Glucocorticoid Metabolism and Adrenocortical Reactivity to ACTH in Myotonic Dystrophy

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Dysfunction of the hypothalamic-pituitary-adrenal axis might contribute to metabolic disturbances frequently encountered in myotonic dystrophy. We hypothesized that abnormal adrenocortical sensitivity to ACTH and/or glucocorticoid metabolism could be important in myotonic dystrophy.

We assessed diurnal rhythmicity of saliva cortisol, adrenocortical reactivity by a low-dose (1 μg) Synacthen test, and glucocorticoid metabolism in blood and urine in 42 myotonic dystrophy patients (22 males) and 50 controls (27 males). CTG triplet repeat expansions were quantified by Southern blot.

Diurnal rhythmicity of saliva cortisol was flattened in both men and women with myotonic dystrophy, with significantly increased afternoon/evening levels \((P < 0.013)\). The cortisol response to ACTH was associated with increased (CTG)\(_n\) expansions in myotonic dystrophy men and women \((P < 0.001)\). Male myotonic dystrophy patients also had increased activation of cortisol from cortisone by 11β-hydroxysteroid dehydrogenase type 1. Both men and women with myotonic dystrophy had an increased 5α/5β-reductase ratio \((P < 0.05\) and \(P < 0.01\), respectively). Cortisol metabolites were related to the genetic defect in myotonic dystrophy men \((P < 0.05)\), whereas ratios reflecting 11β-hydroxysteroid dehydrogenase type 1 activity in myotonic dystrophy women were positively associated with obesity \((P < 0.05)\).

Increased 11β-hydroxysteroid dehydrogenase type 1 activity and adrenocortical reactivity to ACTH are related to the genetic defect in myotonic dystrophy men, whereas abnormal glucocorticoid metabolism is associated with alterations in body composition in female myotonic dystrophy patients. These disturbances may explain altered circulating cortisol levels and contribute to features of the metabolic syndrome in myotonic dystrophy. \(J\) Clin Endocrinol Metab \(86: 4276–4283, 2001\)

MYOTONIC DYSTROPHY (DM1) is the most common inherited form of muscle dystrophy among adults, associated with muscle atrophy and the characteristic myotonia (1). The genetic defect causing DM1 is an expansion of a CTG triplet repeat at chromosome 19, encoding a protein kinase named myotonic dystrophy protein kinase (2). The number of CTG repeat expansions has not, to our knowledge, been associated with clinical features, notably cognitive dysfunction and male hypogonadism (3–5).

Features of the metabolic syndrome, including insulin resistance and hypertriglyceridemia, in conjunction with hyperinsulinemia and increased fat mass, are present in DM1 (1, 6–9). Abnormal regulation of the hypothalamic-pituitary-adrenal (HPA) axis has been suggested to be associated with these metabolic abnormalities (10). Earlier studies in DM1 patients show multiple abnormalities of the HPA axis, including an increased ACTH response to CRH-mediated stimuli (11–14). Recently, we have reported increased median 24-h cortisol levels with a concomitant increase in proinflammatory cytokines in DM1 (15).

An enhanced adrenal responsiveness to ACTH stimulation could contribute to increased HPA axis activity, but earlier studies of adrenal responsiveness in DM1 patients have yielded conflicting results (11, 16–21). Most studies suffer from methodological weaknesses such as a small number of patients, lack of controls, supraphysiological doses, and/or im administration of ACTH (Synacthen), and almost exclusively measurements of urinary 17-hydroxycorticosteroids rather than plasma cortisol. Whether an increased sensitivity of the adrenal cortex to “physiological” ACTH stimulation is present in DM1 has not, to our knowledge, been studied.

Alternatively, altered circulating cortisol levels in DM1 may reflect abnormal metabolism of glucocorticoids. Glucocorticoids are metabolized by several enzymes, including irreversible inactivation by A-ring reductases (5α- and 5β-reductases) and reversible interconversion between active cortisol and inactive cortisone by 11β-hydroxysteroid dehydrogenases (11βHSDs) (Fig. 1). Alterations in peripheral metabolism of glucocorticoids have been proposed to influence cortisol secretion and circulating levels in other syndromes including obesity (22, 23).

Our hypothesis was that an increased sensitivity of the adrenal cortex and/or abnormal glucocorticoid metabolism could contribute to the disturbed regulation of cortisol in DM1. To evaluate this hypothesis, we assessed 1) diurnal rhythmicity of cortisol in saliva, 2) reactivity of the adrenal cortex by a low-dose Synacthen test, and 3) glucocorticoid metabolism and adrenocortical reactivity to ACTH in myotonic dystrophy.

