Cortisol, Obesity, and the Metabolic Syndrome: A Cross-Sectional Study of Obese Subjects and Review of the Literature

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Objective: Circulating cortisol and psychosocial stress may contribute to the pathogenesis of obesity and metabolic syndrome (MS). To evaluate these relationships, a cross-sectional study of 369 overweight and obese subjects and 60 healthy volunteers was performed and reviewed the previous literature.

Design and Methods: Overweight and obese subjects had at least two other features of Cushing’s syndrome. They underwent measurements representing cortisol dynamics (24 h urine cortisol excretion (UFC), bedtime salivary cortisol, 1 mg dexamethasone suppression test) and metabolic parameters (BMI, blood pressure (BP); fasting serum triglycerides, HDL, insulin, and glucose). Subjects also completed the Perceived Stress Scale (PSS). UFC, salivary cortisol, and weight from 60 healthy volunteers were analyzed.

Results: No subject had Cushing’s syndrome. UFC and dexamethasone responses were not associated with BMI or weight. However, salivary cortisol showed a trend to increase as BMI increased (P < 0.0001), and correlated with waist circumference (WC) in men (rₙ = 0.28, P = 0.02) and systolic BP in women (rₙ = 0.24, P = 0.0008). Post-dexamethasone cortisol levels were weak to moderately correlated with fasting insulin (rₙ = −0.31, P = 0.01) and HOMA-IR (rₙ = −0.31, P = 0.01) in men and systolic (rₙ = 0.18, P = 0.02) and diastolic BP (rₙ = 0.20, P = 0.009) in women. PSS results were higher in obese subjects than controls, but were not associated with cortisol or metabolic parameters. As expected, WC correlated with fasting insulin, HOMA-IR, and systolic BP (adjusted for BMI and gender; P < 0.01). Literature showed inconsistent relationships between cortisol and metabolic parameters.

Conclusion: Taken together, these data do not support a strong relationship between systemic cortisol or stress and obesity or MS.

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Introduction

The current “epidemic” of overweight and obesity in the United States is associated with a high prevalence of co-morbidities characterized as metabolic syndrome (MS), including hypertension, diabetes, and dyslipidemia. This may be why obesity confers a higher risk of death from cardiovascular disease, diabetes, and some cancers (1). Thus, insight into factors that cause and/or maintain obesity and the MS have important therapeutic implications.

Like obesity, Cushing’s syndrome is associated with components of the MS as well as increased mortality from cardiovascular disease (2).

Hypercortisolism is the pathophysiologic underpinning of Cushing’s syndrome. The similarity of co-morbidities raises the question of whether cortisol plays a role in the development and maintenance of obesity and the MS.

Some previous reports suggested a causal relationship between cortisol and obesity or cortisol and MS. In 87 obese women, 24 h urine cortisol excretion correlated significantly with abdominal diameter and abdominal obesity (3). Also, cortisol responses to adrenocorticotropic hormone (ACTH) and corticotropin-releasing factor were increased in 16 obese women with abdominal compared to peripheral fat distribution (4). Two studies identified a significant relationship between
0900-h fasting plasma cortisol and components of the MS (5,6). In addition to direct relationships between cortisol, obesity, and MS, evidence also suggests that perceived stress may exert adverse metabolic effects through cortisol (7,8). These putative relationships have reached the lay press (9), which has deemed cortisol “the real culprit” for obesity, and underlie sales of weight loss products that claim to block cortisol action (10).

To further examine the role of cortisol in obesity and MS, we investigated associations between various measures of systemic hypercortisolism and weight, MS, and psychosocial stress in an obese population. To extend this analysis to lower BMI ranges we added data from healthy volunteers to evaluate relationships between urine and salivary cortisol and weight. We reviewed the available literature on this topic.

Methods

The NICHD Institutional Review Board approved both studies and all subjects provided written informed consent.

Overweight and obese subjects

The primary outcome measure of the study (NCT00361777), the diagnostic accuracy of screening tests for Cushing’s syndrome, has been published (11). This report is a prospectively planned secondary analysis.

From October 2003 to April 2008, obese and overweight individuals presenting for weight loss treatment at The George Washington University Weight Management Program were invited to participate in this study. Inclusion criteria were age 18-75 years, weight gain, and the presence of at least two other features of Cushing’s syndrome from the following list: impaired short-term memory, lethargy, osteopenia or recent fracture, recent onset or difficult to control hypertension, plethora, hirsutism, ecchymoses, weakness, edema, female balding, decreased libido, irritability, decreased concentration, changes in appetite, menstrual changes, headache, glucose intolerance, recurrent infections, striae wider than 1 cm and purple in color, abnormal fat distribution, thin skin, and acne (11). Exclusion criteria included weight > 350 lbs (159 kg); serum creatinine > 2.6 mg/dl; pregnancy; serious medical conditions that might alter pituitary-adrenal function; and recent or anticipated use of medications affecting glucocorticoid physiology, including glucocorticoids, black licorice, chewing tobacco, phenytoin, barbiturates, loperamide, and opiates.

At the first visit, staff reviewed the medical history and performed a physical examination including measurements of weight, height, and waist circumference, systolic and diastolic blood pressure, SBP, DBP. Fasting blood sugar, insulin, triglyceride, and high density lipoprotein (HDL) levels were measured. Subjects without known diabetes underwent an oral glucose tolerance test.

Each subject underwent at least two screening tests for Cushing’s syndrome: 1) 1 mg overnight dexamethasone suppression test (DST) with measurement of serum dexamethasone (radioimmunoassay [RIA] October 2003 to January 2005; high pressure liquid chromatography and isotope dilution mass spectrometry January 2005 onwards; \( R^2 = 0.972 \); Esoterix Laboratories [ETX], Calabasas Hills, CA) and cortisol (ETX, RIA October 2003 to July 2004; liquid chromatography tandem mass spectrometry [LC-MS/MS] July 2004 onwards; \( R^2 = 0.985 \); the reported lower limit of detection in both assays was 1.0 ug/dl [27.6 nmol/l]); 2) measurements of 24-h urine creatinine and cortisol excretion (UFC) (tandem mass spectrometry, [LC-MS/MS], Mayo Laboratories, [Mayo] Rochester, MN); or 3) measurement of bedtime salivary cortisol (LC-MS/MS and/or RIA), as described previously (11). Biochemical testing and the Perceived Stress Scale (PSS) questionnaire were completed before beginning the weight loss program, usually within two weeks after the first visit (12).

