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ORIGINAL ARTICLE

Severe fatigue in patients with adrenal insufficiency: physical, psychosocial and endocrine determinants

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Abstract
Background Fatigue is a frequently experienced complaint in patients with adrenal insufficiency (AI) and may be influenced by cortisol levels.
Aim The objective of this study was to determine the prevalence of severe fatigue in adrenal insufficiency (AI) patients, to assess which dimensions contribute to fatigue severity and to determine the association between salivary cortisol levels and momentary fatigue.
Subjects and methods We performed a cross-sectional study in the outpatient department of a university hospital. Included were 27 patients with congenital adrenal hyperplasia (CAH), 26 patients with primary AI (PAI), 24 patients with secondary AI (SAI) and 31 patients with adrenal insufficiency after treatment for Cushing's syndrome (Cush-AI). Measurements included computerised questionnaires to determine fatigue severity and physical and psychosocial contributors. Patients took four saliva samples at home, in which cortisol levels were measured.
Results Severe fatigue was experienced by 41 % of the CAH patients, 42 % of the PAI patients, 50 % of the SAI patients and 42 % of the Cush-AI patients. Psychological distress, functional impairment, sleep disturbance, physical activity, concentration problems and social functioning contributed to the subjective experience of fatigue. Salivary cortisol levels were not correlated with momentary fatigue.
Conclusions A considerable proportion of AI patients experience severe fatigue. Salivary cortisol level is not a significant predictor for momentary fatigue in AI patients.

Keywords Fatigue · Primary adrenal insufficiency · Secondary adrenal insufficiency · Congenital adrenal hyperplasia · Cortisol

Abbreviations

AI	Adrenal insufficiency
CAH	Congenital adrenal hyperplasia
PAI	Primary adrenal insufficiency
SAI	Secondary adrenal insufficiency
Cush-AI	AI-after treatment for Cushing's syndrome
CFS	Chronic fatigue syndrome
CIS	Checklist Individual Strength
AFQ	Abbreviated Fatigue Questionnaire
BDI	Beck Depression Inventory
SCL-90	The 90-item Symptom Checklist
SIP	Sickness Impact Profile
SF-36	Short Form Health Survey

Introduction

Patients with primary adrenal insufficiency (PAI), secondary adrenal insufficiency (SAI), congenital adrenal hyperplasia (CAH) and patients with adrenal insufficiency after treatment for Cushing's syndrome (Cush-AI) require

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lifelong substitution with glucocorticoids, and in some cases (especially PAI and CAH), also substitution with mineralocorticoids. Epidemiological studies and studies of glucocorticoid and mineralocorticoid replacement strategies suggest that patients with primary or SAI have persistent fatigue, lack of energy and reduced quality of life [1–4]. Recent multicenter studies [5, 6] show impaired health status in CAH patients. Although results suggest that fatigue is a significant problem in CAH, PAI, SAI and Cush-AI patients, no studies were found with fatigue as the main outcome.

Fatigue is a subjective experience that affects everyone. For people with specific diseases, fatigue often becomes a major distressing symptom. Based on results of research with patients with chronic fatigue syndrome (CFS), disease-free breast cancer patients, multiple sclerosis and other chronic diseases, fatigue is considered a multidimensional phenomenon [7–9]. To get more insight into the dimensions that are independently associated with fatigue in adrenal insufficiency (AI), multivariate analysis is needed, including multiple psychosocial and physical dimensions.

The most plausible cause of fatigue in AI is dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis. Data suggest a failure of the current replacement regimen to mimic the physiological circadian rhythm of cortisol with its nocturnal rise and morning peak [10]. As a consequence, patients suffer from early morning fatigue and report an increased exhaustion tendency during the day. In addition Arlt et al. [11] showed that symptoms indicative of underreplacement with glucocorticoids in AI patients, such as fatigue and loss of energy, correlate with repeated serum cortisol measurements. Furthermore, dysfunction of the HPA axis is the most investigated biological risk marker in functional somatic disorders, such as CFS. A recent meta-analysis of 85 studies demonstrated that baseline cortisol levels were significantly lower in CFS, but not in irritable bowel syndrome [12].

