



## Brief report

# Salivary cortisol output before and after cognitive behavioural therapy for chronic fatigue syndrome

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## Abstract

**Background:** There is evidence that patients with chronic fatigue syndrome (CFS) have mild hypocortisolism. One theory about the aetiology of this hypocortisolism is that it occurs late in the course of CFS via factors such as inactivity, sleep disturbance, chronic stress and deconditioning. We aimed to determine whether therapy aimed at reversing these factors – cognitive behavioural therapy for CFS – could increase cortisol output in CFS.

**Methods:** We measured diurnal salivary cortisol output between 0800 and 2000h before and after 15 sessions (or 6 months) of CBT in 41 patients with CDC-defined CFS attending a specialist, tertiary outpatient clinic.

**Results:** There was a significant clinical response to CBT, and a significant rise in salivary cortisol output after CBT.

**Limitations:** We were unable to control for the passage of time using a non-treated CFS group.

**Conclusions:** Hypocortisolism in CFS is potentially reversible by CBT. Given previous suggestions that lowered cortisol may be a maintaining factor in CFS, CBT offers a potential way to address this.

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**Keywords:** Chronic fatigue syndrome; Myalgic encephalomyelitis; Cognitive behavioural therapy; HPA axis; Cortisol; Neuroendocrinology

## 1. Introduction

Chronic fatigue syndrome (CFS) is probably a multifactorial condition in which psychological and social factors act alongside biological changes (Wessely et al.,

1998). Much biological research has focussed on the hypothalamo-pituitary-adrenal (HPA) axis, with evidence for reduced cortisol output, detectable by sequential salivary samples (Cleare, 2003). Low cortisol may contribute to symptoms since cortisol replacement can ameliorate fatigue and other features of CFS (Cleare et al., 1999; McKenzie et al., 1998).

However, most patients studied have been ill for many years; it is not clear whether HPA-axis disturbances are also present before onset or early in the course of CFS, nor to what extent observed HPA-axis disturbances are secondary to inactivity, sleep disturbance, deconditioning or stress

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(Cleare, 2004). Indeed, it is possible that there is a vicious cycle present in which low levels of cortisol may exacerbate fatigue and other symptoms, leading to a worsening of some of the factors that had initially contributed to lowered cortisol levels.

Cognitive behavioural therapy (CBT) is an effective treatment for CFS (Whiting et al., 2001). The primary aim of therapy is to identify, modify and change factors that may be maintaining symptoms. Therapy is individually tailored; components include changing unhelpful patterns of rest and activity, improving sleep patterns, increasing exercise capacity, identifying unhelpful cognitions about the illness or the coping strategies used, using problem solving techniques to reduce stress, and treating anxiety and depression if present (Wessely et al., 1998).

In this study we hypothesised that hypocortisolism in CFS is at least partly secondary to inactivity, sleep disturbance, deconditioning and perceived stress, and, therefore, that CBT, which aims to reverse these factors, would lead to increased salivary cortisol output.

## 2. Method

### 2.1. Subjects

#### 2.1.1. Subject selection

Patients aged 18–65 were recruited from referrals to the CFS clinic at King's College Hospital, London. Detectable organic illness was excluded by a minimum of physical examination, urinalysis, full blood count, urea and electrolytes, thyroid and liver function tests, 9 a.m. cortisol (to screen for Addison's Disease) and ESR. Patients underwent semi-structured interview for CFS (Sharpe et al., 1997) and were included if they met both international consensus criteria for CFS (Fukuda et al., 1994; Sharpe et al., 1991), did not have fibromyalgia (Wolfe et al., 1990) and were suitable for CBT. Suitability for CBT was judged by the assessing clinician using the framework laid out by Sharpe et al. (1997); essentially the process was to exclude factors that could interfere with CBT (such as untreated severe anxiety or depression, personality disorder or unwillingness to change) and seek patient agreement. DSM-IV psychiatric diagnoses were assessed using the Schedules for Clinical Assessment for Neuropsychiatry (SCAN) (WHO, 1994). Female patients were tested during days 1–7 of their menstrual cycle on both occasions, pregnancy having been excluded.