Healthy volunteers

To evaluate cortisol relationships over a larger BMI range, we included data from a separate study (NCT00156767) performed at the NIH Clinical Center. In that study, healthy volunteers provided urine and saliva collections for measurement of daily cortisol excretion (chemiluminescence immunometric assay, Nichols Advantage one site, NIH, earlier in the study; and LC-MS/MS, Mayo later in the study) and bedtime salivary cortisol levels (LC-MS/MS, Mayo). Inclusion and exclusion criteria and subject demographics have been described previously (13). These subjects did not complete the PSS or the 1 mg DST.

Literature review

To evaluate extant data regarding the relationship(s) of basal urine or salivary cortisol levels and dexamethasone suppression testing, and measures of obesity and/or MS in adults, the following text words were searched in MEDLINE: cortisol, hypothalamic-pituitary-adrenal axis, MS, obesity, weight, BMI, urine free cortisol, salivary cortisol, and 1 mg DST. Articles reporting on measures of 17-keto- or 17-hydroxy steroids were excluded, thus, setting the time frame for this search to articles published after 1980. Only English language reports were reviewed. We did not analyze the results of cortisol metabolites or dynamic testing responses of the adrenal axis.

Analysis

Simple descriptive statistics and frequency distributions were used to characterize subject clinical presentation and demographics of the subjects. Data are reported as mean ± SD for demographics and comparison to normative data, but otherwise are median and interquartile range (IQR; 25th percentile, 75th percentile). Subjects who completed only one screening test were excluded from the analysis (n = 6). Women known to be taking estrogenic preparations (n = 50) and those without data regarding estrogen use (n = 41) were excluded from the analyses of post-dexamethasone cortisol levels.

Subjects were considered to have a diagnosis of diabetes if they were taking a glucose-lowering medication, had a fasting blood glucose ≥126 mg/dl [7.0 mmol/l], or a 2-h post glucose ≥200 mg/dl [11.1 mmol/l]. Those with impaired fasting glucose (fasting blood glucose ≥100 mg/dl [5.6 mmol/l]; n = 65) or impaired glucose tolerance (blood glucose of 140-199 mg/dl [7.8-11.0 mmol/l]; n = 24) (14) were excluded from the analyses involving diabetes. Insulin resistance was evaluated by HOMA-IR. Subjects were considered to have hypertension if they were taking a medication to lower blood pressure or if DBP was ≥90 mmHg and/or DBP was ≥90 mmHg.

Subjects were classified as having MS if they had three of the five risk factors listed in the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult
TABLE 1 Modified ATP III criteria for metabolic syndrome

| Risk factor          | Threshold criterion |
|----------------------|---------------------|
| Waist circumference, Women | > 35 inches (89 cm) |
| Waist circumference, Men    | > 40 inches (102 cm) |
| Triglycerides         | ≥ 150 mg/dl (1.7 mmol/l) OR < 150 mg/dl + MED³ |
| HDL cholesterol, Women | < 50 mg/dl (1.29 mmol/l) |
| HDL cholesterol, Men    | < 40 mg/dl (1.03 mmol/l) |
| Systolic Blood Pressure | ≥ 130 (mmHg) OR < 130 + MED³ |
| Diastolic Blood Pressure | ≥ 85 (mmHg) OR < 85 + MED³ |
| Fasting Glucose        | ≥ 100 mg/dl (5.6 mmol/l) OR < 100 + MED³ |

*MED: triglyceride, blood pressure, or glucose lowering medications.

Results

Demographics: Overweight and obese subjects
Three hundred sixty-nine subjects (72.4% women; 82.7% Caucasian) completed at least two screening tests (UFC, n = 348; salivary cortisol by RIA, n = 232; salivary cortisol by LC-MS/MS, n = 269; DST, n = 270) and were eligible for the analysis. Men and women had similar age (50 ± 12 vs. 48 ± 12 years), but not weight (128 ± 29 vs. 102 ± 20 kg), BMI (41 ± 9 vs. 38 ± 7 kg/m²), or waist circumference (125 ± 16 vs. 105 ± 15 cm) (all P < 0.01). The BMI distribution was: 25-29.9 kg/m², 11%; 30-34.9 kg/m², 26%; 35-39.9 kg/m², 25%; 40-83 kg/m², 38%. The frequency distribution of MSRx, MS, diabetes, and hypertension were: 186/348 (53.4%), 159/345 (46.1%), 72/362 (19.9%), and 170/357 (47.6%), respectively.

The most common clinical features reported by subjects were: lethargy, irritability, cognitive impairment, and hypertension. The least common clinical features reported were: change in appetite, weakness, skin problems, recurrent infections, and osteopenia (11).

Demographics: Healthy volunteers
Sixty healthy volunteers were enrolled into the study (50% women; 68% Caucasian) from three age groups (< 40, 40-55, > 55 years, evenly divided). Fifty-six subjects provided 24 h UFC samples and 57 provided salivary samples. Men and women had similar ages (46 ± 5 vs. 45 ± 15 years) and BMI (27 ± 5 vs. 25 ± 5 kg/m²) but not weight (87 ± 11 vs. 67 ± 14 kg). The BMI distribution in this group was: 18.6-24.9 kg/m², 33%; 25-29.9 kg/m², 30-34.9 kg/m², 50%; 30-34.9 kg/m², 15%; 35-35.3 kg/m², 2%; > 35.4 kg/m², 0%.