Gaining more insight into the prevalence and nature of fatigue in AI patients would improve the recognition of fatigue in AI patients and facilitate development of treatment options. In this study we examined the hypothesis that fatigue is a significant, multidimensional problem in AI patients and is influenced by cortisol levels, addressing the following research questions:

1. How prevalent is severe fatigue in a population of AI patients?
2. Which dimensions are associated with fatigue severity in AI patients and what is their contribution to the fatigue severity dimension?
3. Are salivary cortisol levels correlated with momentary fatigue?

Method

Subjects

Patients planned for an outpatient consultation at the Department of Endocrinology of the Radboud University Nijmegen Medical Centre, received prior to their visit an information letter concerning the context of the study ($n = 165$). The study was approved by the Regional Committee for Ethics in Medical Research, and written informed consent was obtained from all patients before participation. Patients willing to participate were asked to return four saliva samples and complete a short questionnaire measuring momentary fatigue accompanying each sample. These samples were collected in the morning after getting up, at noon, at 5 p.m. and just before going to sleep. Saliva samples were provided at the participants' homes and were returned to the hospital the following day, on the day of the outpatient clinic visit. The saliva samples were used to measure salivary cortisol levels. Furthermore, on the day of the outpatient clinic visit the patients completed five questionnaires using a laptop.

The underlying cause of AI was verified by review of the medical records.

The diagnosis CAH was based on biochemical analysis (and in most patients also DNA analysis was performed), as described before [13]. PAI was defined as the combination of a decreased early morning cortisol level (<80 nmol/l), or an insufficient cortisol response to intravenously administered $ACTH_{1-24}$ (Synacthen), in combination with elevated ACTH levels [14]. SAI was defined as a dysfunction of the pituitary-adrenal axis, documented by the combination of a decreased early morning cortisol level (<80 nmol/l), or an insufficient cortisol response to intravenously administered $ACTH_{1-24}$ (Synacthen) or insufficient cortisol response to insulin-hypoglycemia test, in combination with low or low-normal ACTH levels [14]. The Cush-AI group consisted of patients with PAI or SAI as a result of treatment of Cushing's syndrome. Information about co-morbidity was also obtained from the medical records. All patients included required lifelong glucocorticoid substitution therapy and had an age of >18 years. Doses of glucocorticoids were converted to hydrocortisone equivalents using anti-inflammatory equivalents (30 mg hydrocortisone = 37.5 mg cortisone acetate = 7.5 mg prednisone = 0.75 mg dexamethasone) [15].

Measurements

Salivary cortisol levels

Saliva was collected by salivation into a plastic cup. Saliva samples were frozen and stored at the domestic refrigerator

until storage in the laboratory at −20 °C. Cortisol was measured by radioimmunoassay (RIA) after extraction with dichloromethane and subsequent paper chromatography, according to the method described earlier for cortisol measurement in plasma and saliva [1]. Briefly, 0.25 ml of saliva, to which ^{3}H-cortisol had been added as a recovery tracer, is extracted by means of dichloromethane. The extracts are dried and transferred to paper chromatography strips and run in descending mode. After localisation by means of a radiochromatogram scanner, the area containing the ^{3}H-cortisol is cut out and soaked in elution medium. RIA is performed in aliquots of this medium and results are calculated taking into account the contribution of the recovery tracer in the RIA and correcting for procedural loss. The within-assay coefficient of variation is 4.4 % at a level of 360 nmol/l. The between-assay coefficient of variation is 6.3 % at a level of 360 nmol/l. The limit of detection is 0.47 nmol/l when a sample volume of 0.25 ml is assayed [16].

Questionnaires

In this study, fatigue was the primary outcome measure. We used several dimensions relevant for fatigue in patients with CFS, disease-free breast cancer patients, multiple sclerosis and other chronic diseases [6–8, among others].

