Psychological morbidity and impaired quality of life in patients with stable treatment for primary adrenal insufficiency: cross-sectional study and review of the literature

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Abstract

Context: A high prevalence of psychological morbidity and maladaptive personality as well as impaired quality of life (QoL) is observed in patients with and without hydrocortisone dependency following (cured) Cushing's syndrome. However, it is currently unclear whether a similar pattern is present in patients with chronic glucocorticoid replacement for primary adrenal insufficiency (PAI).

Objective: To evaluate psychological functioning, personality traits, and QoL in patients with PAI.

Design and subjects: A cross-sectional study including 54 patients with stable treatment for PAI and 54 healthy matched controls. Both patients and controls completed questionnaires on psychological functioning (Apathy Scale, Irritability Scale, Mood and Anxiety Symptoms Questionnaire short form, and Hospital Anxiety and Depression Scale), personality traits (Dimensional Assessment of Personality Pathology short form), and QoL (Multidimensional Fatigue Inventory, Short Form 36, EuroQoL-5D, Nottingham Health Profile, and Physical Symptom Checklist).

Results: Patients with PAI suffered from more psychological morbidity (i.e. irritability and somatic arousal) and QoL impairments compared with controls (all $P<0.01$). There were no differences regarding maladaptive personality traits between patients and controls. However, there was a strong and consistent positive association between the daily hydrocortisone dose and prevalence of maladaptive personality traits (i.e. identity problems, cognitive distortion, compulsivity, restricted expression, callousness, oppositionality, rejection, conduct problems, social avoidance, narcissism, and insecure attachment, all $P<0.05$). There was also a strong relation between the mean daily hydrocortisone dose and both psychological morbidity (i.e. depression, $P<0.05$) and QoL impairments (i.e. general health perception, several measures of physical functioning, and vitality, all $P<0.05$).

Conclusion: Patients on stable glucocorticoid replacement therapy for PAI report psychological morbidity and impaired QoL. Psychological morbidity, impaired QoL, and maladaptive personality traits were all associated with higher dosages of hydrocortisone.

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Introduction

Primary adrenal insufficiency (PAI) is characterized by insufficient secretion of glucocorticoids and mineralocorticoids, most frequently caused by autoimmunity or following bilateral adrenalectomy. Replacement therapy consists of hydrocortisone, fludrocortisone, and sometimes, additional DHEA replacement.

Cortisol has a crucial function in the CNS via stimulation of both the mineralocorticoid receptor (MR) and glucocorticoid receptor (GR). An appropriate balance between the activation of these two receptors is necessary for adequate stress responses, including behavioral adaptations. Imbalance between MR and GR activations might enhance vulnerability to disease in predisposed individuals. The current notion is that the effects of glucocorticoids binding to MR and GR include an inverted u-shape dose–response curve, indicating that both pathologically low and high cortisol levels negatively affect the mediating functions of these receptors as is the absence of physiological circadian pulsatile secretion (1). The negative influence of glucocorticoid excess on psychological functioning in humans is clearly evident during active Cushing's disease because serious co-morbid psychopathology, such as major depression and anxiety, is prevalent (2). Although these symptoms improve substantially after correction of cortisol excess, consistent residual impairments persist even after prolonged cure of cortisol excess. This is reflected by an increased prevalence of psychopathology and maladaptive personality traits, as well as impairments in quality of life (QoL) (3, 4, 5, 6, 7) in many patients, either hydrocortisone dependent or independent.

Conversely, it is possible that previous exposure to insufficient glucocorticoid levels and recent imperfections in replacement therapy in mimicking the pulsatile secretion of cortisol, such as in PAI, may also be associated with persistent psychosocial effects, considering the inverted u-shape of optimal corticosteroid receptor function. However, in contrast to the large number of reports on patients with Cushing's syndrome, less is known about the effects of previous insufficient cortisol exposure on psychological functioning and QoL in PAI (see Table 1 for an overview). Heijmans & de Ridder (1998) (8) reported a significant relation between personality-related variables (i.e. optimism/pessimism, locus of control) and illness perceptions. However, there are no studies on personality traits in patients with PAI. To date, studies in patients with PAI have demonstrated impaired QoL (9, 10, 11, 12, 13, 14, 15), and a higher risk for the development of affective disorders such as depression or bipolar disorder (16). The QoL impairments in patients with PAI have been attributed, at least in part, to intrinsic imperfections of hormone replacement therapy (12). In accordance, some studies demonstrated a positive effect of DHEA replacement on QoL (13, 17, 18, 19). On the other hand, strategies aiming at adjusting cortisol replacement therapy mimicking a more diurnal profile by adjusting the time and frequency of hydrocortisone intake did not positively affect QoL (9, 11, 20). Furthermore, dosages above 30 mg hydrocortisone/day were associated with worse subjective health status (11).