Abnormal cortisol test results
Sixty-three subjects in the overweight and obese group had one abnormal result and 21 had two or more abnormalities. After further evaluation, none was diagnosed with Cushing’s syndrome (11). Two subjects in the healthy volunteer group had an abnormal salivary cortisol level (402 ng/dl and 300 ng/dl, respectively; ≥ 100 ng/dl, abnormal), but their 24 h UFC values were normal. Repeat salivary cortisol level in the subject with an initial value of 402 ng/dl was abnormal, but their 24 h UFC values were normal. Repeat salivary cortisol level in the subject with an initial value of 402 ng/dl was 114 ng/dl, still slightly abnormal. The second patient was lost to follow-up. On history and physical examination, neither patient had

TABLE 2 24 h UFC (ug/24 h) and salivary cortisol (ng/dl)

| BMI (kg/m²) | Test       | N  | Median (IQR) |
|-------------|------------|----|--------------|
| 18.6–24.9   | Salivary cortisol | 18 | 26 (20, 56) |
|             | 24 h UFC    | 19 | 17 (14, 22)  |
| 25–29.9     | Salivary cortisol | 56 | 20 (12, 44) |
|             | 24 h UFC    | 60 | 16 (12, 24)  |
| 30–34.9     | Salivary cortisol | 78 | 26 (15, 50) |
|             | 24 h UFC    | 103| 20 (12, 27)  |
| 35–83       | Salivary cortisol | 174| 24 (15, 51) |
|             | 24 h UFC    | 222| 18 (12, 27)  |

To convert UFC ug/24 h to nmol/24 h multiply by 2.76; to convert salivary cortisol ng/dl to nmol/l multiply by 0.0276.
signs or symptoms of Cushing’s syndrome. Median 24 h UFC and salivary cortisol values of the combined healthy volunteer and overweight and obese group are provided in Table 2.

**Association of cortisol levels with BMI**

We found no correlation between BMI or weight and any cortisol parameter in the overweight and obese study population (Figures 1 and 2; Table 3).

The BMI distribution of the combined healthy volunteer and overweight and obese study group was: <24.9 kg/m², \( n = 20 \) 4.7%; 25-29.9 kg/m², \( n = 69 \) 16%; 30-34.9 kg/m², \( n = 106 \) 25%; 35-39.9 kg/m², \( n = 93 \) 22%; 40-83 kg/m², \( n = 141 \) 33%. In the combined group, there were no significant differences in the median salivary cortisol or 24 UFC levels in the highest and lowest BMI groups. Specifically, the median salivary cortisol or 24 h UFC values in those with BMI < 24.9 compared to those with BMI > 40.0 were not different. However, there was a statistically significant trend in salivary cortisol but not UFC with increasing BMI values (\( P < 0.0001 \)).

**Association of cortisol levels with metabolic abnormalities**

Subjects with MS, MSRx, diabetes, and/or hypertension were not more likely to have abnormal cortisol results compared to those without metabolic disorders (Figure 3). There were no significant differences in UFC, salivary cortisol levels, or post-dexamethasone cortisol levels between men and women or between men with MSRx, MS, diabetes, or hypertension compared to those without the respective disorders. The same was true for women, except that women with MSRx (14 [10-24] vs. 19 [13-27] mcg/24 h), diabetes (12 [8-24] vs. 18 [12-26] mcg/24 h), and hypertension (13 [10-24] vs. 20 [13-29] mcg/24 h) had normal but statistically significant (all \( P < 0.01 \)) lower UFC levels compared to those without the disorder. There was no significant correlation between any cortisol parameter and the number of features of MS.

When stratified by gender, UFC was not related to waist circumference, HDL, triglycerides, SBP or DBP. Similarly, no relationship was seen between post-dexamethasone cortisol levels and waist circumference, HDL or triglycerides. However, women showed weak correlations between post-dexamethasone cortisol levels and systolic and diastolic blood pressure \( (r_s = 0.18, P = 0.02; r_d = 0.20, P = 0.009) \), and a weak correlation between SBP and bedtime salivary cortisol by LC-MS/MS \( (r_s = 0.24, P = 0.0008) \). Men showed a moderate correlation between waist circumference and bedtime salivary cortisol measured by RIA \( (r_s = 0.32, P = 0.01) \) and LC-MS/MS \( (r_s = 0.28, P = 0.02) \). Otherwise, salivary cortisol did not show any significant relationships with metabolic parameters (Figure 3, Table 3).

When subjects on glucose-lowering medications were excluded (\( n = 51 \)), there was no correlation between UFC or salivary cortisol and fasting insulin, fasting glucose, or HOMA-IR. Post-dexamethasone cortisol levels were negatively associated with fasting insulin \( (r_s = -0.31, P = 0.01) \) and HOMA-IR \( (r_s = -0.31, P = 0.01) \) in men.

**Associations between waist circumference and metabolic parameters**

Waist circumference was correlated significantly with fasting insulin \( (r_p = 0.37, P < 0.0001) \), fasting glucose \( (r_p = 0.57, P = 0.02) \), HOMA-IR \( (r_p = 0.40, P < 0.0001) \), and weakly with SBP \( (r_p = 0.22, P < 0.0001) \) and DBP \( (r_p = 0.19, P = 0.0005) \). When adjusted for gender, waist circumference maintained statistically significant correlations with fasting insulin (adj \( r_p = 0.37, P < 0.0001) \), HOMA-IR (adj \( r_p = 0.39, P < 0.0001) \), and SBP (adj \( r_p = 0.22, P = 0.004) \), but not with fasting glucose or DBP. When adjusted for BMI, these associations remained statistically significant (all \( P < 0.01) \), except for that between waist circumference and fasting glucose.

**Cortisol and stress**

PSS scores were significantly higher in study subjects than in published population controls by gender and age groups 18-64 years (score ranges 17-20 vs. 12-14, \( P < 0.001 \) for each age group). Mean scores were similar in subjects 65 years and older and same age population controls (11 ± 5 vs. 12 ± 6, \( P = 0.61) \). We found no
significant relationship between PSS scores and UFC, waist circumference, or BMI in either sex.