1. *Fatigue* Fatigue severity was assessed by using the fatigue subscale of the Checklist Individual Strength (CIS), a validated and reliable questionnaire with an established cut-off point for severe fatigue. The CIS measures level of fatigue for the previous 2 weeks. The fatigue subscale ranges from 8 to 56 and includes eight items scored on a 7-point Likert scale [7, 8, 17–21]. Based on scores in healthy controls, a score below 35 indicates a normal experience of fatigue. A score of 35 or higher, 2 SD above the mean, indicates severe fatigue: similar to results in patients with CFS. The psychometric properties of the CIS-fatigue subscale have been tested in various patient populations (e.g. CFS, multiple sclerosis, neuromuscular disorders, stroke), and results have confirmed its validity [9, 21, 22]. Momentary fatigue at the time of taking each saliva sample was measured with the Abbreviated Fatigue Questionnaire (AFQ). The AFQ is derived from the CIS and contains four of the eight items of the Fatigue Severity Scale of the CIS [23]. Fatigue severity of the CIS is validated and used in several studies [7, 8, 17–21]. This brief questionnaire was used to assess momentary fatigue.
2. *Psychological distress* This dimension was measured with the Beck Depression Inventory for primary care (BDI-pc) and the 90-item Symptom Checklist (SCL-90). The BDI-pc was used instead in order to prevent an overlap between physical aspects of fatigue with the somatic symptoms of depression [24]. This shortened version of the BDI [25] has seven items and consists of cognitive and affective symptoms. A score of 4 or more is indicative of clinical depression. The anxiety, agoraphobia, depression, somatisation, obsessive–compulsive behaviour, interpersonal sensitivity and hostility subscales of the SCL-90 were used [26].
3. *Functional impairment* Functional impairment was measured with the subscales home management, work, and recreation from the Sickness Impact Profile (SIP). This widely used test has good reliability and content validity [27]. Furthermore, the role limitations caused by physical health problems subscale of the Short Form Health Survey (SF-36) was used. The SF-36 is a validated, self-administered, internationally used questionnaire. Domain scores range from 0 to 100, with lower scores indicating poorer health status [28].
4. *Sleep* Sleep disturbance was measured with the sleep/rest subscale of the SIP and the sleep subscale of the SCL-90.
5. *Physical activity* Restrictions in physical activity was measured with the mobility subscale of the SIP and the physical functioning subscale of the SF-36.
6. *Concentration problems* The subscale alertness of the SIP measures limitations in concentrating.
7. *Social functioning* was measured with the social interaction subscale of the SIP and the social functioning subscale of the SF-36.

Statistical analysis

Data analysis was performed using Statistical Package for Social Science (SPSS; version 18.0). Descriptive statistics were used for description of the sample. Chi-square tests, independent samples *t* tests and analysis of variances general linear model were performed to test differences between groups. In order to examine the contribution of each dimension to the dimension of fatigue severity, linear regression analysis (enter-method) was performed by taking the four subgroups together. Pearson correlations were used to investigate the association between salivary cortisol levels and momentary fatigue. Furthermore, linear regression was performed to examine the correlation between cortisol levels and momentary fatigue.

Results

Study cohort

Of a total of 165 patients, planned for an outpatient consultation at the Department of Endocrinology in a

Table 1 Demographic and medical characteristics of AI patients included in this study ($n = 108$)

	CAH ($n = 27$)	Primary AI ($n = 26$)	Secondary AI ($n = 24$)	Cush-AI ($n = 31$)
Gender				
Male, *n* (%)	11 (41)	10 (39)	17 (71)	6 (19)
Female, *n* (%)	16 (59)	16 (61)	7 (29)	25 (81)
Age (years mean ± SD)	32.9 ± 9.7	55.0 ± 13.4	58.0 ± 11.1	55.3 ± 12.1
Duration of disease (years mean ± SD)	31.1 ± 10.1	19.3 ± 11.1	18.6 ± 8.6	21.2 ± 9.4
Significant co-morbidity *n* (%)	4 (15)	6 (24)	6 (25)	11 (36)
AI-specific replacement therapy				
Hydrocortisone (*n*)	25	10	0	6
Cortisone acetate (*n*)	1	11	23	24
Dexamethasone (*n*)	6	1	0	1
Predniso(lo)ne (*n*)	0	4	1	0
Daily dose (mean ± SD)[a]	23.4 ± 8.4	26.0 ± 7.2	31.1 ± 10.4	27.4 ± 11.7
Other substitution hormone therapy				
Fludrocortisone, users,	20	25	1	27
Fludrocortisone daily dose mg (mean ± SD)	0.13 ± 0.09	0.11 ± 0.06	0.19	0.10 ± 0.09
L-thyroxine	1	7	21	15
Testosterone	1	0	11	3
Growth hormone	0	0	3	7
Dehydroepiandrosterone	0	3	1	3