#### 2.1.2. Medication

All subjects were free from psychotropic medication, steroids, or medication known to affect the HPA axis for at least 2 months prior to endocrine testing.

#### 2.1.3. Sample size

41 patients (26 female) entered the study (mean age 38.4 years (SD 11.3). The mean length of illness at assessment was 57 (SD 48) months. 16/41 patients had a comorbid DSM-IV diagnosis of a current major depressive episode. Table 1 shows other clinical descriptors.

### 2.2. Clinical assessment procedures

Patients: filled out the following instruments before and after CBT.

Fatigue: Chalder Fatigue Scale (Chalder et al., 1993); Psychiatric symptoms: General Health Questionnaire-12 (Goldberg and Blackwell, 1970); Beck Depression Inventory (Beck et al., 1961).

Functional capacity: Medical Outcomes Survey Short Form-36 (Ware and Sherbourne, 1992); Work and Social Adjustment Scale. (Mundt et al., 2002)

Sleep: Pittsburgh Sleep Quality Index (Buysse et al., 1989).

Response to therapy was defined using a therapist-rating of "very much improved" or "much improved" on the clinical global impression improvement (CGI) scale (Guy, 1976) blind to cortisol results.

The institutional ethics committee approved all procedures. After complete description of the study to the subjects, written informed consent was obtained.

### 2.3. Cognitive behavioural therapy

CBT for CFS has been described in detail elsewhere (Wessely et al., 1998). We used experienced therapists and adhered to set protocols (Deale et al., 1997). Standard therapy comprises 12–15 sessions; to standardize procedures, we retested after 6 months or 15 sessions, whichever was sooner.

### 2.4. Salivary cortisol

A detailed protocol for saliva collection is described elsewhere, including precautions taken to avoid false high values (Roberts et al., 2004). Testing was undertaken at home on any normal weekday except Mondays. Samples were taken at 0800h, 1200h, 1600h and 2000h, kept refrigerated overnight and returned by post in the morning. On arrival at the laboratory, they were frozen at  $-20^{\circ}\text{C}$  until assay. After defrosting and centrifuging, cortisol was measured in duplicate using a time-resolved fluoroimmunoassay as described elsewhere (Pariente et al., 2002) except that the rabbit cortisol antibody

Table 1  
Clinical measures before and after CBT

Variable	Before CBT	After CBT	95% CI for difference
<i>Fatigue</i>			
Chalder Fatigue Scale (0–33)	24.8 (6.1)	21.2 (6.2)	2.6–6.7 ( $t=4.6^{***}$ )
Chalder Fatigue Scale (0–11)	11 (4–11)	8.5 (0–11)	N/A ( $z=3.3^{***}$ )
<i>Psychiatric symptoms</i>			
General Health Questionnaire (0–36)	17.7 (7.5)	15.3 (8.0)	0.4–5.5 ( $t=2.4^*$ )
Beck Depression Inventory (0–62)	14.9 (9.1)	12.2 (8.2)	0.8–4.0 ( $t=3.0^{**}$ )
<i>Disability</i>			
SF–36 physical functioning scale (0–100)	39.7 (23.3)	50.7 (24.8)	–17.3 to –6.6 ( $t=-4.5^{***}$ )
SF–36 physical role limitations scale (0–100)	25.8 (33.4)	44.4 (34.3)	–33.4 to –8.7 ( $t=-3.5^{***}$ )
Work and Social Adjustment Scale (0–40)	29.0 (7.8)	25.5 (9.0)	2.3–5.8 ( $t=4.6^{***}$ )
<i>Sleep</i>			
PSQI-global score	7.7 (4.2)	6.8 (4.3)	–0.37–2.0 ( $t=1.4$ )
<i>Clinical global impression</i>			
Very much or much improved (responders)	–	18 (47%)	
Minimally improved	–	13 (34%)	
No change	–	4 (11%)	
Minimally, much or very much worse	–	3 (8%)	
Missing data		3	

