Urinary Cortisol and Cortisol Metabolite Excretion in Chronic Fatigue Syndrome

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Objectives: Reduced basal hypothalamic–pituitary–adrenal (HPA) axis output in chronic fatigue syndrome (CFS) has been inferred from low cortisol levels in blood, saliva, and urine in some studies. Because > 95% of cortisol is metabolized before excretion, we assessed cortisol output by assay of both cortisol metabolites and free cortisol in 24-hour urine collections and also investigated sex differences in these between CFS and control groups. **Method:** We calculated total urinary cortisol metabolites (TCM) and cortisol metabolite ratios from individual steroid data in 40 patients (20 males and 20 females) with CFS who were free of medication or comorbid psychiatric disorder likely to influence the HPA axis. Results were compared with those of 40 healthy volunteers (20 males and 20 females) well matched for age and body mass index. Data for free cortisol was obtained on 28 of the patients and 27 of the controls. **Results:** The mean of TCM and cortisol metabolite ratios was not significantly different between patients and controls for either sex ($p > .05$ for all parameters). Previously established sex differences were confirmed in our controls and were found to be similar in CFS for TCM and the ratios 11OH/11OXO, 5α/5β THF, and 20OH/20OXO (see text) ($p < .005$, $p < .05$, $p < .05$, and $p < .005$, respectively). Urinary free cortisol values were numerically (but not statistically) lower in patients with CFS than controls, and correlated inversely with fatigue levels in patients. **Conclusion:** The finding of normal urinary cortisol metabolite excretion in patients with CFS is at variance with earlier reports that CFS is a hypocortisolemic state. If serum and saliva cortisol levels are lower in CFS, this would suggest that metabolic clearance of cortisol is faster in patients with CFS than controls. This study also demonstrates that sex differences must be taken into account when interpreting results in patients with CFS. **Key words:** chronic fatigue syndrome, cortisol metabolites, cortisol metabolite ratios, excretion, sex differences, hypoadrenalism.

HPA = hypothalamic–pituitary–adrenal; **UFC** = urinary free cortisol; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; **CDC** = Centers for Disease Control and Prevention; **CBG** = cortisol binding globulin; **11β HSD** = 11β hydroxysteroid dehydrogenase activity; **TCM** = total urinary cortisol metabolites; **THE** = tetrahydrocortisone; **THF** = tetrahydrocortisol; **5αTHF** = allo-tetrahydrocortisol; **α-Cort** = α-cortolone; **β&β** = β-cortolone and β-cortol; **α-cortol** = α-cortol.

INTRODUCTION

Chronic fatigue syndrome (CFS) is a controversial condition of uncertain etiology that is characterized by debilitating fatigue and associated with myalgia, sleep disturbance, cognitive symptoms, anxiety, and low mood. Some of these symptoms are shared with Addison's and Cushing's diseases (1), which initially led to the suggestion of an abnormality in the hypothalamic–pituitary–adrenal axis (HPA) in patients with CFS. Reduced HPA axis activity in CFS is indicated by various approaches, but not all studies permit this conclusion. Demitrack et al. (2) and Cleare et al. (3) demonstrated low basal serum cortisol levels based on evening and morning samples, respectively. Because there is a circadian variation of serum cortisol, careful attention to timing of collection is required, and there is a risk that differing sleep–wake cycles in CFS and control groups might render comparisons invalid.

Salivary concentrations of cortisol may be a more reliable indicator of HPA activity (4), and this approach facilitates multiple sampling. The concentration in saliva reflects the free fraction in blood but is approximately 50% of blood levels as a result of 11β-hydrosteroid dehydrogenase (11β-HSD) activity in the parotid gland (5). Findings in CFS include lower levels in the evening (6) and a blunted early morning rise (7). Our group recently found reduced salivary free cortisol in CFS throughout a 15-hour daytime period (8) with no phase difference, whereas others using less frequent sampling found no change (9,10).

Urinary free cortisol (UFC) in 24-hour samples has been widely used to assess basal cortisol secretion and has the theoretical advantage of being unaffected by possible cortisol circadian rhythm differences. Of six studies to date, four have reported reductions in CFS (11). However, UFC may provide an unreliable indicator of HPA axis activity, because assays have a large variability at the lower part of the analytical range (12), are subject to interference (13), and UFC represents only 2% to 3% of the daily adrenal cortisol output.