[a] Daily dose in hydrocortisone-equivalent [15]

3 months' period, 108 patients (66 %) agreed to participate. For further analysis, patients were divided into four subgroups based on medical diagnosis (27 CAH, 26 PAI, 24 SAI, 31 Cush-AI). Causes of SAI were: 19 pituitary adenoma, 5 other causes. Of the 19 patient with pituitary adenoma, 12 patients had a non-functioning pituitary adenoma, 7 patients had a functioning pituitary adenoma of which 6 patients had acromegaly and 1 had a prolactinoma. The five other causes were chondrosarcoma, meningioma, empty cella, cranio-pharyngioma and germinoma in the pituitary region.

In the Cush-AI group, 27 patients had PAI (as a result of bilateral adrenalectomy) and 4 patients had SAI (as a result of pituitary surgery and/or radiotherapy).

Patients' characteristics with regard to age, duration of disease, hormone replacement therapy, and co-morbidity are summarized in Table 1.

In the SAI and Cush-AI group, 15 male patients were on testosterone replacement therapy. The mean testosterone level was 15.2 nmol/l (SD 13.9). Ten patients were on GH replacement therapy. The mean IGF1 for the group of GH users was 16.6 nmol/l. When expressed in SD for sex and age, the median SD was −0.25 (range −2.5 to +1.5 SD).

Significant co-morbidity was defined as the presence of asthma or COPD, severe heart disease, stroke, severe intestinal disorder for more than 3 months, severe kidney disease, diabetes type 1 or 2, (rheumatoid) arthritis or malignancy.

Fatigue scores

For the CAH group, the mean CIS-fatigue severity score was 30.9 ± 15.9 (mean ± SD) and 11 patients (41 %) met the cut-off criteria for severe fatigue (CIS-fatigue ≥35). In the PAI group, the mean CIS-fatigue severity score was 31.2 ± 14.3 and 11 patients (42 %) met the cut-off criteria for severe fatigue. For the SAI group, the mean CIS-fatigue severity score was 32.6 ± 14.6 and 12 patients (50 %) met the cut-off criteria for severe fatigue. For the Cush-AI group, the mean CIS-fatigue severity score was 28.5 ± 12.7 and 13 patients (42 %) met the cut-off criteria for severe fatigue. Differences between male and female patients were found in the PAI and the Cush-AI group: a significant difference in fatigue severity in the PAI group between male and female patients (36.2 ± 13.6 versus 23.2 ± 12.2, $P = 0.021$) and in the Cush-AI group (19.2 ± 6.6 versus 30.8 ± 12.9, $P = 0.042$).

Which dimensions are associated with fatigue severity in AI patients and what is their contribution to the fatigue severity dimension?

Table 2 shows the results of severely fatigued AI patients (CIS-fatigue ≥35) and non-severely fatigued AI patients with regard to the dimension of psychological distress, functional impairment, sleep disturbance, physical activity, concentration problems and social functioning.

Table 2 Comparisons between severely fatigued and non-severely fatigued CAH, PAI, SAI and Cush-AI patients with regard to the different dimensions of fatigue