Clinical measures in 41 patients with chronic fatigue syndrome before and after cognitive behavioural therapy. Mean values with SD or percentage in parentheses (except Chalder Fatigue Scale 0–11 scoring, where median and range is given). Asterisks represent values significantly improved after CBT by paired  $t$ -test or, for Chalder Fatigue Scale 0–11 scoring, Wilcoxon test ( $*P<0.05$ ;  $**P<0.01$ ;  $***P<0.001$ ).

(product no 2330-5105, batch 21051565; Biogenesis, Poole, UK) and the Europium labelled cortisol were diluted 1/4500 and 1/65 respectively in assay buffer before use. The minimal detectable concentration was about 0.1 nmol/l. The percentage cross-reactivity of the antiserum with other steroids was: prednisolone (28%), 11-deoxycortisol (10%), cortisone and corticosterone (1%). There was none for progesterone, dexamethasone, aldosterone and pregnenolone. All samples of one subject were analyzed in the same run.

Table 2  
Salivary cortisol measures before and after CBT

Measure	Before CBT	After CBT	95% CI for difference
0800–2000h total output (AUC) (nmol/l h)	68.2 (19.6)	79.4 (21.8)	2.6–19.8 ( $t=2.62^*$ )
Mean value (nmol/l)	6.0 (1.7)	6.8 (1.7)	0.12–1.5 ( $t=2.37^*$ )
Diurnal change (nmol/l)	–8.3 (4.6)	–8.6 (4.8)	–2.0–1.4 ( $t=-0.35$ )

Mean values with SD in parentheses in 41 patients with chronic fatigue syndrome before and after cognitive behavioural therapy. Asterisks show those variables showing a significant alteration after CBT by paired  $t$ -test ( $*P<0.05$ ).

## 2.5. Statistical analysis

All data were normally distributed (SPSS version 16). The main outcome measure was total 0800–2000h salivary cortisol output calculated as the area under the curve (AUC) using the trapezoidal method. In addition, we took two secondary measures: the mean of the four samples and the diurnal change (difference between first and last samples), since this latter variable may be altered in CFS (Cleare, 2003).

Endocrine and clinical measures were compared: before and after CBT using a paired  $t$ -test; and between responders and non-responders using an independent samples  $t$ -test (on 38 patients due to missing CBT response data). We calculated Pearson's product-moment coefficients to look at the relation between the post-CBT cortisol and clinical measures.

Means are given with SDs or 95% confidence intervals.

## 3. Results

### 3.1. Effect of CBT on clinical measures

CBT was moderately effective, with significant reductions in fatigue, disability and psychiatric symptoms

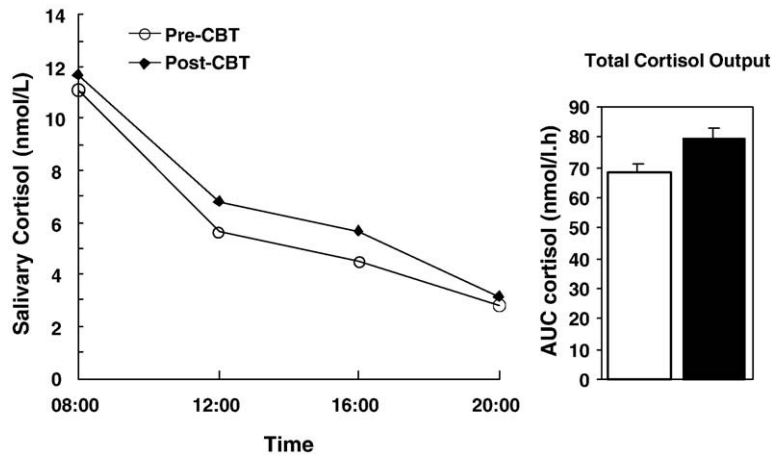


Fig. 1. Line graph shows salivary free cortisol across the day in 41 patients with CFS tested both before (open circles) and after (closed diamonds) cognitive behavioural therapy (CBT). Inset bar chart shows mean total cortisol output across the day measured as the integrated area under the curve with standard errors of the mean (open bar pre-treatment, closed bar post-treatment; post-treatment output significantly increased [ $P < 0.05$ , see Table 2]).

