; †,  $P < 0.001$ ; ‡,  $P = 0.09$ .

creasing features of MS appears to be primarily due to the relationship between cortisol and systolic blood pressure and may in part be mediated by intraabdominal fat. To the best of our knowledge, this is the first report linking the presence of relative hypercortisolemia to the MS in a pediatric population.

The overall prevalence of MS in North American youth approximates 4% in all ethnic groups, 6% among Mexican-American youth, and over 25% among overweight youth (2). Our cohort in this report of overweight Latino children and teens shows a prevalence of 35%. We have previously shown that an increased degree of insulin resistance is associated with increased number of features of MS in this cohort (3), whereas others have similarly shown a relationship between insulin resistance and MS in other adolescent populations (19). The relationship between MS and future cardiovascular disease in adults (18, 20) suggests overweight youth with MS may be at significantly increased risk for early morbidity from cardiovascular disease. Although the link between insulin resistance and MS has been clearly established in both adult and pediatric populations, other possible mechanisms mediating MS have not been as clearly elucidated, including the link between MS and cortisol. Reinehr and Andler (10) found significant associations between the degree of cortisolemia and fasting hyperinsulinemia in obese children, and both insulin and cortisol levels were reduced after weight loss. These findings led us to hypothesize that the relationship between cortisol and MS would be mediated by insulin sensitivity. However, our findings suggest this is not the case, in that even after adjustment for insulin sensitivity, cortisol remained significantly associated with the MS overall as well as with certain individual features of MS, namely blood pressure and plasma glucose.

These findings suggest that cortisol may be relevant to certain of the individual features of MS, but not to others, and that this relationship is not due to insulin resistance. The relationship between cortisol and blood pressure was the strongest among all features of the MS, followed by the relationship between cortisol and fasting blood glucose. Others have similarly shown relationships between morning serum cortisol, blood pressure, and glycemia (21). The relationship between fasting glucose and cortisol could be due to glucocorticoid effects on hepatic glucose metabolism or insulin secretion (22–25). Despite the relationship between cortisol and fasting glucose, we saw no difference in mean fasting glucose levels in children with or without MS. However, a separate analysis in the current subject cohort showed that children with impaired fasting glucose ( $n = 24$ ) did have a significantly higher morning cortisol levels than those with normal fasting glucose ( $n = 181$ ;  $11.1 \pm 3.7$  vs.  $9.2 \pm 3.1$   $\mu\text{g/dl}$ ;  $P < 0.01$ ). Although cortisol may directly influence blood pressure through its effects on salt and water retention or vascular smooth muscle tone, it has been suggested that the relationship between cortisol and blood pressure in MS is more likely indicative of a general increase in the stress response, which includes both elevated HPA axis activity and heightened autonomic nervous system sympathetic tone (26, 27). The presence of a heightened adrenergic tone in MS is consistent with the findings of Brunner *et al.* (8), who found elevated levels of both cortisol and catecholamine metabolites in the urine of subjects with

MS, along with increased heart rate and heartbeat variability. Whatever the exact relationship, our findings clearly suggest that cortisol is linked to some, but not all, features of MS in this population, with the strongest relationship seen with systolic blood pressure.

We were surprised to find no relationship between cortisol and waist circumference, which have been linked in a number of previous adult studies (6, 7, 28, 29). There could be several explanations for this. First, we studied a rather homogeneous population, all of whom were obese and over 70% of whom had increased waist circumference based on pediatric standards (14). Thus, the relative lack of a wide distribution in waist circumference in this population may have obscured an actual relationship between cortisol and waist size. In addition, the clinical importance of abdominal girth is presumably due to its ability to reflect underlying IAAT. In this regard, we have previously shown waist circumference to be a relatively weak predictor of actual IAAT stores in our study cohort (30). In the current report, we have shown that cortisol is indeed significantly related to directly measured IAAT and that adjusting for IAAT weakened the relationship between cortisol and blood pressure as well as cortisol and MS. These data suggest that despite the lack of relationship with waist circumference, cortisol is associated with the metabolically active depot of IAAT in these overweight youth and that this may account, in part, for the relationship between cortisol and MS.

Although the association between cortisol and MS does not prove a causative effect, there is evidence to suggest this could be the case. Individuals with pathological primary hypercortisolism, *e.g.* Cushing's disease, develop all the features of MS as part of their disorder (31, 32). In addition, a number of psychosocial disorders with elevated activity of the HPA axis in adult populations, including anxiety, depression, and chronic stress, have also been shown to have a tendency toward the development of MS (33–35). The hypothesis that chronic life stress results in subtle hyperactivity of the HPA axis leading to increases in IAAT and MS finds support in the findings of several groups (4) (6, 7). Pasquali and Vicennati (28) also described heightened cortisol secretion in women with abdominal obesity using several measures of HPA activity. Recent findings suggest that chronic stress mechanisms could be active in youth, as stressful life events were linked to the presence of MS in adolescents and young adults (36). More investigation is clearly needed to determine whether chronic life stress actually plays a role in hyperactivity of HPA axis and chronic disease risk in pediatric and adolescent populations.

The strengths of this study include the direct measurement of important metabolic outcomes of interest (*e.g.* insulin sensitivity, IAAT, and total body fat mass) rather than less specific indices of these important metabolic parameters (*e.g.* fasting insulin, BMI, and anthropometrics). Another strength is the homogeneous cohort of children at risk for type 2 diabetes, which has been well characterized in previous reports (12, 37). This minimizes to some extent the metabolic heterogeneity of ethnically mixed populations that could obscure important findings. On the other hand, the homogeneity of the

population precludes generalization to other ethnic or age groups. This study has the limit of being cross-sectional, and we therefore cannot state that the MS is the result of the high cortisol levels rather than vice versa. Despite the above points of discussion that suggest a directional relationship of higher cortisol leading to MS, it has also been shown that IAAT may increase cortisol production due to local conversion of cortisone to cortisol, suggesting the opposite direction of causality (38, 39). Longitudinal studies could clarify these issues. Finally, a single morning cortisol measure is not the optimal way to explore links between HPA activity and MS. Adult studies have used more sophisticated measures including measurement of salivary cortisol, urinary free cortisol, dynamic stimulation, and suppression tests of the HPA axis (40). Such measures may ultimately be more discriminating in elucidating the relations between HPA activity and features of MS in children.

In conclusion, we have shown that the MS in overweight, Latino children with a family history of diabetes is associated with significantly higher morning serum cortisol levels, independent of body fat, insulin sensitivity, age, and gender. Only certain features of MS in this population, most notably blood pressure and fasting glucose, are related to cortisol levels, whereas others are not (waist circumference, triglycerides, and HDL). Additional studies are needed to tease apart these relationships and delineate the role of relative hypercortisolism and chronic stress in obesity-related metabolic disorders in children.

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Address all correspondence and requests for reprints to: Marc J. Weigensberg, M.D., Department of Pediatrics, University of Southern California, 2250 Alcazar Street, CSC 200, Los Angeles, California 90089-9073. E-mail: weigensb@usc.edu.

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