PSS scores in men (14 [8-20] vs. 18 [15-24], P = 0.01) and women (17 [12-21] vs. 20 [15-24], P < 0.02) with MS were lower than in those without MS. Women with MSRx had lower PSS scores than those without the disorder (17 [12-22] vs. 20 [16-23], P = 0.01) (Figure 4). In men only, we found inverse correlations between post-dexamethasone cortisol levels and PSS (r = −0.24, P < 0.03) and salivary cortisol by RIA and PSS (r = −0.35, P = 0.007).

**Literature review**

Twenty studies (including this one) investigated relationships between parameters of obesity or MS and various cortisol measures: UFC (n = 6), morning or evening salivary cortisol (n = 4), morning plasma cortisol (n = 14), or dexamethasone responses (n = 6) (Table 3).

No study found a significant positive association between BMI and cortisol parameters including UFC (n = 1) (17), salivary cortisol (n = 1) (18), or the responses to 1 mg DST (2/2 studies) (17,19). One study showed greater inhibition (percent cortisol suppression) after a lower dexamethasone dose in obese compared to normal weight women (19). Among studies evaluating relationships between morning plasma cortisol and BMI (n = 9), four studies showed no significant association (17,20–22) and five studies showed a negative relationship (5,6,23–25).

No consistent relationship was found between abdominal obesity and cortisol parameters. Positive associations were found with UFC (3/6 studies) (3,19,26), morning (1/2 studies) (27) but not evening salivary cortisol (1 study) (18), or the response to 1 mg dexamethasone (n = 1) (3). One of three studies evaluating lower dexamethasone suppression doses (28) reported increased cortisol suppression in women with an abdominal vs. peripheral body fat distribution while one showed no difference in suppression (27). One of the three studies showed less suppression of cortisol after 0.5 mg dexamethasone dose in men with a WHR > 1.0 vs WHR < 1.0 (29). Nine studies found inconsistent relationships between morning plasma cortisol and abdominal obesity: no relationship (n = 5), (5,6,24,27,28), positive association (n = 1) (29), and negative association (n = 3) (3,22,23). One study did not find a correlation between 24 h UFC and abdominal circumference (30).

The relationships between cortisol parameters and features of the MS also were variable. Positive associations were found between blood pressure and higher pre-lunch salivary cortisol (1/1 study) (31) and between insulin and free cortisol (1/1 study) (24). Morning plasma cortisol had inconsistent associations with glucose (3/6 positive) (5,6,23), blood pressure (3/6 positive) (5,6,20), and triglycerides (positive, negative, and no relationship in one study each) (5,6,32). There was no relationship between morning plasma cortisol and HDL (4/4 studies) (5,22,23,32) or insulin (3/3 studies) (6,22,24).

No study analyzed relationships of UFC or dexamethasone suppression testing and MS.

**Discussion**

This study evaluated three parameters of activity of the hypothalamic-pituitary-adrenal (HPA) axis: its nadir (by salivary cortisol levels), its integrated daily cortisol production (by UFC), and its sensitivity to negative feedback (by the post-1 mg dexamethasone cortisol level). Though some studies report positive associations between cortisol and obesity and MS (3,5,6) and cortisol was implicated as a major causal factor in a recent review (33), our data, along with a critical review of relevant literature, do not reveal...
| Article                        | Mean BMI ± SD or BMI (range) | HPA axis Evaluation & Statistical Analysis | Measure of Abdominal Adiposity | Systolic Blood Pressure | Diastolic Blood Pressure | Fasting Insulin | Fasting Glucose | HOMA-IR | Triglyceride | HDL |
|-------------------------------|-----------------------------|------------------------------------------|---------------------------------|------------------------|------------------------|-----------------|----------------|---------|-------------|------|
| **Unstimulated 24 h Urine Free Cortisol (UFC)** |                             |                                          |                                 |                        |                        |                 |                |         |             |      |
| Abraham et al., 2012         | 102 M, 50 ± 12              | 41.0 ± 9                                 | 24 h UFC                        | r = 0.11               | r = 0.14               | r = 0.15          | r = 0.01        | r = 0.02 | r = 0.30    | r = 0.03 |
| DM                            | 267 W, 48 ± 12              | 38.0 ± 7                                 | Spearman correlation            | p = 0.36               | p = 0.16               | p = 0.15          | p = 0.90        | p = 0.85 | p = 0.09    | p = 0.12 |
| Duclos et al., 2005          | 22 W, P-BFD, 33.6 ± 8.9     | 39.1 ± 7                                 | 24 h UFC to urine cortisol ratio| –                     | NS                     | –                | –               | –        | –           | –     |
| EX-DM                         | 31 W, A-BFD, 35.4 ± 8.9 (PREM) | 40.1 ± 5                           | ANOVA                           | –                     | NS                     | –                | –               | –        | –           | –     |
| Stewart et al., 1999         | 18 M (n = 12)               | 36.2 ± 3.9                             | Group A 22.3 ± 1.4              | NS difference b/w groups | –                     | –                | –               | –        | –           | –     |
| EX-DM                         | Group A 27.9 ± 1.6          | 39.8 ± 1.4                             | ANOVA                           | –                     | NS                     | –                | –               | –        | –           | –     |
| Abraham et al., 2012         | 102 M, 50 ± 12              | 41.0 ± 9                                 | ANOVA                           | –                     | NS                     | –                | –               | –        | –           | –     |
| EX-DM                         | 37 W, 52.0 ± 2.5 (POST)     | 25.2 ± 41                               | Pearson correlation            | r = 0.05               | NS                     | –                | –               | –        | –           | –     |
| Pasquari et al., 1993        | 12 A-BFD, 340 ± 4.6         | 35.0 ± 4.1                              | 24 h UFC                        | NS                    | Higher in A-BFD vs P-BFD | P < 0.05 | –              | –        | –           | –     |
| EX-DM                         | 13 P-BFD, 281 ± 7.1         | 35.9 ± 4.0                              | ANOVA                           | –                     | NS                     | –                | –               | –        | –           | –     |
| Martin et al., 1992          | 87 W, 41 ± 3.7 (PREM)       | 30.9 ± 14                               | Pearson correlation            | r = 0.48               | NS                     | –                | –               | –        | –           | –     |
| **Unstimulated Salivary Cortisol Studies** |                             |                                          |                                 |                        |                        |                 |                |         |             |      |
| Abraham et al., 2012         | 102 M, 50 ± 12              | 41.0 ± 9                                 | Bedtime salivary cortisol       | r = 0.14               | r = 0.28               | r = 0.06          | r = 0.16        | r = 0.10 | r = 0.02    | r = 0.08 |
| DM                            | 267 W, 48 ± 12              | 38.0 ± 7                                 | Spearman correlation            | p = 0.25               | p = 0.02               | p = 0.64          | p = 0.19        | p = 0.45 | p = 0.91    | p = 0.59 |

