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Cortisol Metabolism in Human Obesity: Impaired Cortisone→Cortisol Conversion in Subjects with Central Adiposity*

PAUL M. STEWART†, ABIGAIL BOULTON, SUDHESH KUMAR, PENNY M. S. CLARK, AND CEDRIC H. L. SHACKLETON

Endocrinology, Division of Medical Sciences, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham, United Kingdom B15 2TH; the Regional Endocrine Laboratory, University Hospital Birmingham National Health Service Trust (P.M.S.C.), Birmingham, United Kingdom B29 6JD; and the Steroid Laboratory, Children's Hospital Oakland Research Institute (C.H.L.S.), Oakland, California 94609-1809

ABSTRACT

For a given body mass index (BMI), mortality is higher in patients with central compared to generalized obesity. Glucocorticoids play an important role in determining body fat distribution, but circulating cortisol concentrations are reported to be normal in obese patients. Our recent studies show enhanced conversion of inactive cortisone (E) to active cortisol (F) through the expression of 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1) in cultured omental adipose stromal cells; the autocrine production of F may be a crucial factor in the pathogenesis of central obesity.

We have now analyzed F metabolism in subjects with BMIs between 20–25 kg/m^2 (group A), 25–30 kg/m^2 (group B), and more than 30 kg/m^2 (group C; n = 12 in each group; six males and six premenopausal females; aged 23–44 yr). Glucose/insulin were measured using a 75-g oral glucose tolerance test, and each subject had total body and regional fat (scapular, waist, hip, and thigh) quantified using dual energy x-ray absorptiometry. Urinary total F metabolites (measured by gas chromatography/mass spectrometry) were increased in subjects with obesity [group A, 11,176 ± 1,530 μg/24 h (mean ± SE); group C, 13,661 ± 1,444], although not significantly so ($P = 0.08$). There was a significant reduction in the urinary tetrahydrocortisol (THF) +/− 5α-THF/tetrahydrocortisone (THE) and the cortol/cortolone ratio in obesity (group A *vs.* C, 1.06 ± 0.08 *vs.* 0.84 ± 0.04 and 0.41 ± 0.03 *vs.* 0.34 ± 0.03, respectively; both $P < 0.05$). Urinary free F (UFF) excretion was similar in all three groups, as was the UFF/urinary free E (UFE) ratio. The 0900 h circulating F, E, and ACTH pre- and postovernight 1-mg dexamethasone suppression values were similar in all three groups, but a reduction in the generation of serum F from dexamethasone-suppressed values after oral cortisone acetate (25 mg) was evident in both obese groups [*e.g.* 546 ± 37 nmol/L in group A *vs.* 412 ± 40 in group B ($P < 0.05$) and 388 ± 38 in group C ($P < 0.01$) 180 min post-E]. Insulin resistance was present in groups B and C, but regression analysis revealed no relationship between F metabolites or the THF+5α-THF/THE ratio and insulin action (homeostasis model assessment analysis and insulin values in the oral glucose tolerance test). There was, however, a highly significant relationship between the THF+5α-THF/THE ratio and BMI ($t = -3.44$; $P < 0.01$) and total body fat ($t = -2.27$; $P < 0.05$). Stepwise regression analyses indicated an inverse relationship between THF+5α-THF/THE and scapular and waist fat ($t = -2.25$; $P = 0.03$) and a direct relationship with hip and thigh fat ($t = 2.42$; $P = 0.02$) in both sexes.

The fall in the THF+5α-THF/THE ratio but unchanged UFF/UFE ratio together with impaired F concentrations after oral E indicates inhibition of 11βHSD1 in subjects with obesity. This results in an increased MCR for F, explaining the increased F secretion rate in obesity in the face of normal circulating F concentrations. 11βHSD1 activity is highly related to body fat distribution, with android or central obesity, but not gynoid obesity, associated with reduced activity in both sexes. This reduction in 11βHSD1 activity raises new questions as to the primary role of 11βHSD1 in the pathogenesis of insulin resistance and central obesity. (*J Clin Endocrinol Metab* **84:** 1022–1027, 1999)