(Table 1). Overall, 47% of the patients had responded to therapy at the time of repeat testing.

### 3.2. Effect of co-morbid depression

There was no significant effect of comorbid depression on total salivary cortisol output: values were 67.9 (SD 23.9) nmol/l h in those with comorbid depression and 68.4 (SD 16.8) nmol/l h in those without (95% CI –12.4–13.3,  $t = 0.07$ ). This mirrors previous results suggesting no major effect of depression on endocrine variables in CFS (Cleare et al., 2001; Roberts et al., 2004) and we did not stratify for depression in the subsequent analyses.

### 3.3. Effect of CBT on cortisol output

Patients showed increased cortisol levels after CBT both on the AUC and the mean level across the day (Table 2). The salivary day curves are shown in Fig. 1.

The mean time of awakening was not different before (0730h, SD 62 min) and after (0750h, SD 57 min) treatment ( $t = -1.9$ ,  $P > 0.05$ ).

The diurnal pattern of cortisol release was not altered by CBT (Table 2).

### 3.4. Outcome of CBT and cortisol measures

There was no differential effect of whether patients were judged to have responded to CBT or not apparent in salivary cortisol measures (Table 3). We also calculated the change in the endocrine variables after CBT (i.e. pre-treatment values subtracted from post-treatment values) and performed an independent  $t$ -test on these values between responders and non-responders. There were no significant differences detectable (data not shown).

We also looked to see if there were any correlations between clinical and cortisol measures after CBT. There were no correlations with total or mean cortisol output.

Table 3

Salivary cortisol output in CBT responders and CBT non-responders

Measure	Treatment non-responders	Treatment responders	95% CI for difference
0800–2000h total output (AUC) (nmol/l h) before CBT	65.2 (17.2)	71.2 (22.0)	–19.2–7.2 ( $t = -0.92$ )
0800–2000h total output (AUC) (nmol/l h) after CBT	78.0 (22.8)	79.2 (22.5)	–16.2–13.8 ( $t = -0.17$ )
Mean value (nmol/l) before CBT	5.7 (1.4)	6.3 (2.0)	–1.7–0.5 ( $t = -1.2$ )
Mean value (nmol/l) after CBT	6.6 (1.8)	6.9 (1.7)	–1.4–0.9 ( $t = -0.5$ )
Diurnal change (nmol/l) before CBT	–7.5 (3.9)	–8.9 (5.4)	–1.8–4.5 ( $t = 0.86$ )
Diurnal change (nmol/l) after CBT	–7.6 (4.8)	–8.8 (4.9)	–1.9–4.4 ( $t = 0.80$ )

Cortisol total output, mean output and diurnal change before and after cognitive behavioural therapy in those responding to the therapy ( $n = 18$ ) and those not responding to therapy ( $n = 20$ ). Mean values with SD in parentheses. No differences significant using independent  $t$ -test.

However, after CBT, a flatter cortisol day curve (i.e. a reduced diurnal change) was associated with worse functioning on the SF-36 social function subscale ( $r = -0.40$ ,  $P = 0.015$ ) and higher BDI depression scores ( $r = 0.41$ ,  $P = 0.013$ ).