Note: SD = standard deviation, Y = years, NS = not significant.
| Article                  | N, gender, mean age ± SD, age (Y) range, race if not Caucasian | Mean BMI ± SD or BMI (range) | HPA axis Evaluation & Statistical Analysis | Measure of Abdominal Adiposity | Systolic Blood Pressure | Diastolic Blood Pressure | Fasting Insulin | Fasting Glucose | HOMA-IR | Triglyc | HDL |
|-------------------------|----------------------------------------------------------------|-----------------------------|------------------------------------------|-------------------------------|---------------------------|------------------------|-----------------|----------------|----------|---------|-----|
| Oltmanns et al., 2006   | 190 M+W; Bm 1959–1968 N = 63, high cortisol group only; 21%W; 53±4.8 all have type 2 diabetes | 31.2 ± 5.6                 | Pre-lunch salivary cortisol determined low, med, high cortisol groups; difference between high vs other groups presented‡ | –                            | P = 0.029                 | P = 0.015               | –               | –              | P = 0.001 | –       | NS  |
| Dudas et al., 2005 EX-DM| 22 W, 33.6 ± 8.9                                               | 39.1 ± 7.0                 | 0800 fasting salivary cortisol            | Higher in A-BFD vs B-FD      | –                         | –                      | –               | –              | –        | –       | –   |
|                         | 31W, 35.4 ± 8.9                                                |                            |                                            |                               |                           |                        |                 |                 |          |         |     |
| Steptoe et al., 2004    | 89 M, 52.5 ± 2.6                                              | 25.6 ± 3.3                 | Cortisol evening maximum r = 0.1          | r = 0.15                     | –                         | –                      | –               | –              | r = 0.11  | –       | NS  |
|                         | 83 W, 51.9 ± 2.7                                              | 25.4 ± 4.0                 | Partial product-moment correlations†      | r-values not given           |                           |                        |                 |                 |          | –       | NS  |
|                         |                                                              |                            |                                             |                               |                           |                        |                 |                 |          |         |     |
| Dudas et al., 2001 EX-DM| 27 W, 38.0 ± 7.1                                              | 39.7 ± 9.4                 | 0800 fasting salivary cortisol            | –                            | –                         | –                      | –               | –              | –        | –       | –   |
|                         | 23 W, 38.0 ± 5.3                                               | 39.8 ± 14                  |                                            |                               |                           |                        |                 |                 |          | –       |     |
| Deamethasone Suppression Test |                                                                    |                            |                                           |                               |                           |                        |                 |                 |          |         |     |
| Abraham et al., 2012    | 102 M, 50 ± 12                                                | 41.0 ± 9                   | 1 mg DST r = –0.17 r = –0.12 r = –0.01 r = –0.09 r = –0.31 r = –0.63 r = –0.03 r = 0.12 | –                            | –                        | –                      | –               | –              | –        | –       |     |
|                         | 267 W, 48 ± 12                                                | 38.0 ± 7                   | Spearman correlation coefficient r = –0.04 r = 0.22 r = 0.18 r = 0.20 r = –0.08 r = –0.03 r = –0.09 r = 0.08 | –                            | –                        | –                      | –               | –              | –        | –       |     |
| Dudas et al., 2005 EX-DM| 22 W, 33.6 ± 8.9                                              | 39.1 ± 7.0                 | 0.25 mg DST                               | –                            | –                        | –                      | –               | –              | –        | –       |     |
|                         | 31 W, 35.4 ± 8.9                                               | 40.1 ± 4.5                 |                                            |                               |                           |                        |                 |                 |          | –       |     |
| Pasquali et al, 2002    | 13 M, nl wt, 35.6 ± 13.3                                       | 22.4 ± 1.8                 | 1 mg DST r = –0.04 r = –0.04 r = –0.04 r = –0.04 r = –0.04 r = –0.04 r = –0.04 r = –0.04 | –                            | –                        | –                      | –               | –              | –        | –       |     |
|                         | 36 M, obese, 39.7 ± 13.6                                       | 37.3 ± 9                   | 0.003 mg DST                               | nl wt vs obese, P = 0.04 (W) | –                        | –                      | –               | –              | –        | –       |     |
|                         | 21 W, nl wt, 31.6 ± 8.1                                       | 30.6 ± 1.7                 | 0.007 mg DST                               | nl wt vs obese, P = 0.002 (W) | –                        | –                      | –               | –              | –        | –       |     |
|                         | 57 W, obese, 347 ± 11.0                                        | 36.2 ± 5.7                 | 0.0015 mg DST                               | nl wt vs obese, P = 0.04 (W) | –                        | –                      | –               | –              | –        | –       |     |
| Article                     | N, gender, mean age ± SD, age (Y) range, race if not Caucasian | Mean BMI ± SD or BMI(range) | HPA axis Evaluation & Statistical Analysis | Measure of Abdominal Adiposity | Systolic Blood Pressure | Diastolic Blood Pressure | Fasting Insulin | Fasting Glucose | HOMA-IR | Triglyc | HDL |
|----------------------------|---------------------------------------------------------------|----------------------------|------------------------------------------|-------------------------------|--------------------------|-------------------------|----------------|---------------|---------|---------|-----|
| Duclos et al., 2001        | 27 W, P-BFD, 38.0 ± 7.1                                      | 39.7 ± 9.4                 | 0.25 mg DST                              | 0.25 mg DST, A-BFD greater inhibition vs P-BFD, P = 0.002; 0.5 mg DST, A-BFD vs P-BFD, NS | –                         | –                       | –              | –              | –       | –       |     |
| EX-DM                     | 23 W, A-BFD, 38 ± 5.3                                         | 39.8 ± 1.4                 | 05 mg DST                                | ANOVA                         | –                         | –                       | –              | –              | –       | –       |     |
| Stewart et al., 1999       | 18 M, Group A 22.3 ± 1.4                                      | 1 mg DST                   | NS difference b/w groups                |                                | –                         | –                       | –              | –              | –       | –       |     |
| 18 W (PREM)                | Group B 27.9 ± 1.6                                            | 1 mg DST                   | NS difference b/w groups                |                                | –                         | –                       | –              | –              | –       | –       |     |
| Ljung et al., 1996         | 22 M 40-60 Y                                                  | 8 M < 25.0                  | 0.5 mg DST                               | WHR > 1.0 less inhibition than WHR < 1.0, P = 0.05 | –                         | –                       | –              | –              | –       | –       |     |
| EX-DM                     | 14 M > 25.0                                                  | 0.25 mg DST                 | No difference b/w WHR groups            |                                | –                         | –                       | –              | –              | –       | –       |     |
| Groups divided by WHR for analysis: n in these groups unknown | 0.125 mg DST                                              | No difference b/w WHR groups |                                |                                | –                         | –                       | –              | –              | –       | –       |     |
| Marin et al., 1992         | 87 W, 41 ± 3.7 (PREM)                                        | 30.9 ± 14                   | 1 mg DST                                | NS b/w WHR groups             | –                         | –                       | –              | –              | –       | –       |     |
| EX-DM                     | Subgroup 10 W WHR > 0.87                                       | Analysis not stated         | –                                        |                                | –                         | –                       | –              | –              | –       | –       |     |
| Morning Plasma Cortisol Studies Including Diabetics |                          |                             |                                          |                                | –                         | –                       | –              | –              | –       | –       |     |
| Reynolds et al., 2010      | 483 M, 68.0 ± 4.1                                             | 30.2 ± 4.8                  | 0800–0830 fasting cortisol              | M                             | M                          | M-W                     | M-W            | –              | –       | –       |     |
| DM                         | 436 W, 67.7 ± 4.3                                             | 32.4 ± 6.2                  | Pearson correlation or multiple linear regression | r = -0.139, P = 0.001         | r = -0.166, P = 0.001     | β = 0.5 ± 0.4, 95%CI (-0.2 to 1.3) | β = 0.5 ± 0.7, 95%CI (-0.9 to 1.9) | –              | –       | –       |     |
|                           |                                                              |                            |                                          | M                             | M                          | M-W                     | M-W            | –              | –       | –       |     |