OBESITY is a prevalent condition and is associated with premature mortality from vascular disease. For any given body mass index (BMI), mortality is higher if fat is distributed centrally (visceral adiposity) compared with a more generalized pattern of distribution (1). This has renewed interest in the factors that control adipose tissue distribution in addition to adipose tissue mass and function (2). Glucocorticoids appear to be one such factor. Patients with Cushing's syndrome develop central obesity, which improves with resolution of the hypercortisolism (3, 4). On this basis, several studies have evaluated the hypothalamic-pituitary-adrenal axis in patients with obesity, but these have invariably focused on circulating and urinary concentrations and secretion rate. Overall, the results would suggest that although circulating cortisol (F) concentrations are normal in patients with obesity (independent of adipose tissue distribution), secretion rates are higher, particularly in patients with visceral adiposity (5–12). Despite this, F metabolism has not been thoroughly evaluated in obese subjects, even though recent observations indicate the importance of F metabolism in the pathogenesis of human disease processes (13). Two isozymes of 11β-hydroxysteroid dehydrogenase (11βHSD) catalyze the interconversion of hormonally active F and inactive cortisone (E) (14, 15). Defects in the type 2 11βHSD isozyme result in hypertension due to failure of inactivation of F to E in the kidney (16). In such a scenario, F acts as a potent mineralocorticoid, and although the defect

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Address all correspondence and requests for reprints to: Prof. Paul M. Stewart, Division of Medical Sciences, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham, United Kingdom B15 2TH. E-mail: p.m.stewart@bham.ac.uk.

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† Medical Research Council Senior Clinical Fellow.

in F to E conversion increases the F half-life, secretion rates fall concomitantly so that normal circulating concentrations are maintained (17). By contrast, the type 1 isozyme of 11βHSD predominantly acts as a reductase *in vivo* (E to F) and has been localized to human tissues, including liver and adipose tissue (18–20). Within adipose stromal cells, enzyme expression is higher at omental compared to sc sites, and it is possible that this autocrine generation of active F may be a crucial factor explaining the differential effects of glucocorticoids on different adipose tissue depots and, in turn, the pathogenesis of visceral obesity (21).

The aim of this study was to evaluate F metabolism in patients with varying degrees of obesity.

Subjects and Methods

The study had the full approval of the local hospital ethics committee. Three groups of subjects were studied, each comprising six males and six premenopausal women: group A had BMI values less than 25 kg/m^2, group B had BMI values from 25–30 kg/m^2, and group C had BMI values greater than 30 kg/m^2. No subject was taking regular medication, and all females had normal menstrual cycles. Subjects were between 23–44 yr of age, and there were no significant age differences between the groups. Each subject underwent a standard protocol. On day 1, patients had fasting blood drawn at 0900 h for serum F/E, plasma ACTH, thyroid function tests, and total cholesterol and triglycerides measurements, and waist/hip ratio and blood pressure were determined. After this, total fat, and percent regional fat were determined, using dual energy x-ray absorptiometry (DEXA). Patients completed a 24-h urine collection for urinary free F determination. In addition, a urinary steroid metabolite profile was analyzed, using gas chromatography/mass spectrometry, as previously reported (22, 23), measuring free and conjugated F metabolites. Results are presented for total F metabolites [tetrahydrocortisol (THF), 5α-THF, tetrahydrocortisone (THE), cortols, cortolones, and free F], urinary free F (UFF)/urinary free E (UFE), THF+5α-THF/THE, cortols/cortolones, THF/5α-THF, and etiocholanolone/androsterone.

On day 2, an oral glucose tolerance test was undertaken, giving 75 g oral glucose to a fasted subject at 0900 h and measuring plasma glucose and insulin at 30-min intervals for 120 min; samples were collected on ice and centrifuged immediately, and the plasma was stored before analysis.

At 2300 h on day 2, subjects were given 1 mg dexamethasone, orally, to suppress endogenous F production. All subjects reattended at 0900 h the following morning, and after baseline 0900 h measurements of F and ACTH, cortisone acetate (25 mg) was given orally. Serum F and cortisone acetate were then measured at 30- to 60-min intervals for 240 min as previously reported (24).