A more promising, novel approach is the measurement of 24-hour urinary total cortisol metabolite (TCM) excretion. The principal metabolites of cortisol, generated primarily in the liver, account for >95% of cortisol excretion. This potentially offers a more sensitive means of detecting changes in rates of cortisol secretion than UFC and lessens the possibility of confusion resulting from differences in circadian rhythm of cortisol secretion or metabolism (14). It has enabled, for example, detection of subtle reduction in cortisol production in asthmatics treated with inhaled glucocorticoid (15). Our group has previously noted an increase of TCM in patients with major depression (16), a finding that is consistent with many other studies of the HPA axis in this disorder.

Cortisol metabolism begins with reduction of the A ring to form tetrahydrocortisol and allo-tetrahydrocortisol through action of β- and α-reductases followed by 3α- and 3β-hydroxy-

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steroid dehydrogenases (3-HSDs). Cortisone, produced from cortisol through the action of 11β-HSD, similarly gives rise through 5β reduction to tetrahydrocortisone. Further reduction of tetrahydrocortisol and tetrahydrocortisone by 20α- and 20β-HSD results in the formation of α and β cortols and α and β cortolones, respectively. These metabolites are excreted in the urine predominantly as glucosiduronates with smaller amounts as sulfates (17).

This study was designed firstly to compare this approach with UFC in 24-hour urine collections from patients with CFS selected by rigorous criteria; second, to provide a more reliable test of the hypothesis that there is reduced activity of the HPA axis in CFS compared with healthy volunteers; third, to investigate possible abnormalities in cortisol metabolism in patients with CFS; and finally, to investigate whether the gender differences in urinary cortisol metabolites we have previously established in normal volunteers (14) are present in CFS.

MATERIALS AND METHODS

Subjects

Forty adult patients with CFS (20 males and 20 females) were recruited through the specialist CFS clinic at King's College Hospital (KCH). All patients met the 1994 Centers for Disease Control and Prevention (CDC) criteria for diagnosis of CFS (18) and were interviewed using the semistructured format of Sharpe et al. (19). All patients were interviewed by two psychiatrists (A.C. and S.W.) at KCH to check for the presence of any exclusionary psychiatric disorder as per the CDC criteria. As well as this categorical delineation, we obtained a dimensional measure of the severity of fatigue using the Chalder fatigue scale (20), scored using the Likert method, to give a range of 0 to 33. Further inclusion criteria stipulated the age range 25 to 55 years and the absence of any history of neurologic, endocrine, or cardiovascular disorders. To obtain as accurate a measure of HPA axis activity as possible, we tested only patients who were not taking any psychotropic medication or other medication that might affect the HPA axis and had been free of such medication for at least 2 months. Although the modifications in 1994 of the original CDC diagnostic criteria permitted inclusion of patients with comorbid major depression or anxiety disorders, patients with a current major depressive episode or anxiety disorder as defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria were excluded from this study because of their potential impact on the HPA axis.

Forty healthy subjects (20 males and 20 females) were recruited among the staff and student body at KCH and were well matched for age, sex, and body mass index (BMI) with the patients with CFS. They were all assessed by a research nurse to be in good health without any serious medical illness or history of psychiatric disorder. All had normal dietary habits, taking breakfast, lunch, and dinner at about the same time. All subjects habitually went to bed between 11:30 PM and 12:30 AM and got up between 7:00 AM and 8:00 AM. All subjects gave written, informed consent and ethical approval for the study was obtained from the local research ethics committee. Urine samples for controls and CFS subjects were based on collections from January 1997 to January 2001.

Urinary Collections

Subjects were provided with a standard container for 24-hour urine collection and given clear instructions on how to complete the collection. They were told to start each collection at 9:00 AM, having emptied their bladder just before 9:00 AM. Thereafter, they were to collect all the urine they passed into the bottle, and at 9:00 AM the next day, they were to empty their bladder into the bottle to complete the collection. On receipt of the specimen at the laboratory, the volume was noted, and after vigorous shaking, two 20-mL aliquots were taken for freezing at −40°C before subsequent analysis.