95%CI (43.6 to 331)
| Article | N, gender, mean age ± SD, age (Y) range, race if not Caucasian | Mean BMI ± SD or BMI(range) | HPA axis Evaluation & Statistical Analysis | BMI | Measure of Abdominal Adiposity | Systolic Blood Pressure | Diastolic Blood Pressure | Fasting Insulin | Fasting Glucose | HOMA-IR | Triglyc | HDL |
|--------|-----------------------------------------------------------|-----------------------------|---------------------------------------------|-----|-------------------------------|------------------------|------------------------|-----------------|---------------|--------|--------|-----|
| Traxler et al., 2007 | 999 M, 62.6 ± 8.3 | 27.7 ± 4.4 | nonfasting cortisol 4 h post-waking | – | – | – | – | – | – | – | – | – |
| DM | | | | | | | | | | | | | |
| Maggio et al., 2006 | 398 M (-MS)³, 75 ± 2 | 26.0 ± 3 | 0700-0800 fasting cortisol | NS (WC) | NS | – | – | NS | – | NS | – | NS | NS |
| DM | 76 M (-MS), 74 ± 6 results presented for combined group | 30.0 ± 3 | | | | | | | | | | | |
| Ward et al., 2003 | 258 M, 47 ± 4.7 | 22.9 ± 4.1 | 0900 fasting cortisol | NS | r = 0.25 | r = 0.24 | r = 0.12 | r = 0.26 | r = 0.20 | r = 0.17 | – | |
| DM | 25 W, 47 ± 4.9 | 24.8 ± 4.9 | partial correlation coefficients & multiple linear regression | – | – | – | – | – | – | – | – | – |
| Walker et al., 2000 | 105 M, 52 ± 15.4 (range only) | 26.2 ± 3.3 | AM fasting cortisol | r = 0.03 | r = 0.04 | r = 0.17 | r = 0.19 | r = 0.12 | r = 0.12 | r = 0.12 | – | r = 0.10 | r = 0.10 |
| DM | 110 W, 48.4 ± 13.6 (range only) | 25.2 ± 4.2 | simple regression analysis² | – | – | – | – | – | – | – | – | – |
| Phillips et al., 1998 | 370 M, 64 ± n, (69-70) | 36.9-27.6 (range only) | 0900 fasting cortisol | P = 0.049 | P = 0.52 (WHR) | P² = 0.02 | P² = 0.03 | – | P² = 0.0002 | P² = 0.006 | P² = 0.009 | P² = 0.006 |
| UNK-DM | | | | | | | | | | | | |
| Dudas et al., 2005 | 22 W, P-BFD | 39.1 ± 7.0 | 0800 fasting cortisol | – | P = 0.27 | – | – | – | – | – | – |
| EX-DM | 33 W, A-BFD | 40.1 ± 4.5 | ANDWA | – | – | – | – | – | – | – | – |
| Dudas et al., 2001 | 27 W, P-BFD | 39.7 ± 9.4 | 0800 fasting cortisol | – | NS | – | – | – | – | – | – |
| EX-DM | 38 W, A-BFD | 39.8 ± 14 | ANDWA | – | – | – | – | – | – | – | – |
| Rask et al., 2001 | 11 M, 46.8 ± 8.7 | 22.9 ± 14 | 0830 cortisol (fasting status unknown) | NS | – | – | – | – | – | – | – | – |
| EX-DM | 11 M, 49.6 ± 8.5 | 26.4 ± 7.0 | – | – | – | – | – | – | – | – | – | – |
| EX-DM | 12 M, 51.9 ± 12.1 | 31.7 ± 4.0 | – | – | – | – | – | – | – | – | – | – |
| Stewart et al., 1999 | 18 W (PREM) | 27.9 ± 5.2 | – | – | – | – | – | – | – | – | – | – |
| UNK-DM | Group A (n = 12) | 27.9 ± 5.2 | – | – | – | – | – | – | – | – | – | – |
| | Group B (n = 12) | 33.1 ± 6.9 | – | – | – | – | – | – | – | – | – | – |
| | Group C (n = 12) | 33.8 ± 10.7 | – | – | – | – | – | – | – | – | – | – |