	CAH		PAI		SAI		Cush-AI	
	Non-severely fatigued $n = 16$	Severely fatigued $n = 11$	Non-severely fatigued $n = 15$	Severely fatigued $n = 11$	Non-severely fatigued $n = 12$	Severely fatigued $n = 12$	Non-severely fatigued $n = 18$	Severely fatigued $n = 13$
Psychological distress								
BDI-pc (clinical depressed)	0.38 ± 0.5	1.9 ± 2.7	0.4 ± 0.8	2.1 ± 2.3*	0.3 ± 0.7	2.4 ± 3.6	0.7 ± 1.2	0.9 ± 1.2
Anxiety (SCL)	12.6 ± 3.9	14.6 ± 4.5	10.5 ± 3.3	13.3 ± 4.5	10.6 ± 4.7	13.3 ± 2.6	12.1 ± 4.1	16.9 ± 4.4*
Agoraphobia (SCL)	7.88 ± 2.1	8.55 ± 2.7	6.6 ± 1.9	7.4 ± 0.7	7.2 ± 3.0	8.4 ± 2.2	9.1 ± 4.1	10.2 ± 4.7
Depression (SCL)	19.6 ± 4.6	26.3 ± 10.0	16.8 ± 5.2	26.2 ± 9.1*	17.6 ± 7.0	25.5 ± 11.7	22.5 ± 10.2	26.0 ± 5.8
Somatisation (SCL)	14.5 ± 3.1	22.8 ± 6.9**	15.9 ± 6.2	26.0 ± 8.3*	13.0 ± 5.2	23.58 ± 6.5**	17.4 ± 5.6	24.3 ± 6.6*
Obsess.-comp. behaviour (SCL)	13.1 ± 4.8	16.36 ± 4.9	10.8 ± 4.1	16.5 ± 6.9*	11.7 ± 5.6	17.8 ± 6.5*	12.9 ± 5.2	18.5 ± 6.1*
Interpersonal sensitivity (SCL)	25.3 ± 9.6	24.6 ± 5.9	18.7 ± 5.7	23.9 ± 6.0*	20.9 ± 11.3	23.7 ± 6.5	26.1 ± 15.4	24.5 ± 6.7
Hostility (SCL)	7.2 ± 1.6	8.27 ± 2.9	6.4 ± 2.7	7.2 ± 1.2	5.8 ± 2.0	6.6 ± 0.5	7.4 ± 3.1	7.2 ± 1.2
Functional impairment								
Home management (SIP)	21.0 ± 34.4	79.9 ± 55.1*	29.6 ± 40.7	92.6 ± 48.4*	25.8 ± 34.6	109.6 ± 112.9*	33.2 ± 41.5	95.0 ± 66.3*
Work (SIP)	30.3 ± 90.9	167.2 ± 185.8*	27.4 ± 93.2	53.1 ± 53.7	101.1 ± 158.8	108.6 ± 159.1	72.1 ± 137.0	120.9 ± 167.6
Recreation and pastimes (SIP)	15.9 ± 25.4	72.3 ± 76.9*	16.9 ± 26.3	114.3 ± 94.3*	24.3 ± 40.2	121.2 ± 111.3*	22.3 ± 40.6	86.9 ± 60.6*
Physical role limitations (SF-36)	90.6 ± 25.6	47.7 ± 37.8*	85.0 ± 29.6	38.6 ± 42.4*	85.4 ± 24.9	41.7 ± 38.9*	4.4 ± 13.7	42.3 ± 38.7**
Sleep disturbance								
Sleep/rest (SIP)	18.4 ± 24.5	67.7 ± 73.3	21.7 ± 33.8	81.7 ± 66.1*	16.8 ± 33.3	91.5 ± 60.0*	18.0 ± 40.2	49.1 ± 46.4
Sleep (SCL)	4.0 ± 2.1	7.0 ± 4.3	3.9 ± 1.8	7.8 ± 3.5*	3.3 ± 1.6	7.5 ± 3.6*	4.1 ± 1.4	6.6 ± 3.2*
Physical activity								
Physical functioning (SF-36)	93.4 ± 12.5	65.5 ± 30.9*	82.7 ± 29.5	60.5 ± 18.0*	84.2 ± 19.5	56.7 ± 22.6*	85.0 ± 14.5	61.9 ± 18.4*
Concentration problems								
Alertness (SIP)	29.8 ± 56.9	94.7 ± 93.6*	15.9 ± 45.3	125.1 ± 135.1*	51.7 ± 125.5	90.1 ± 159.9	40.1 ± 92.4	94.0 ± 98.7
Social functioning								
Social interaction (SIP)	32.3 ± 64.4	173.3 ± 161.7*	30.2 ± 45.4	146.6 ± 157.9*	54.6 ± 104.0	126.8 ± 161.0	44.4 ± 74.0	48.9 ± 70.3
Social functioning (SF-36)	89.8 ± 13.9	63.6 ± 25.3*	80.3 ± 33.0	65.9 ± 18.6	91.7 ± 15.9	62.5 ± 26.7*	93.8 ± 10.7	67.3 ± 26.8*
Mean salivary cortisol levels in patients using hydrocortisone or cortisone acetate (nmol/l)	13.1 ± 33.5 ($n = 11$)	12.7 ± 9.0 ($n = 10$)	2.9 ± 2.2 ($n = 10$)	6.4 ± 4.4* ($n = 9$)	3.5 ± 3.0 ($n = 12$)	5.1 ± 2.9 ($n = 12$)	5.2 ± 6.6 ($n = 17$)	11.5 ± 11.6 ($n = 12$)