Urinary Free Cortisol Measurements

Urine cortisol was extracted into dichloromethane and dried extracts were analyzed by radioimmunoassay using Guildhay sheep anticortisol antiserum (HPS 631-1G) and cortisol-3CMO-histamine-[125-I] as tracer (21). Interassay CV% was less than 12% for cortisol concentrations over 50 nmol/L.

Cortisol Metabolite Measurements

Urinary steroid profile analysis was carried out by high-resolution gas chromatography of methyloxime–trimethylsilyl ether (MO-TMS) derivatives as previously described (22). The intra- and interassay CVs were 7.1% to 21.1% and 11.2% to 21.9%, respectively, for individual metabolites and 8.8% and 13.6%, respectively, for TCM. The major cortisol metabolites were assayed and calculated as μg/24 hours. Derived sums were as previously reported (22). These were: TCM, sum (tetrahydrocortisone [THE] + tetrahydrocortisol [THF] + allo-tetrahydrocortisol [5αTHF] + α-cortolone [α-cort] + β-cortolone and β-cortol [$\beta\&\beta$] + α-cortol [α-Cortol]; 11-OH/11-OXO, [THF + allo-THF + $\beta\&\beta$/2] + α-cortol)/(THE + α-cortolone + $\beta\&\beta$/2). 5α/5β THF, 5αTHF/THF; 20OH/20OXO: (α-cortol + $\beta\&\beta$ + α-cortolone))/(THE + THF + 5αTHF). The ratio of 11OH/11OXO was calculated as an index of total net 11β-hydroxysteroid dehydrogenase activity. The ratio 5α/5β THF was calculated as an index of 5α versus 5β reduction and 20OH/20OXO as an index of net 20-hydroxysteroid dehydrogenase activity.

Statistical Analyses

Comparisons were made by nonparametric test (Mann-Whitney test) (using SPSS for Windows version 11), because both controls and CFS subjects showed significant deviations from a normal distribution. Results are given using median and interquartile ranges. The coefficient of correlation between fatigue score and steroid levels was calculated by the general linear regression method.

RESULTS

There was no difference between mean age and BMI between patients with CFS and controls (mean age [years], 34.0 ± 1.6 and 32.6 ± 1.5, $p = .30$) and BMI (kg/m^2) (23.6 ± 0.7 and 23.7 ± 0.7 respectively, $p = .8$). The CFS subjects reported high mean scores for fatigue on the Chalder fatigue scale compared with controls (24.4 ± 2.9; 7.6 ± 2.3, $p < .0001$). The mean duration of illness for patients with CFS was 2.1 ± 0.1 years.

Cortisol Metabolites

TCM excretion in patients was not different from controls for either males or females (Table 1). None of the cortisol metabolite ratios were significantly different in either males or females with CFS compared with controls. There were significant sex differences for TCM and all the cortisol metabolite ratios in both controls and patients with CFS (Table 1).

Urinary Free Cortisol

For technical reasons, urinary free cortisol data were only available for 28 patients and 27 controls. The median UFC (and interquartile range) was 57.5 (37.8–97.3) nmol/24 hours in CFS and 76 (55–107) nmol/24 hours in controls (Mann-Whitney U = 297, $p = .17$). Values for males and females are shown in Table 1. Although these were numerically lower in patients with CFS than controls, there was no statistically significant difference in male, female, or the combined group comparisons. Values were higher in males than females but this only reached significance in controls.

TABLE 1. Excretion of Urinary Cortisol (UFC) and Cortisol Metabolites (TCM) and Their Metabolite Ratios for Patients With Chronic Fatigue Syndrome (CFS) and Control Subjects Over 24 Hours

	Controls (n = 40)		Patients With CFS (n = 40)	
	Males (n = 20)[a]	Females (n = 20)[b]	Males (n = 20)[b]	Females (n = 20)[b]
TCM (μg/24h)	7468 (5837–10,410)	3777 (2383–7059)**	8975 (5430–10,928)	4897 (3238–5993)**
11OH/11OXO	0.78 (0.64–0.89)	0.66 (0.60–0.70)*	0.77 (0.66–0.90)	0.72 (0.56–0.81)*
5α/5β THF	0.74 (0.53–1.40)	0.56 (0.39–0.78)*	0.94 (0.73–1.36)	0.67 (0.43–0.98)*
20OH/20OXO	0.29 (0.27–0.34)	0.32 (0.27–0.43)*	0.27 (0.23–0.30)	0.32 (0.27–0.46)**
UFC (nmol/24h)	99 (71–130)	59 (41–78)*	69 (50–107)	51 (29–87)