Plasma glucose, serum triglycerides, and cholesterol were measured using standard laboratory methods (Instrumentation Laboratory, Warrington, UK). F was measured with an automated competitive chemiluminescent assay on the ACS 180 (Chiron Diagnostics, Halstead, UK), with interassay coefficients of variation (CVs) of less than 10% over the concentration range of 53–944 nmol/L. The 0900 h reference range is quoted at 180–550 nmol/L. E was analyzed by RIA, using antiserum N-137 and 21-acetyl-cortisone-3CMO-histamine[^{125}I] tracer, as previously reported (25). ACTH was measured using an immunoradiometric assay (Nichols Institute Diagnostics Ltd., Saffron Walden, UK), with interassay CVs of less than 15% from 8.4–1333 ng/L. The 0900 h reference range is 9–52 ng/L. Urinary free F was measured by a dichloromethane extraction RIA, with interassay CVs of less than 16% over the range of 153–798 nmol/L. Serum free T_4, free T_3, and TSH were measured by automated luminescent immunoassays on the ACS180 (Chiron Diagnostics), with interassay CVs of less than 12% over the ranges of 6.2–81 pmol/L, 2.5–20 pmol/L, and 0.3–39 mIU/L, respectively. Insulin was measured using an immunoenzymometric assay with no significant cross-reactivity with intact or partially processed proinsulins (Medgenix, Lifescreen, Watford, UK), calibrated against International Reference Preparation 66/304. Interassay CVs were less than 8% over the concentration range of 95–580 pmol/L. Insulin sensitivity was derived from fasting glucose and insulin data, using the homeostasis model assessment (HOMA) mathematical model (26). Insulin sensitivity (HOMA −%S) was expressed as percentage relative to a lean healthy reference population; insulin resistance was inferred from values less than 100%.

Whole body DEXA measurements were performed with a total body scanner (Lunar DPX-L, Lunar Radiation Corp., Madison, WI), and total body fat was recorded. Regions of the body were delineated using previously described landmarks, and regional fat was calculated for subscapular, waist, hip, and thigh regions (27). Waist region was defined within a box area between the upper part of D12 and the iliac crest and subscapular region defined by the same box height immediately above D12. The hip region was the same box height, positioned so that its upper border passed through the superior points of the inner pelvis, and the thigh region was the same box height, with its superior border at the level of the inferior border of the hip region. In each case the sides of the box were lateral to any trunk tissue. The precision of total fat mass measures in terms of CV were less than 3%, and CVs for the regional fat analyses were less than 5%. Regional fat data were expressed as a percentage of the total body fat.

Results are expressed as the mean ± SE. Statistical analyses among the three groups and, where appropriate, between males and females, was undertaken using Student's unpaired *t* test. Stepwise regression and regression analysis were undertaken to define predictive variables. In both cases a Minitab Statistics package was used (version 10.5 for Windows).

Results

There were no differences in basal 0900 h serum F, E, and ACTH among the three groups (Table 1). Serum F concentrations after a 1-mg overnight dexamethasone suppression test were similar in all three groups (27.9 ± 2.0, 27 ± 2.4, and 24.3 ± 1.3 nmol/L, respectively, in groups A, B, and C), as were free T_4, free T_3, and TSH. Basal and peak glucose values after glucose ingestion were also similar in all groups, although the two obese groups (B and C) showed evidence of hyperinsulinemia and an exaggerated insulin response to glucose ingestion. When expressed as HOMA −%S, groups B and C were significantly more insulin resistant than group A (Table 1). Systolic blood pressure was generally increased with increasing obesity, although absolute values did not reach statistical significance (group A *vs.* C, $P = 0.07$).

Urinary F metabolite analyses indicated marked changes in the set-point of F→E conversion, mediated by 11βHSD. Although absolute levels of urinary THF and 5α-THF were similar in all three groups, THE was significantly elevated in group C (Table 2). Compared with subjects with normal BMI, this resulted in a significant reduction in the THF+5α-THF/THE ratio (1.06 ± 0.08 to 0.84 ± 0.04; $P < 0.05$; Fig. 1) and the cortol/cortolone ratio (0.41 ± 0.03 to 0.34 ± 0.03; $P = 0.05$) in this group. This change in 11βHSD activity was not dependent upon gender, with the mean THF+5α-THF/THE ratio falling in men from 1.11 (BMI, <25 kg/m^2) to 0.82 (BMI, >30 kg/m^2) and in women from 0.99 to 0.85. Overall, the THF+5α-THF/THE ratio was similar in males (0.97 ± 0.07) and females (0.94 ± 0.04).