BDI-pc Beck Depression Inventory for primary care, *SCL* Symptom Checklist, *SF36* Short Form Health Survey, *SIP* Sickness Impact Profile, *SF-36* lower scores indicate poorer health status, *SIP* higher scores indicate a higher level of functional disability

* $P < 0.05$, ** $P < 0.001$

Results with regard to the psychological distress dimension show that scores of severely fatigued CAH patients are not significantly different from scores of non-fatigued CAH patients, except for the somatisation subscale of the SCL. Severely fatigued PAI patients have significantly higher scores on the depression scale and have higher mean scores on the depression, somatisation, obsessive–compulsive behaviour and interpersonal sensitivity subscales of the SCL compared with non-fatigued PAI patients. Furthermore, severely fatigued SAI patients have higher mean scores on the somatisation and obsessive–compulsive behaviour subscales of the SCL compared with non-fatigued SAI patients. In the Cush-AI group severely fatigued patients have higher mean scores on the anxiety, somatisation and the obsessive–compulsive behaviour subscales of the SCL. More specifically, according to the results of the BDI-pc, in the group of severely fatigued CAH patients 27 % could be considered as clinically depressed (score 4 or more) [25], compared with non of the non-severely fatigued CAH patients. These percentages are 9 and 0 %, respectively, for the PAI patients, 17 and 0 % for the SAI patients and 6 and 0 % for the Cush-AI patients.

In all four groups, severely fatigued patients reported significantly more functional impairment in daily life compared with non-severely fatigued patients with regard to home management, recreation and physical role limitations.

On the sleep disturbance dimension, severely fatigued PAI and SAI and Cush-AI patients report having more problems with sleep than non-severely fatigued PAI and SAI. Scores of severely fatigued CAH patients are not significantly different from scores of non-severely fatigued CAH patients.

With regard to the physical activity dimension severely fatigued CAH, PAI, SAI and Cush-AI patients report less physical functioning (SF-36) compared with non-severely fatigued patients.

Results with regard to concentration (alertness behaviour subscale of the SIP) show that severely fatigued CAH patients and PAI patients have higher scores than non-severely fatigued CAH patients, indicating a higher level of functional disability. In SAI and Cush-AI patients no such difference was found.

Finally, on the social functioning dimension (SF-36), severely fatigued CAH, SAI and Cush-AI patients report having more problems with social functioning and interaction than non-severely fatigued patients.

Regression analyses were performed to examine the contribution of psychological distress, functional impairment, sleep disturbance, physical activity, concentration problems and social functioning to fatigue severity by taking the four subgroups of AI together. Independent variables were those subscales of questionnaires within the dimensions that correlated most highly with fatigue severity. Results of the regression analysis (Table 3) indicate that psychological distress (SCL-somatisation), functional impairment (SF-36-physical role limitation), sleep disturbance (SCL-sleep), physical activity (SF-36-physical functioning), concentration problems (SIP-alertness) and social functioning (SF-36-social functioning) are associated with fatigue severity. In total 53 % of the variance of fatigue severity was explained.