[a] - except UFC, n = 13;
[b] - except UFC, n = 14.
Values are expressed as median and interquartile ranges in the group. Within each group, asterisks show significant sex differences: * $p < .05$, ** $p < .005$. Between the two groups (CFS vs. controls): $p > .05$ for all parameters.

Correlation With Clinical Measures

There was a significant negative correlation between fatigue score and UFC ($r = -0.55$, $p < .005$), but a negative relationship for fatigue score and TCM did not reach significance ($r = -0.18$, $p = .07$).

DISCUSSION

This study found that neither urinary TCM nor the ratios of cortisol metabolites were different between patients with CFS and the control group. There are no comparable findings in the literature. UFC levels, whereas lower in the CFS group, were also not statistically different but did show a negative correlation with fatigue score. Of six published studies of urinary free cortisol in CFS, four (including those with the largest sample sizes) found a low basal 24-hour UFC (2,23–25), whereas two found no change.

Several causes for the apparent divergence of findings between TCM and UFC may be suggested. First, results for UFC may be subject to interference (13). Higher levels in normals might thus be the result of higher levels of cross-reacting substances. The concentration of cortisol binding globulin (CBG) is higher in CFS (2) and may negatively influence urinary free cortisol excretion.

Second, this sample of patients may not have had the same degree of hypocortisolism as patients in other studies. We have previously suggested this might result from either population differences or because the etiology of the HPA axis dysfunction in CFS is itself multifactorial and variable (4). Nevertheless, in the present study, we used very similar patient selection criteria to our previous studies in which we did find significant reductions in UFC and other indicators of HPA axis dysfunction. Our previous study focusing on UFC had a larger sample, and the difference between patients with CFS and controls was 26.5 nmol/24 hours (24), not dissimilar to that obtained here, which was 20.5 nmol/24 hours for the males and females combined. It is not certain, therefore, whether this sample in fact did not have hypocortisolism or that the degree of hypocortisolism present was too small to be detected statistically given the power of this reduced sample size.

Third, a possible factor of relevance is duration of illness. The duration in our patients was relatively short, at 2.1 years, in comparison to most studies of CFS in the literature. It may be that HPA axis activity is more diminished later in the course of CFS (31). Patients reported by Demitrack et al. (2) had an average duration of 7.2 years associated with reduced basal serum cortisol, whereas there was no difference in the basal cortisol levels in patients reported by Young et al. (9) and Scott et al. (32,33) with a mean duration of illness of 2.5 years and 4.8 years, respectively. Duration of illness has been correlated with the degree of impairment in the adrenocorticotrophic hormone response to the insulin stress test (34). The large cohort studies necessary to test this theory prospectively have not yet been undertaken.

Fourth, patients with CFS judged to be hypocortisolemic by single blood or saliva assays may have a different cortisol rhythm than normals so that differences might result when serum or saliva cortisol values are compared at specified times. There are inconsistencies in the literature on the circadian rhythm in patients with CFS based on serial samples. There are reports of a flattened circadian rhythm in CFS (26,35), whereas other studies, including one of ours, based on saliva, have not found a significant change in cortisol rhythm (8,9,36). Because our data on UFC and TCM were obtained in the same 24-hour collections, circadian rhythm considerations cannot explain our divergent findings.