**Morning Plasma Cortisol Studies Excluding Or Unknown Diabetic Status**

| Phillips et al., 1998 | 370 M, 64 ± n, (69-70) | 36.9-27.6 (range only) | 0900 fasting cortisol | P = 0.049 | P = 0.52 (WHR) | P² = 0.02 | P² = 0.03 | – | P² = 0.0002 | P² = 0.006 | P² = 0.009 | P² = 0.006 |
| UNK-DM | | | | | | | | | | | | |
| Article | N, gender, mean age ± SD, age (Y) range, race if not Caucasian | Mean BMI ± SD or BMI(range) | HPA axis Evaluation & Statistical Analysis BMI | Measure of Abdominal Adiposity | Systolic Blood Pressure | Diastolic Blood Pressure | Fasting Insulin | Fasting Glucose | HOMA-IR | Triglyc | HDL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Stolker et al., 1996 | 102 M, 67.7 ± 5.7, 67-70 Y | 26.4 ± 3.0 | 0800-0900 fasting cortisol Pearson correlation | r = -0.35, P < 0.01 | r = 0.08 | – | – | – | No association | – | – | – |
| EKOM | 116 W, 65.8 ± 6.1, 40-53 Y | 26.4 ± 4.3 | – | – | – | – | – | – | No association | – | – | – |
| Stolker et al., 1996 | 102 M, 67.7 ± 5.7, 67-70 Y | 26.4 ± 3.0 | 0800-0900 fasting cortisol Pearson correlation | r = -0.36, P < 0.01 | r = 0.13 | – | – | – | No association | – | – | – |
| EKOM | 116 W, 65.8 ± 6.1, 40-53 Y | 26.4 ± 4.3 | – | – | – | – | – | – | No association | – | – | – |
| Filipovsky et al., 1996 | 6424 M, 47.1 ± 1.9, 25-53 Y | 25.8 ± 3.1 | – | – | – | – | – | – | – | – | – |
| EKOM | – | – | – | – | – | – | – | – | – | – | – |
| Ljung et al., 1996 | 22 M range: < 25.0, 14 Y, > 25.0 | 25.8 ± 3.0 | 0800 fasting cortisol Linear regression | – | – | – | – | – | – | – | – |
| EKOM | – | – | – | – | – | – | – | – | – | – | – |
| Marin et al., 1992 | 87 W, 41 ± 3.7, 30.9 ± 14.0 | 30.9 ± 14.0 | 0800 non-fasting cortisol 2 h post breakfast Pearson correlation | – | – | – | – | – | – | – | – |
| EKOM | – | – | – | – | – | – | – | – | – | – | – |

Actual statistical values presented if available; statistically significant values are in bold. For this study, analyses presented are for obese and overweight study group only.

Triglyc, triglycerides; M, men; W, women; DM, study included diabetics; EX-DM, study excluded diabetics; UNK-DM, unknown if diabetics included; BFD, body fat distribution; P, peripheral (waist-to-hip ratio <85); A, abdominal (waist-to-hip ratio >85); WC, waist circumference; WHR, Waist-to-Hip ratio; NS, not significant; b/w, between; abd circ, abdominal circumference; PREM, pre-menopausal; POST, post-menopausal; DST testing uses plasma cortisol; nl, normal; inhibition, i.e. percent cortisol suppression.

4Cortisol levels within normal range.
5Results controlled for age, socioeconomic status, smoking, alcohol consumption, and time of waking; cortisol evening minimum is the lower of the values recorded at 2000–2030 and 2200–2230.
6Covariates were age, gender, BMI, duration and treatment of diabetes mellitus, anti-hypertensive treatment, lipodilowering treatment, interaction of BMI by gender.
7Adjusted for age and other significant covariates; estimated cross-sectional trend in BMI per 100 nmol/l increase in serum cortisol concentration.
8NS, metabolic syndrome by ATP III criteria with exception of fasting blood glucose cut-off which was 126 mg/dl; analysis adjusted for age, smoking, alcohol use, physical activity in the year before the visit.
9Except for BMI, results are partial correlation coefficients corrected for age, sex and BMI.
10Patients on anti-hypertensive meds excluded from blood pressure analyses; insulin values log transformed; when adjusted for obesity, plasma cortisol had statistically significant association with diastolic blood pressure (r = 0.21, P = 0.04) in men and with triglycerides and insulin (r = 0.28, P = 0.001; r = 0.19, P = 0.02, respectively) in women.
11P for trend adjusted for age and body mass.
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strong associations between cortisol and weight or features of the MS.