Abbreviations: A4, 4-Androsten-3,17-dione; BIA, bioelectrical impedance analysis; BMI, body mass index; CCR, centered cumulative response; DHEAS, dehydroepiandrosterone sulfate; DM1, myotonic dystrophy; HPA, hypothalamic-pituitary-adrenal; 11βHSD, 11β-hydroxysteroid dehydrogenase; 17 OH, 17α-hydroxyprogesterone; THE, tetrahydrocortisone; THF, tetrahydrocortisol.
metabolism and production in blood and urine in DM1 patients. The influence of gender, body composition, and the genetic defect was considered.

Materials and Methods

Subjects

Clinical data of the subjects are summarized in Table 1. Twenty-two men and 20 women with adult onset DM1 were recruited from the Dystrophia Myotonica Center in Boden, northern Sweden, where the prevalence of the disease is exceptionally high (24). All patients included had clinically overt myotonia and muscular dystrophy. The diagnoses were based on genetic analyses. Three male and 10 female patients were smokers, and 1 patient used snuff. Twenty-seven male and 23 female controls were recruited from healthy volunteers. Two female controls were smokers, two female and three male controls used snuff, and one male and one female control both smoked and used snuff.

Five of the DM1 women were on estrogen replacement therapy, and one had a gestagen implant. Except for this, none of the patients, or controls, was taking glucocorticoids or any other relevant medication; had clinical or laboratory signs of endocrinological dysfunction (including diabetes mellitus and thyroid disease), cardiac failure, renal or hepatic insufficiency, or infection or inflammation; and none was hospitalized at the time of the study. Furthermore, none of the patients, or controls, had a diagnosis or any symptoms of sleep apnea.

This study was approved by the regional ethical committee, and all participants had given their informed consent to participate.

Sampling and measurements

All participants collected urine during 24 h before the blood sampling. Saliva samples were collected at 1100, 1600, 2200, and 0700 h. In participants who had given their informed consent to participate.

At 1000 h the subjects took 25 mg cortisol acetate (Cortone) orally, and blood samples for analysis of cortisol were collected every 15 min for 2 h.

Body composition was measured by bioelectrical impedance analysis (BIA; Akern-RJL Systems BIA 101, EL-DOT K/S, Fredriksvaer, Denmark). The BIA failed to measure seven patients due to too high resistance (>999 ohm). One patient denied to undergo BIA measurements.

Analytical methods

Saliva concentrations of cortisol were determined in untreated samples by RIA using commercial kits obtained from Orion Diagnostica (Esbo, Finland). Serum cortisol, dehydroepiandrosterone sulfate (DHEAS), T, 17α-hydroxyprogesterone (17 OHP), and androstenedione (A4) concentrations were analyzed by immunoassays from Diagnostics Products (Los Angeles, CA) and INCSTAR Corp. (Stillwater, MN). Serum insulin concentrations were analyzed by an immunossay from Abbott Diagnostics (Abbott Park, IL).

Urinary cortisol, cortisone, and their metabolites were measured by gas chromatography and electron impact mass spectometry following Sep-Pak C18 extraction, hydrolysis with β-glucuronidase, and formation of methoxy-trimethylsilyl derivative, as described previously (26). Epi-cortisol and epi-tetrahydrocortisol were used as internal standards that were added to samples before extraction. Peaks of interest were quantified by the ratio of (area under the peak)/(area under internal standard peak). Ratios were compared against standard curves for each steroid included in every assay batch.

Detection limits were: saliva cortisol, 0.19 nmol/liter; serum cortisol, 7 nmol/liter; A4, 0.4 nmol/liter; 17 OHP, 0.2 nmol/liter; DHEAS, 0.05 µmol/liter; T, 0.2 nmol/liter; insulin, 1.0 mU/liter; urine steroids, 1 µg/liter.

Genetic analyses

Genomic DNA was prepared from blood collected in EDTA tubes according to standard procedures and digested with EcoRI or PstI according to the manufacturer’s instructions. Southern blotting and hybridizations were performed with standard methodology (27). The probe used was p110myx6 (2), a 1.4-kb fragment that flank the expanded region of the myotonic dystrophy protein kinase gene.

The allele sizes were calculated with the computer program DNAfrag, version 3.03.

Data interpretation

The HPA axis was evaluated by several indices: 1) diurnal variation of salivary cortisol; 2) stimulation of cortisol release by exogenous ACTH; and 3) cortisol production rate via estimation of total cortisol metabolite excretion [i.e. the sum of the daily excretion of the principal urinary metabolites of cortisol and cortisone: 5β-tetrahydrocortisol (β-THF), 5α-tetrahydrocortisol (α-THF), tetrahydrocortisone (THE), α- and β-cortols, and α- and β-cortolones (28)].