Stepwise regression indicated that BMI and the waist/hip ratio were independent variables for predicting the THF+5α-THF/THE ratio ($t = -3.44$; $P < 0.01$ and $t = 2.39$; $P < 0.05$, respectively), suggesting that regional fat distribution may be of importance. When quantified by DEXA scanning, significant relationships were observed between the THF+5α-THF/THE ratio, percent total fat, and regional fat distribution (Table 3). Inverse associations were observed between the THF+5α-THF/THE ratio and android fat distribution (scapular and waist), and direct associations were

TABLE 1. Age, blood pressure, plasma glucose and insulin concentrations, HOMA analysis, serum cortisol (F), cortisone (E), ACTH, 24-h urinary free cortisol (UFF), cholesterol, triglycerides, and thyroid function tests in 36 normal subjects, analyzed on the basis of BMI

Parameter	A (<25 kg/m^2)	B (25–30 kg/m^2)	C (>30 kg/m^2)
BMI (kg/m^2)	22.3 ± 0.41	27.9 ± 0.45	35.0 ± 0.83
Age (yr)	27.9 ± 1.5	33.1 ± 2.0	33.9 ± 3.1
Waist/hip ratio	0.80 ± 0.02	0.86 ± 0.08[a]	0.93 ± 0.02[b]
Systolic BP (mm Hg)	118.3 ± 2.8	120.3 ± 3.2	125.4 ± 3.5
Diastolic BP (mm Hg)	78.8 ± 1.9	81.2 ± 2.9	81.2 ± 1.6
Fasting insulin (pmol/L)	49.2 ± 4.1	83.1 ± 9.3[c]	105.3 ± 6.4[b]
Peak insulin (pmol/L)	444 ± 71	760 ± 152	972 ± 186[a]
Fasting glucose (mmol/L)	5.01 ± 0.1	4.99 ± 0.1	5.10 ± 0.1
Peak glucose (mmol/L)	7.67 ± 0.5	8.91 ± 0.9	8.30 ± 0.5
HOMA (%S)	66.7 ± 10.3	46.0 ± 9.7[c]	29.0 ± 2.1[b]
0900 h F (nmol/L)	467 ± 36	481 ± 54	421 ± 56
0900 h E (nmol/L)	66.5 ± 3.9	60.1 ± 2.9	61.9 ± 4.1
F/E	7.3 ± 0.7	7.8 ± 0.6	6.7 ± 0.6
0900 h ACTH (ng/L)	30.1 ± 6.1	25.8 ± 4.5	32.4 ± 4.6
UFF (nmol/24 h)	130 ± 20.7	145 ± 13.0	127 ± 15.9
Cholesterol (mmol/L)	4.36 ± 0.19	4.72 ± 0.31	5.09 ± 0.25[a]
Triglycerides (mmol/L)	1.01 ± 0.11	1.19 ± 0.16	1.44 ± 0.17[a]
TSH (mU/L)	1.98 ± 0.21	1.98 ± 0.32	1.68 ± 0.15
Free T_4 (pmol/L)	12.7 ± 0.4	12.9 ± 0.7	12.5 ± 0.5
Free T_3 (pmol/L)	4.1 ± 0.2	4.1 ± 0.2	4.0 ± 0.1

Results are expressed as the mean ± SE.
[a] $P < 0.05$. *vs.* group A.
[b] $P < 0.001$ *vs.* group A.
[c] $P < 0.01$ *vs.* group A.