Correlation between salivary cortisol levels and fatigue severity

Salivary cortisol levels and momentary fatigue (measured with the AFQ) were assessed in the morning after getting up (T1), at noon (T2), 5 p.m. (T3) and just before going to sleep (T4). The correlation between saliva cortisol levels and momentary fatigue was investigated by taking the four subgroups of AI together, after excluding patients using dexamethasone ($n = 8$) and prednisone ($n = 5$). The results are shown in Fig. 1. The mean salivary cortisol levels show a peak at T2. The mean momentary fatigue is relatively stable. The relationship between saliva cortisol levels and momentary fatigue was investigated using Pearson correlation. The correlation coefficients for momentary fatigue and cortisol level at T1, T2, T3 and T4 were not statistically significant. In order to investigate a delayed effect of cortisol on momentary fatigue the corresponding correlations were assessed: cortisol at T1 with fatigue at T2, cortisol at T2 with fatigue at T3 and cortisol at T3 with fatigue at T4. These correlation coefficients were also not statistically significant. The correlation

Table 3 Linear regression (enter) to predict fatigue severity in AI patients

Independent variables	Dependent variable: CIS-fatigue severity Beta (95 % CI)	*P* value
Psychological distress–somatisation (SCL)	0.505 (0.16 to 0.85)	0.004
Functional impairment–physical role limitations (SF-36)	−0.107 (−0.19 to −0.03)	0.007
Sleep disturbance–sleep (SCL)	1.016 (0.25 to 1.78)	0.010
Physical activity–physical functioning (SF-36)	−0.088 (−0.20 to 0.02)	0.117
Concentration problems–alertness (SIP)	0.008 (−0.01 to 0.03)	0.468
Social functioning–social functioning (SF-36)	−0.003 (−0.12 to 0.12)	0.964
Total R^2 (adjusted)	0.532	

SCL Symptom Checklist, *SF-36* Short Form Health Survey, *SIP* Sickness Impact Profile

between the overall mean level of cortisol and the mean score of momentary fatigue was not significant. A significant difference in the mean salivary cortisol level between severely fatigued versus non-severely fatigued patients was found in the PAI group, 6.4 ± 4.4 versus 2.8 ± 2.2, $P = 0.04$, but not in the other groups (Table 2). The value of cortisol as predictor for momentary fatigue was assessed using regression analysis. Because of the relatively stable scores of momentary fatigue during the day, the mean score was used as dependent variable. The results (Table 4) indicate that saliva cortisol levels measured at different times of the day and the overall mean level of cortisol are not significant predictors for momentary fatigue.

Discussion

This is the first study in AI patients with fatigue as main outcome and to investigate the relation between repeated salivary cortisol measurements and repeated measurements of momentary fatigue.

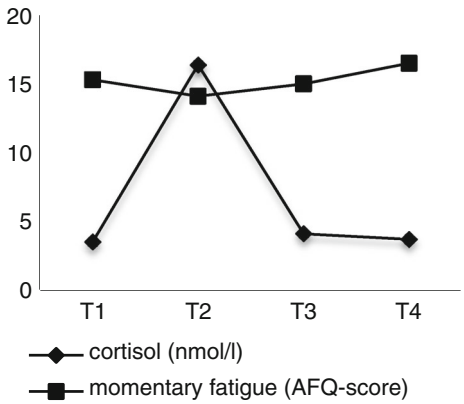

Fig. 1 Salivary cortisol levels and momentary fatigue during the day in patients using hydrocortisone or cortisone acetate. *T1* in the morning after getting up, *T2* at noon, *T3* 5 p.m., *T4* just before going to sleep

Table 4 Linear regression (enter) to predict momentary fatigue in AI patients using hydrocortisone or cortisone acetate

Independent variables	Dependent variable: momentary fatigue mean score Beta (95 % CI)	*P* value
Cortisol T1	−0.592 (−1.73 to 0.55)	0.304
Cortisol T2	−0.509 (−1.63 to 0.62)	0.370
Cortisol T3	−0.422 (−1.55 to 0.70)	0.457
Cortisol T4	−0.477 (−1.59 to 0.64)	0.396
Cortisol mean score	2.114 (−2.31 to 6.54)	0.344

T1, in the morning after getting up; T2, at noon; T3, 5 p.m.; T4, just before going to sleep

In this study a large part of AI patients turned out to be severely fatigued. 41–46 % of the patients met the cut-off criteria for severe fatigue. On average, AI patients have higher fatigue levels than reported for cancer survivors, lower levels of fatigue compared with patients with multiple sclerosis and comparable scores with patients with rheumatoid arthritis [8, 18, 29]. Probably having a chronic disease in general is a risk factor for fatigue. The women in the PAI and the Cush-AI group were significantly more severely fatigued than men. This difference between men and women could not be found in the CAH and SAI group. Other studies with CAH patients have previously shown more impaired health related quality of life symptoms in women compared with men, because of specific problems with cosmetic appearance and surgical procedures [6, 30]. Although severe fatigue might be associated with age, this relationship could not be found.