Metabolism of glucocorticoids was estimated by: 1) ratios of urinary

TABLE 1. Characterization of 42 DM1 patients and 50 healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>DM1 patients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Number (n)</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>Postmenopausal (n)</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>42.0</td>
<td>24.2–56.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.2</td>
<td>21.5–30.1</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>22.8</td>
<td>17.0–30.6</td>
</tr>
<tr>
<td>WHR (cm)</td>
<td>0.90</td>
<td>0.80–1.1</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>91.0</td>
<td>76.8–107.6</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>129.0</td>
<td>109.2–168.1</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>81</td>
<td>70.4–94.8</td>
</tr>
<tr>
<td>Insulin (mU/liter)</td>
<td>6.8</td>
<td>3.0–11.4</td>
</tr>
<tr>
<td>Glucose (mmol/liter)</td>
<td>4.9</td>
<td>4.2–5.6</td>
</tr>
<tr>
<td>T (nmol/liter)</td>
<td>15.7</td>
<td>10.9–21.5</td>
</tr>
</tbody>
</table>

Values are given as medians and 10th and 90th percentiles. WHR, Waist to hip ratio; BP, blood pressure.

A P < 0.001, B P < 0.01, and C P < 0.05 compared with controls of the same gender.
FIG. 2. Serum cortisol levels after oral intake of 25 mg cortisone acetate in: A, healthy men (□, n = 27) and healthy women (○, n = 23) (CCR, P < 0.001); B, male DM1 patients (■, n = 22) and male controls (□, n = 27) (Δ60 min, P < 0.05, Δmaximum increase; CCR, P < 0.01 for both); C, male DM1 patients with long (●, n = 11) and short (▲, n = 11) CTG repeat expansions (more or less than 679 CTG repeat expansions) and in male controls (□, n = 27) (Δ60 min, Δmaximum increase; CCR, P < 0.01 for all; long repeats vs. controls); D, female DM1 patients (●, n = 18) and female controls (○, n = 23). a, P < 0.0055, b, P < 0.0055 (long repeats vs. controls) (median levels; Bonferroni correction for repeated analyses).

**TABLE 2.** Urinary glucocorticoid metabolite excretion and ratios

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>DM1 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n = 27)</td>
<td>Women (n = 23)</td>
</tr>
<tr>
<td>Total glucocorticoid</td>
<td>12060</td>
<td>6716–32750</td>
</tr>
<tr>
<td>metabolite excretion (µg/24 h)</td>
<td>8230&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4156–18698</td>
</tr>
<tr>
<td>Cortisol/cortisone ratio</td>
<td>1.0</td>
<td>0.57–2.1</td>
</tr>
<tr>
<td>α-THF/β-THF ratio</td>
<td>1.7</td>
<td>0.81–2.9</td>
</tr>
<tr>
<td>THFs/THE ratio</td>
<td>1.9</td>
<td>0.86–4.6</td>
</tr>
</tbody>
</table>

Values are given as median and 10th and 90th percentiles.
<sup>a</sup> P < 0.01 and <sup>b</sup> P < 0.05 vs. males in the same study group.
<sup>c</sup> P < 0.05 and <sup>d</sup> P < 0.01 vs. controls of the same gender.
metabolites of cortisol, from which 11βHSD activities are reflected in the (α-THF + β-THF)/THE ratio, and the balance of 5α and 5β reductase activities are reflected in the α-THF/β-THF ratio; 2) the accumulation of cortisol in peripheral serum following oral administration of cortisone, which predominantly reflects hepatic 11βHSD1 activity (29, 30).

**Statistical analyses**

All statistics were performed using a commercial computer program, SPSS (SPSS, Inc., Chicago, IL). We used Spearman's rank correlation test for correlation analyses and Mann-Whitney U test exact P value for comparisons between groups. As post hoc test for individual time points in tests with repeated measurements we used the Mann-Whitney U test with Bonferroni correction for relevant time points.

To adjust for different baselines when comparing responses in the Synacthen and the conversion tests, we used the centered cumulative response [CCR = (area under the curve) – (baseline level × total minutes of sampling)].

For subgroup analyses we divided DM1 patients into two groups according to the number of CTG repeats, using the median as cut-off.

In cases where the hormone level was below the detection limit, the value was set to half the detection limit for statistical calculations. A P value of less than 0.05 was considered significant.

**Results**

**CTG triplet repeat expansions**

The median number of CTG triplet repeat expansions in the entire group was 679 and was used as cut-off for subgroup analyses. Median CTG repeat length was for men 666 (409–1168; 10th and 90th percentiles, respectively) and for women 691 (71–1100).