In the combined group there was a significant trend in salivary cortisol values by increasing BMI. This was an interesting finding given that there was no significant difference between median salivary cortisol values in those with the lowest (<24.9 kg/m²) versus highest (>40 kg/m²) BMI. Other than this significant trend, our study and others found no significant relationships between weight or BMI and any cortisol parameter (17–19).

It is possible that visceral or abdominal adiposity (as measured by waist circumference) reflect metabolic risk better than BMI. As expected, waist circumference correlated strongly with insulin resistance and weakly with blood pressure (34). However, apart from a weak correlation with salivary cortisol in men, we found no relationship between waist circumference and any cortisol parameter. Along with the data reported in Table 3, these results do not support an association between increased systemic cortisol levels and obesity or abdominal adiposity.

Other features of the MS might be associated with cortisol. Interestingly, we observed significantly lower UFC levels in women with MSRx, hypertension, and diabetes, a finding counter to the hypothesis that cortisol may be causal. Our results and the previous data (Table 3) do not show consistent relationships between basal or suppressed levels of cortisol, and obesity or components of the MS. Of note, most studies with significant P-values had weak correlations (r values < 0.3).

One might argue that dynamic testing is a more appropriate tool to assess HPA axis activity. A few small studies reported increased cortisol responses to ACTH or corticotropin releasing hormone (CRH) stimulation or to metabolic or psychological challenges in subjects with abdominal versus peripheral fat distribution (3,26–28). Unfortunately, these findings have not been replicated.

Given the intense interest in the area yet conflicting results, an obvious question is: why has it been so difficult to define HPA function in MS? One reason is the different study designs. Previous studies are heterogeneous in terms of gender, age, cortisol parameters and timing, and presence and severity of co-morbidities.

Second, assay variability may cause variable results. In this study, the relationship between salivary cortisol and SBP in women was significant by LC-MS/MS, but not by RIA. We previously reported discrepancies between these assays (35). Calibration of the LC-MS/MS assay can lend to discrepant results between it and immunoassays. Another possible explanation is that RIA measures non-cortisol steroid metabolites whereas LC-MS/MS does not. Cross-reactivity of cortisol metabolites in immunoassays also may contribute to overestimation of UFC levels, both in normal and obese individuals (17,21).

In addition to study design, measurement, and interpretation differences in the literature, obesity itself may confound the results. Strain et al. reported that cortisol production rates showed a significantly positive linear correlation with “relative” (percent deviation from desirable weight) weight in men and women, but the ratio was weight invariant (36). Purnell et al. showed that cortisol production rates increased in proportion to body weight in lean to obese healthy volunteers. However, when corrected for body surface area, there was no association with fat mass or non-fat mass. They also showed that cortisol clearance rates were significantly higher in obese vs. lean patients with adrenal insufficiency (37). Others have demonstrated increased clearance of cortisol with increasing weight in women, but not in men (38). Thus, it is possible that seemingly elevated UFC levels in an obese patient may be due to increased cortisol production with increased excretion of metabolites that cross-react in the cortisol assay.

This study could not evaluate subtle dysregulation of cortisol in obesity and MS. The increasing trend of salivary cortisol levels by BMI hints at the idea that perhaps very slight increases in nadir cortisol levels contribute to obesity. One must also consider the idea that cortisol dysregulation may occur only in various sub-populations, which still need to be identified.

In addition, although the data are inconsistent, there is a suggestion that local glucocorticoid action may be amplified by up-regulated activity of 11βHSD in visceral and hepatic tissue of obese subjects (39). In addition, serum-free cortisol levels and cortisol production rates, adjusted for body surface area, are associated with accumulation of visceral fat and insulin resistance in men (39). Perceived stress and psychiatric disorders may influence HPA axis function, obesity, and MS. In the current study, overweight and obese individuals had higher perceived stress scores than population-based gender and age-matched controls up to age 64. However, no clinically relevant associations were found between perceived stress and any cortisol parameter, or weight. Perceived stress scores were significantly lower in subjects with versus without MS, which was unexpected. Similar findings have been reported: in a longitudinal study of 425 middle-aged women, questionnaires reflecting depression, tension

![Graph showing Perceived Stress Scale (PSS) scores in women and men with (gray bar), without (white bar) MS (using modified ATP III criteria), and the total group (gradient bar); Error bars represent inter-quartile range (IQR; 25th percentile, 75th percentile); *P < 0.05, PSS in women vs. men; **P = 0.005, PSS in women vs. men.](http://www.obesityjournal.org)
and anger measures were associated with MS. However, PSS scores were not significantly associated with MS (40). This suggests that specific trait questionnaires may be more useful than general stress questionnaires in understanding the role of stress in MS.

This study shows that systemic cortisol levels are similar in the presence or absence of MS, hypertension, and diabetes. A literature review highlighted a lack of consistency in relationships between cortisol and weight or metabolic parameters. Taken together, these data raise doubts about the role of systemic cortisol in the development and maintenance of obesity and the MS.

Strengths of our study include the large number of subjects and use of cortisol parameters that reflect both basal values and dynamic response. Limitations include the study’s cross-sectional design, which prevented us from evaluating whether people who become obese or develop MS have subtle cortisol excess over time. Selection bias may have skewed the results as the subjects enrolled were motivated to attend a weight loss clinic and may have failed other treatments. From a socioeconomic standpoint, these subjects did not have financial restrictions preventing them from participating in the weight loss program. Also, the investigation focused on systemic hypercortisolism and did not evaluate the role of cortisol within tissues or cortisol production rates.

Minor alterations in various systems—e.g., the HPA axis, sympathetic nervous system, inflammatory system, and psychological system—may contribute jointly to the pathogenesis of obesity and MS. A study designed to evaluate these systems collectively and longitudinally with strict attention to population characteristics, and a better understanding of cortisol metabolism, might lead to an improved understanding of the pathophysiology of these conditions.

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