TABLE 2. Urinary cortisol metabolites expressed as micrograms per 24 h in subjects with varying BMI

Cortisol metabolite	A (<25 kg/m^2)	B (25–30 kg/m^2)	C (>30 kg/m^2)
THF	1,824 ± 243	2,035 ± 490	2,185 ± 185
5α-THF	1,957 ± 458	2,078 ± 489	1,898 ± 391
THE	3,580 ± 476	4,384 ± 1,038	4,946 ± 503[a]
Total F	11,176 ± 1,530	12,669 ± 2,638	13,661 ± 1,444
THF + 5α-THF/THE	1.06 ± 0.08	0.97 ± 0.07	0.84 ± 0.04[a]
Cortols/cortolones	0.41 ± 0.03	0.4 ± 0.04	0.34 ± 0.03[a]
THF/5α-THF	1.18 ± 0.20	1.22 ± 0.26	1.88 ± 0.44
Etiocholanolone/androsterone	0.82 ± 0.08	0.83 ± 0.14	1.18 ± 0.19
UFF/UFE	0.56 ± 0.06	0.45 ± 0.05	0.59 ± 0.05

Values are the mean ± SE.
[a] $P < 0.05$ *vs.* group A.

seen with gynoid fat (hip and thigh) independent of sex. Stepwise regression indicated that total fat and percent thigh fat were independent variables in the group as a whole ($t = -2.77$; $P = 0.009$ and $t = 2.89$; $P = 0.007$, respectively). Although regression analysis indicated a relationship between the percent waist fat and insulin sensitivity (HOMA −%S; $t = -3.46$; $P < 0.001$), no independent relationship between the THF+5α-THF/THE ratio and insulin/glucose levels (basal or stimulated) and HOMA −%S was observed.

The THF/5α-THF ratio was higher in the obese group, and the absolute levels of THF and 5α-THF suggested that this may be due to enhanced 5β-reductase activity. The etiocholanolone/androsterone ratio was also higher in the obese group (Table 2), although these changes did not reach statistical significance and were not correlated with BMI, waist/hip ratio, total body fat, or regional fat distribution. A nonsignificant increase ($P = 0.08$) in the excretion of total F metabolites (reflecting the underlying F secretion rate) was seen in the most severe obese group, but there was no relationship between total F metabolites and BMI, waist/hip ratio, or regional adiposity as measured by DEXA analysis.

There was no change in the UFF/UFE ratio between groups, suggesting similar levels of 11βHSD2 (23) (Fig. 1). After the oral ingestion of E acetate, there was a significant reduction in serum F levels in obese subjects (Fig. 2); taken together, these data suggest that the changes in the THF+5α-THF/THE ratio were indeed secondary to inhibition of 11βHSD1.

Discussion

We have demonstrated a significant change in the set-point of F→E interconversion toward E, indicative of inhibition of the type 1 isozyme of 11βHSD in patients with obesity. Several studies, some conducted over 30 yr ago (5, 10), have demonstrated an increased MCR for cortisol in patients with obesity (9, 11), yet until now the underlying basis for this has remained unknown. Our demonstration of inhibition of conversion of E to F would result in an increased net MCR of F. Circulating F concentrations, however, are normal in obese subjects, suggesting that this enhanced F metabolism is offset by an increase in secretion rate. In our

study, total F metabolites (known to accurately reflect the F secretion rate) (28) were increased in obese subjects, but not significantly so. Other studies have reported increased F secretion rates in obesity and indicate that this may reflect enhanced hypothalamic-pituitary-adrenal drive (11). Perhaps the most florid example of this is seen in patients with the so-called syndrome of apparent cortisone reductase deficiency. Such patients present with ACTH-mediated hyperandrogenism and excrete F metabolites almost exclusively as THE. The presumed genetic defect in 11βHSD1 results in failure to convert E to F, an increased metabolic rate for F, and an enhanced F secretion rate at the expense of ACTH-mediated androgen excess (29, 30). It seems highly likely, therefore, that obesity reflects a milder, presumably acquired, form of the apparent cortisone reductase deficiency disorder. A similar picture has been reported in some studies evaluating women with polycystic ovary syndrome (31).

Although this is the first study to evaluate F metabolism in this way in an obese cohort, our data are in keeping with a recent report analyzing the effect of obesity on F metabolism in patients with hypopituitarism, where a reduction in the ratio of F/E metabolites was observed, but in a sex-dependent fashion, in patients with android obesity (32). These studies conflict with a recent report by Andrew and colleagues, who claim an increase in the THF/THE ratio in obese males and reduced THF/5α-THF in obesity in both sexes (33). However, that paper did not examine a controlled obese population *per se*, but reported multiple regression analyses from a normal cohort population. Furthermore, the absolute levels of the urine F metabolites and their ratios were highly discrepant from published data from our own and other groups.