**Gender differences**

Serum cortisol levels at all sampling times after cortisone intake, and accordingly the area under the curve response, were higher in female controls compared with male controls (Fig. 2A). Female controls also had significantly lower total urinary glucocorticoid metabolite excretion (Table 2) and lower urinary levels of α-THF, β-THF, and THE than male controls (P < 0.001, P < 0.001, and P < 0.05, respectively).

There were no other gender differences in controls or patients. Given these differences between men and women, all data were analyzed separately for each gender group.

**HPA axis**

Total urinary glucocorticoid metabolite excretion did not differ significantly between male or female patients and controls (Table 2). In DM1 men, diurnal rhythmicity of saliva cortisol was abnormal with increased levels from noon onward (Fig. 3A) and increased median 24-h levels compared with male controls (P < 0.01).

In the subgroup of nine male patients and eight male controls who participated in the nocturnal sampling, median 24-h levels of cortisol were increased in DM1 patients (P < 0.0125, P < 0.01, and P < 0.01, respectively).
Patients with a large number of CTG triplet repeat expansions (i.e. above median) had a flattened diurnal rhythm and increased median 24-h levels compared with controls ($P < 0.01$) and to patients with fewer CTG repeats ($P < 0.05$) (Fig. 3C).

In DM1 women, the diurnal rhythmicity of cortisol was abnormal with increased late evening cortisol levels (Fig. 3B). Median 24-h levels were, however, not increased, and there were no relationships to the number of CTG triplet repeat expansions.

**Adrenocortical sensitivity to ACTH**

There were no significant differences between men with DM1 and healthy men regarding adrenal reactivity to ACTH. However, the response to iv Synacthen was significantly increased in males with long CTG repeat expansions compared with male controls and to DM1 males with short CTG repeat expansions (Fig. 4A). In DM1 men, increasing number of CTG repeats correlated significantly to increased serum cortisol levels at 30 and 40 min after Synacthen administration ($r_\alpha = 0.58$ and $r_\beta = 0.60$; $P < 0.01$).

There was no difference in cortisol response to ACTH between female DM1 patients and female controls (Fig. 4B). However, serum cortisol levels at 30 min after Synacthen administration correlated significantly and positively to increasing number of CTG triplet repeat expansions ($r_\alpha = 0.62$; $P < 0.01$), whereas the area under curve response to Synacthen correlated to body mass index (BMI) ($r_\alpha = 0.47$; $P < 0.05$) in DM1 women.

**Glucocorticoid metabolism**

The generation of cortisol from cortisone was markedly increased in DM1 men (Fig. 2B). When divided into two groups based on CTG repeat numbers, there was a significant increase in cortisone→cortisol conversion in men with long CTG repeats vs. controls (Fig. 2C). Conversion of cortisone to cortisol did not differ between female DM1 patients and female controls (Fig. 2D).

Urinary glucocorticoid metabolite excretion and metabolite ratios are summarized in Table 2 and Fig. 5 whereas correlations between BMI/insulin and urinary glucocorticoid metabolite ratios are shown in Table 3.

Although total glucocorticoid metabolite excretion was not different from controls, relative excretion of 5β-reduced metabolites (5β-THF) was lower than excretion of 5α-reduced metabolites (α-THF) in both men and women with DM1 (Table 2). There were trends toward positive associations between 5α/5β-THF ratios and obesity or hyperinsulinemia, but these did not reach statistical significance. Urinary ratios reflecting 11β-HSD activities (cortisol/cortisone and THFs/THE ratios) were not different between DM1 patients, and controls but were positively associated with BMI and fasting insulin levels in DM1 women (Table 3).

The number of CTG repeats correlated negatively to α-THF ($r_\alpha = -0.55$; $P = 0.01$) and to β-THF ($r_\beta = -0.52$; $P < 0.05$) among male patients.
There were no significant correlations between cortisol data and adrenal/gonadal androgens (androstenedione, DHEAS, 17 OHP, or T) in DM1 patients.

**Body composition**

Fat mass was significantly increased in DM1 patients. There were no significant differences in BMI or body fat mass between patients with long and short CTG repeat expansions.

No association between urinary glucocorticoid metabolites or adrenocortical reactivity, on one hand, and body fat mass, on the other, was seen in DM1 males, except for the E/THE ratio (rs = -0.54; P < 0.05). In females, the pattern of correlations paralleled those for BMI in large.