#### 4. Discussion

As outlined, hypocortisolism is one of the most often reported biological changes in CFS (Cleare, 2003). We have shown for the first time that cortisol levels can be increased by CBT, with a 16% increase in total cortisol output from 0800–2000h apparent after 6 months of therapy. Our findings are robust due to the careful selection of medication-free subjects, and because patients acted as their own controls before and after CBT, thus excluding other inter-individual factors that might complicate comparisons of HPA axis assessments. Other advantages of the present study include the careful assessment of psychiatric and other comorbidities, and the use of salivary cortisol, a non-stressful method of assessing biologically active hormone.

We are not directly able to deduce the mechanism by which CBT increases cortisol levels from this study. However, there is accumulating evidence that HPA axis changes are not a primary feature of CFS, but instead could be a secondary effect of illness. Thus, chronic fatigue six months after Epstein–Barr virus (Candy et al., 2003) or surgery (Rubin et al., 2005) is not associated with HPA axis changes. However, patients who have had CFS for several years, do show HPA axis changes (Cleare, 2003). Since sleep pattern, habitual physical activity levels, physical deconditioning and perceived stress can all exert marked effects on the HPA axis (Cleare, 2003), we hypothesise that these factors, together with potential effects of comorbid psychiatric illness and medication, are largely responsible for the varying degrees of hypocortisolism in longstanding CFS (Cleare, 2004). Since CBT for CFS concentrates on addressing many of these factors, it is plausible that it is via the reversal of these cognitive–behavioural factors that both clinical and endocrine change is produced.

This was not a trial of CBT. We found an overall response rate of 47% in this group, with reductions in fatigue and increased physical function, when assessed immediately after six months of therapy, but further improvement may occur in the subsequent six months (Deale et al., 1997). Furthermore, we recruited a group of patients selected also to be suitable for endocrine assessment so this may not represent the response rate for all those given CBT.

This study did not assess the response of the HPA axis to challenge. However, as yet no specific HPA axis

abnormality has been identified (Cleare, 2003) and the explanation for lowered cortisol levels is most likely multifactorial (Cleare, 2004). Nevertheless, we cannot say what aspects of the HPA axis were changed by CBT to lead to increased cortisol output. Although we interpret the results as indicating a normalisation of whatever has led to hypocortisolism, it is also possible that CBT induces some form of compensation for an underlying deficit.

There was no clear link between the clinical response to CBT and the change in cortisol output. This is consistent with cortisol being just one of many factors influencing symptoms in CFS; alternatively, low cortisol could represent an epiphenomenon having little link with symptoms. However, we did find that some clinical measures (social function and depressive symptoms) were linked to a flattened diurnal cortisol profile that persisted after CBT.

A final limitation was that we did not use an untreated group of CFS sufferers: since there is clear evidence of the efficacy of CBT we did not feel it would be ethical to delay this for 6 months to act as a control for this experiment. Thus, we cannot exclude the increase in cortisol output being due to factors independent of CBT such as illness progression or repeated testing. However, given the chronicity of our group and the poor prognosis of untreated CFS in specialist care (Wessely et al., 1998) we feel that spontaneous change in the illness is an unlikely explanation for the changes we found. Furthermore, studies following up the long-term stability of cortisol levels in non-elderly adult age groups have overwhelmingly found either no change (Diaz et al., 1989; Schell et al., 2008; Steptoe et al., 1998; Yehuda et al., 2007) or a decrease (Burleson et al., 2003; Evolahti et al., 2006; Feldman et al., 2002; King et al., 2000; Shalev et al., 2008) over time, rather than an increase.

In conclusion, we found that CBT for CFS is associated with increased cortisol output from 0800h to 2000h CBT, perhaps through effects of CBT on sleep, perceived stress and physical activity levels. Although previous research suggests that some CFS patients may benefit from low dose hydrocortisone replacement, we suggest that our results, together with the superior evidence base for CBT in CFS, point to CBT being the treatment of choice for the observed mild hypocortisolism in CFS at this time.

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### Conflict of interest

All authors declare that they have no conflicts of interest in relation to this paper.

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