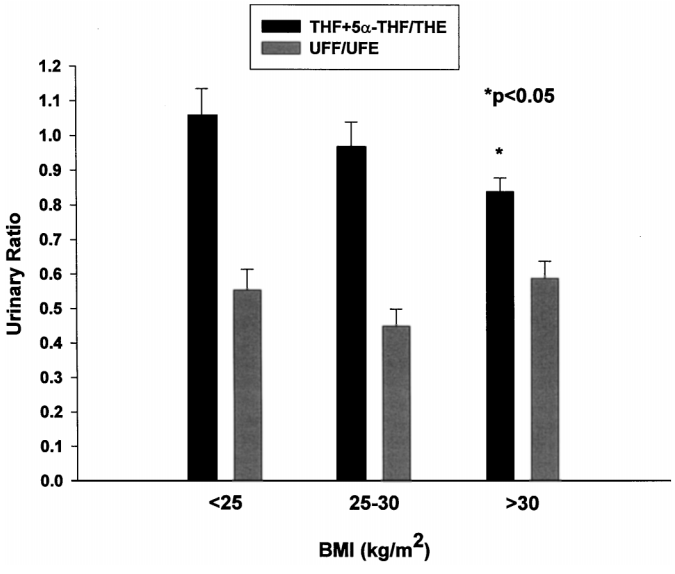

FIG. 1. Urinary THF+5α-THF/THE and UFF/UFE in subjects with increasing BMI. Each group comprises 12 subjects (6 males and 6 premenopausal females), and results are presented as the mean ± SE for the group. The THF+5α-THF/THE ratio was significantly reduced in the most severe obese group compared to that in subjects with BMI, but no such differences were observed in the UFF/UFE ratio.

The cause of the inhibition of 11βHSD1 activity remains obscure. Thyroid hormone is known to regulate 11βHSD activity (34, 35), but free thyroid hormone concentrations and TSH were similar in both groups. Similarly, some studies have shown an inhibitory effect of insulin on 11βHSD1 expression (36, 37), although we have been unable to confirm these findings in our studies on primary cultures of human adipose stromal cells. Nevertheless, we have meticulously analyzed insulin sensitivity, and despite demonstrating significant insulin resistance in our obese subjects, there was no relationship between insulin levels or sensitivity and the THF+5α-THF/THE ratio. Similarly, the change in 11βHSD1 activity with obesity was observed independent of gender, arguing against a major role for sex steroids in explaining the differences. Striking findings were the correlations between regional fat distribution and the THF+5α-THF/THE ratio; android obesity (scapular and waist fat) was inversely related, and gynoid obesity (hip and thigh fat) was directly related to this ratio, suggesting that E→F conversion is reduced in central obesity but increased in patients with gynoid fat distribution.

At an autocrine level, 11βHSD1 expression has been shown to facilitate glucocorticoid hormone action in most tissues expressing the enzyme, that is liver (38), gonad (39, 40), central neural tissues (41, 42), and adipose tissue itself. In paired fat biopsy samples, we have recently demonstrated increased expression of 11βHSD1 in human adipose stromal cells from omental compared with sc depots (21). 11βHSD1 plays a key role in modulating glucocorticoid-induced adipocyte differentiation (our personal observations, submitted for publication). We have proposed that this differential expression of 11βHSD1 may explain the discrepant actions of glucocorticoids on different adipose tissue depots and may also be of relevance in the pathogenesis of central obesity. Patients with Cushing's syndrome develop a reversible form of central obesity, and it is possible that the enhanced conversion of E to F within the omentum itself via 11βHSD1 expression could result in the same phenotype in non-Cushingoid individuals. The reduction in E to F conversion with increasing central adiposity in this study argues against this hypothesis. The major organ responsible for E to F conversion is probably the liver, and it is possible that the

TABLE 3. Regression analyses for THF + 5α-THF/THE ratio against regional fat distribution

	% Total fat	% Scap fat	% Waist fat	% Hip fat	% Thigh fat
Total group	T − 2.27	T − 1.81	T − 2.25	T 1.92	T 2.42
P	0.03	0.08	0.03	0.06	0.02
Males	T − 1.53		T − 2.27		T 2.33
P	0.15		0.04		0.03
Females	T − 2.43		T − 1.48		T 2.26
P	0.03		0.15		0.04

Eighteen males and 18 females comprised the total group.