In multiple regression analyses, body fat mass was an independent predictor of urinary F/E levels; otherwise no significant associations were found between glucocorticoid measures and body fat mass when gender, age, and disease *per se* were included in the multivariate models.

**Discussion**

This study of a large cohort of male and female DM1 patients contributes to the understanding of previous reports on disturbed diurnal rhythmicity and increased circulating 24-h levels of cortisol in male DM1 patients (14, 15). The main findings of this study are an association between the reactivity of the adrenal cortex to ACTH and the number of CTG repeat expansions, together with alterations in glucocorticoid metabolism in DM1, including an increased reactivation of cortisone to cortisol. These abnormalities are present mainly in males with DM1.

Previous studies have documented alterations in hypothalamic control of ACTH secretion in DM1 (12, 13, 31). In the current study, we show, using a physiological dose of ACTH,
that adrenal responsiveness is increased in males with long CTG repeat expansions. In line with results from a recent study showing an unaltered cortisol response to naloxone (stimulating hypothalamic CRH secretion) in DM1 women (31), we found no difference between our DM1 women and healthy females.

We found no increase in 24-h total cortisol metabolite excretion in urine, suggesting that cortisol production may not be increased and the elevated circulating cortisol concentrations in DM1 may reflect impaired metabolism of cortisol.

Glucocorticoid metabolism and clearance has earlier been reported mainly normal in DM1 (17, 18, 20, 21, 32), based on analyses of either urinary 17-hydroxycorticosteroids or 17-ketogenic steroids, methods that also measure noncortisol metabolites (33). Using specific gas chromatography and electron impact mass spectrometry assays, we found evidence for altered A-ring reduction of cortisol in both men and women with DM1. This would be consistent with impaired 5β-reductase activity in DM1. The observation is complicated, however, by the previous findings in men and women that idiopathic obesity is associated with enhanced 5α-reductase activity (23, 34). DM1 patients have a greater proportion of body fat, which may have contributed to the changes in urine metabolite excretion. However, in multiple regression analyses, only the urinary F/E ratio was independently associated with increased fat mass. Furthermore, we can not exclude differences in other metabolic pathways, such as 6β-hydroxylation or side-chain cleavage.

An alternative explanation for impaired peripheral clearance of cortisol in DM1 men is the increased reactivation of cortisone to cortisol that we show here for the first time. Enhanced regeneration of the inactive glucocorticoid cortisone to the active compound cortisol suggests an increased 11βHSD1 activity in male DM1 patients. Increased 11βHSD1 activity has been postulated to be important for the development of insulin resistance by increasing cortisol concentrations and gluconeogenesis in the liver (35), and it has been shown that knockout of this enzyme in mice impairs gluconeogenesis, thereby lowering circulating glucose levels (36). However, 11βHSD1 activity was recently reported to decrease in the liver (i.e. decreased conversion of cortisone to cortisol) with increasing BMI (37, 38). In contrast, fat cells have been suggested as an important target for reactivation of cortisone (38, 39).

Our study emphasizes gender differences in 11βHSD1 activity and suggests hormonal regulation of this enzyme. Possible hormonal mediators of 11βHSD1 activity include gonadal/adrenal androgens, insulin, and GH (40–45). No associations to circulating levels of androgens or insulin were found in the present study, but these hormones could explain the gender-specific differences in 11βHSD1 activity, which was lower in control men than in control women and DM1 patients of either gender. The genetic defect of DM1 may indirectly, through one of these hormonal regulators, account for “feminization” of 11βHSD1 activity in DM1 men. In line with this, gender-specific differences have recently been shown in the expression of genes from the DM1 locus (46). Other factors seem to affect 11βHSD1 activity in women, including a more potent effect of obesity, reflected in the relationship between obesity/hyperinsulinemia and urinary cortisol/cortisone metabolite ratios shown in Table 3.

The activity of 11βHSD1 is also influenced by cytokines, including TNF-α and IL-1β (47). Circulating 24-h TNF-α levels are increased in DM1 (15) and may increase 11βHSD1 activity in the liver and fat cells (48). Whether fat cell production of TNF-α is increased in DM1 remains to be studied. TNF-α production might, thus, constitute a link between the profound insulin resistance, increased fat mass, and increased tissue-specific glucocorticoid concentrations in DM1 patients.

In conclusion, adrenal cortex reactivity to ACTH and enhanced 11βHSD1 activity in DM1 are related to the number of CTG repeat expansions in men. In DM1 women, these abnormalities are less striking and altered glucocorticoid metabolism is associated with body composition. Increased concentrations of cortisol in the circulation and in key target tissues including liver and fat may contribute to the features of the metabolic syndrome in DM1, notably insulin resistance and hypertriglyceridaemia.

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