In an attempt to describe the severely fatigued AI patient we found that severe fatigue is associated with several dimensions: more psychological distress, more functional impairment, more sleep disturbance, less physical activity, more concentration problems and less social functioning. Except for the dimension sleep disturbance in the CAH group and the dimension concentration problems in the SAI and Cush-AI group, all dimensions contributed significantly to the differences in severely fatigued and non-fatigued AI patients. Servaes et al. [8] found the same significant differences between severely fatigued and non-severely fatigued, disease-free breast cancer patients. In the PAI group there was a significant association between fatigue and depression measured by the BDI-pc. Thus, although in some patients the depression–fatigue association cannot be ruled out as a possible explanation for the experienced fatigue, it is only a partial explanation. Within the group of severely fatigued CAH patients, 27 % could be considered as clinically depressed, based on the scores on the BDI-pc. In the other patient groups (PAI, SAI, Cush-AI) these percentages are substantially lower (9, 17 and 6 % respectively). We do not have an explanation for this. The negative relationship between fatigue and physical activity has previously been shown in several patient groups [7, 8, 21, 29, 31], although there are mixed results on the efficacy of increasing exercise to reduce fatigue [32–35]. The dimensions of severe fatigue derived from previous studies in cancer survivors and rheumatoid arthritis patients [8, 32], appear to be applicable in AI patients as well.

Our results indicate that there are no significant correlations between salivary cortisol levels and momentary fatigue measured at different times during the day and that cortisol is not a significant predictor for momentary fatigue during the day. Previous studies [11, 12] showed a negative relationship between fatigue and cortisol levels, where lower cortisol levels would correspond with more

complaints of fatigue. In this study we could not find this relationship.

A limitation of this study was that the number of variables measured was high in relation to the number of participants in each of the four groups. In order to increase the power of the statistical test the four subgroups were taken together for conducting regression analysis. This could have led to bias. Furthermore, selection bias cannot be ruled out since patients who experienced more feelings of fatigue could be more willing to participate in this study. This could result in a overrepresentation of the percentage of patients experiencing severe fatigue in this study. No direct comparisons with a control group were possible; instead we used control data from referenced publications. In our study group it was difficult to provide a detailed instruction for saliva sample collection in relation to administering of steroids, because of great variation in dosage schemes. Therefore it is unknown how the salivary cortisol samples were timed in relation to doses of hydrocortisone or cortisone acetate, possibly leading to a bias. This paper is characterized by an underlying theoretical perspective of fatigue, the multidimensional model of fatigue. However, it could be argued that the dimensions do not perpetuate fatigue, but represent, for example, psychosocial consequences of stress. Our study is characterized by an emphasis on central fatigue. One can only speculate about the mechanisms behind the self reported or central fatigue and the other dimensions of fatigue in patients with AI. Longitudinal research is necessary to get further insight into the most important determinants influencing chronic fatigue in AI patients as well as the course of fatigue over a longer period.

In summary this study shows that a large number of CAH, PAI, SAI and Cush-AI patients experience severe fatigue. Severe fatigue in AI patients is related to psychological distress, functional impairment, sleep disturbance, physical activity, concentration problems and social functioning. Salivary cortisol levels are not correlated with momentary fatigue in AI patients. In clinical practice, assessing symptoms of fatigue in AI patients should play an important role and treating symptoms of fatigue stretches beyond the scope of cortisol.

Conflict of interest V. Giebels, H. Repping-Wuts, G. Bleijenberg, J.M. Kroese, N. Stikkelbroeck, A. Hermus declare they have no conflict of interest.

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