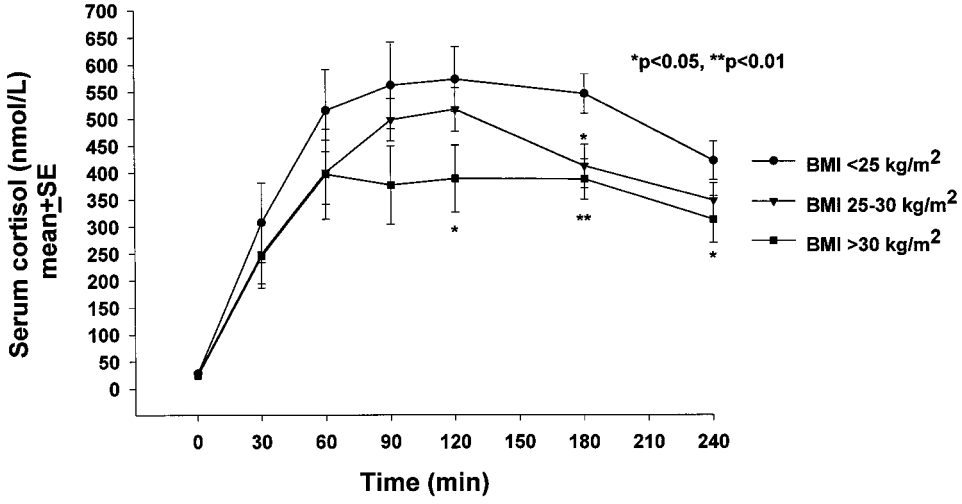

FIG. 2. Serum F (nanomoles per L) after the oral administration of 25 mg cortisone acetate at 0900 h. Each subject had been given dexamethasone (1 mg, orally) at 2300 h on the previous day. The data represent the mean ± SE of 12 individuals (6 males and 6 premenopausal females) in each group. Compared to the subjects with BMI values between 20–25 kg/m^2, the obese groups show a significant reduction in serum F concentrations.

11βHSD1 enzyme is regulated differently within liver and adipose tissue. Furthermore, the set-point of F to E conversion may vary at these different sites. In intact hepatocytes, 11βHSD1 acts exclusively as a reductase (18, 37), and although reductase activity is also present in primary cultures of adipose stromal cells, we have consistently also observed dehydrogenase activity (21). Studies are required to analyze 11βHSD1 expression and the set-point of F to E conversion in adipose tissue samples from obese and nonobese individuals to clarify whether the reduction in 11βHSD1 activity observed in our *in vivo* study is reflected *in vitro* within adipose tissue. Even so, it has been suggested that inhibition of hepatic 11βHSD1 activity may improve insulin sensitivity by lowering hepatic glucose output (43). Many of our obese patients demonstrated features of the so-called metabolic syndrome, with central obesity, insulin resistance, and higher lipid levels and blood pressure compared with lean controls, but nevertheless already had reduced hepatic 11βHSD1 activity. The rationale that further inhibition of 11βHSD1 activity may be of therapeutic benefit in this group should be reevaluated.

In summary, we have demonstrated striking differences in F metabolism in patients with obesity. The set-point in the interconversion between F and E is shifted toward E, and this occurs because of inhibition of 11βHSD1 in the setting of unaltered activity of 11βHSD2. Altered 11βHSD1 activity cannot be explained by differences in insulin action or thyroid hormone status, but is closely related to body fat distribution, with impaired E to F conversion seen in patients with android or central obesity independent of sex. These data may explain the reported increase in the F MCR seen in obesity, but cast new doubts on the primary role of 11βHSD1 expression in the pathogenesis of obesity and insulin resistance.

Acknowledgments

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