Lastly, it might be that patients with CFS clear cortisol faster than controls. No direct measures of cortisol clearance have been undertaken in CFS to date. An increase in cortisol metabolite levels coupled with an increased metabolic clearance rate of cortisol has been demonstrated in patients with obesity (27) and apparent cortisone reductase deficiency (28), whereas our group found high levels of TCM in patients with polycystic ovary syndrome (29). There was a decrease in the 11OH/11OXO ratio, and we proposed that increased cortisol oxidation had resulted in enhancement of the cortisol metabolic clearance rate. Others have proposed an increase of 5α-reduction to explain this phenomenon (30). We found no such alterations in cortisol metabolism in this study, but, as noted, free cortisol in urine represents only 2% to 3% of the

urinary cortisol metabolites (14) so that a metabolic shift too small to detect by our methodology might still be sufficient to decrease UFC significantly. The ratio of 11OH/11OXO represents an index of 11β-hydroxysteroid dehydrogenase (11β-HSD) activity: the type I is predominant in the liver and acts as a reductase (cortisone to cortisol (37)), whereas type II is predominantly renal and acts as a dehydrogenase (cortisol to cortisone (38)). We have found increases of 11OH/11OXO ratio in females but not males with major depression so that the gender difference was abolished (16), whereas Poor et al. (39) found an increase of 11OH/11OXO ratio in both depressed men and women. We have also demonstrated increases in 5α/5β THF ratio in both males and females with major depression (40,41). None of these changes was found in the present group of nondepressed patients with CFS.

Sex differences were present for TCM and for all urinary cortisol metabolite ratios in the controls in line with our previous publication (14) and all these differences were also found in the CFS group. Similarly, published higher values for UFC in normal males (42,43) are supported by our data. Sex differences for UFC in CFS have not been previously examined. A larger sample size might have confirmed a sex difference for the CFS group as well. These findings reinforce the need to be aware that quantification of cortisol and cortisol metabolites in urine collections may be misleading if gender is not taken into account.

Despite the still conflicting results on HPA axis changes in CFS, reports of symptom improvement during glucocorticoid treatment (44,45) suggest that cortisol deficiency plays some part in the symptom profile of CFS. Our finding that patients with higher fatigue scores have lower urinary free cortisol is consistent with this. Mineralocorticoids, on the other hand, do not produce benefit in CFS (46–48).

There are some limitations to this article. We did not use dynamic measures of HPA axis function nor make comparisons with salivary or serum cortisol levels. It may be helpful in the future to take several of these measures concurrently. Regarding the urinary assessments, although we standardized the procedure as much as possible between patients and controls (e.g., time of meals and sleeping pattern), other factors that may affect the HPA axis could not be standardized such as the level of physical activity. The volumes of urine collected were not significantly different between groups, indicating a similar degree of compliance with our instructions. Also, although our sample size of 40 patients with CFS and 40 controls represents one of the largest in the literature on the HPA axis in CFS, our power to detect small differences between groups was obviously limited by this. A preliminary power calculation based on our results suggests that at 5% significance, we had 80% power to detect a medium effect size difference of TCM between groups (i.e., a difference between groups of approximately 2000 μg/24 hours, representing an effect size of approximately 0.6). We would not have been able to detect a difference representing a small effect size between groups. A final issue relates to psychiatric comorbidity. Depression is associated with HPA axis overdrive and hypercortisolism in approximately 50% of cases and because approximately half of patients with CFS have a concurrent depressive illness, comorbid depression might cancel out any hypocortisolism resulting from CFS itself. In our sample, the possibility that depressive symptomatology contributed to an elevation of cortisol level in our patients with CFS appears slight, because none met the criteria for major depression. Many patients with CFS have a history of depression, because this is one of the most consistently identified risk factors for developing CFS (49), and we did not attempt to tease out any contribution of this to the findings in the present study. Although previous depression may confer long-term alterations to the HPA axis, when we compared urinary free cortisol in over 120 patients with CFS, we found no difference between those with and without a psychiatric history (24). Nevertheless, accurate retrospective ascertainment of depression is fraught with difficulty (50).

CONCLUSION

Urinary cortisol metabolite assay provides no new evidence that in CFS, the symptoms of fatigue result from a reduction of cortisol secretion, although hypocortisolemic states are claimed to be common in patients with CFS. Patients with CFS may have a faster clearance of cortisol than controls, but our finding of normal proportions of cortisol metabolites provides no positive support for this. On the other hand, lower free cortisol–the biologically active fraction–is correlated with higher fatigue levels. The present study clearly demonstrates sex differences in cortisol metabolite excretion between CFS males and females, which are similar to those in normal subjects.

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