Considering the limited amount of studies on psychological functioning in patients with PAI and the fact that studies on personality traits are lacking, the aim of the present study was to evaluate psychological functioning and personality traits, as well as QoL in patients with stable treatment for PAI. In accordance to previous studies, we hypothesized that patients with PAI not only would report impaired QoL, but also psychological morbidity, despite long-term stable replacement with hydrocortisone. Furthermore, we hypothesized that patients with PAI demonstrate maladaptive personality traits. The second aim was to explore a potential association between hydrocortisone intake and psychological functioning, personality traits, and QoL in patients with PAI.

Patients and methods

Participants

Patients with PAI were recruited via the Outpatient Clinic of the Department Endocrinology of the Leiden University Medical Center (LUMC) and by advertisement via the Dutch Adrenal Patient Society for Addison and Cushing Patients (NVACP; www.nvacp.nl). Thirty-nine patients were recruited from the patient network and 15 patients were recruited from the LUMC outpatient clinic. There were no differences regarding gender and age between patients derived from the patient network and patients derived from the outpatient clinic.

Patients with current or previous drug or alcohol abuse or with neurological problems were excluded. A total of 54 participants were included in this study (21 men and 33 women). The mean age of the patients was 50 ± 12 years. Each patient was asked to provide a control person of comparable gender, age (± 10 years), and educational level in order to create a control group. The self-selection of controls enabled a perfect match for

an additional parameter, i.e. social-economic status. Exclusion criteria for controls were present or previous drugs/alcohol abuse or neurological problems.

PAI had been diagnosed based on the classical clinical symptoms and biochemical confirmation of AI in the presence of increased adrenocorticotropic hormone (ACTH) concentrations. AI was diagnosed when basal cortisol concentrations were below the reference range of normal (<0.12 μmol/l) or below 500 nmol/l after stimulation with ACTH. Forty-four patients (82%) had been diagnosed with PAI due to autoimmune disease with positive autoantibodies against adrenal cortex, five patients (9%) had been diagnosed with PAI due to non-autoimmune causes (e.g. congenital adrenal aplasia and adrenal calcification), and two patients (4%) were treated with bilateral adrenalectomy for pheochromocytomas. The origin of PAI was unknown for three patients (5%).

All patients were on stable hydrocortisone and fludrocortisone replacement therapy for a mean duration of 10.1 ± 8.5 years (range, 2–38 years), as prescribed by their individual physicians. Eighty-three percent of the patients also used fludrocortisone in addition to hydrocortisone. Additional medical therapy included DHEA (26% of patients), levothyroxine for Hashimoto's thyroiditis (46%), anti-hypertensive drugs (13%), and oral contraceptives (9%). Sixty-five percent of female patients were postmenopausal.

The Medical Ethics Committee of the LUMC approved the protocol and written informed consent was obtained from all subjects.

Questionnaires

Both patients and controls were asked to complete the following questionnaires on psychological functioning, personality traits, and QoL at home and to return the questionnaires in a prepaid envelope.

The Apathy Scale consists of 14 questions on a four point scale measuring different features of apathy in the previous 2 weeks. The score for each item ranges from 0 (no apathy) to 3 (maximum intensity of apathy). The total score ranges from 0 to 42 points, with higher scores indicating greater apathy. A total score ≥ 14 points is being used to characterize subjects as apathetic (21, 22).

The Irritability Scale consists of 14 items measuring different features of irritability in the previous 2 weeks. The total score ranges from 0 to 42 points, with higher scores indicating greater irritability. A total score ≥ 14 points is being used to characterize subjects as irritable (22).

The Mood and Anxiety Symptoms Questionnaire short form (MASQ-30) assesses symptoms that occur in mood and anxiety disorders subdivided into the three subscales: negative affect, lack of positive affect, and somatic arousal. The scores for each subscale range from 10 to 50, with higher scores indicating more severe negative affect, more positive affect, or more somatic arousal. There are no formal cutoff scores (23).

The Hospital Anxiety and Depression Scale (HADS) consists of 14 items, and both the anxiety and the depression subscale scores range from 0 to 21 points. Higher scores indicate more severe anxiety and/or depression. A score >8 points on one of the subscales is being used to characterize subjects as being anxious or depressed respectively (24, 25).

The Multidimensional Fatigue Inventory (MFI-20) assesses fatigue. Five different dimensions of fatigue are calculated: i) general fatigue, ii) physical fatigue, iii) reduced activity, iv) reduced motivation, and v) mental fatigue. Scores vary from 0 to 20, with higher scores indicating greater fatigue (26).

The Short Form 36 (SF-36) assesses functional status and general well-being during the previous month (23, 24). The items cover nine health concepts: i) physical functioning, ii) social functioning, iii) role limitation (physical), iv) role limitation (emotional), v) mental health, vi) vitality, vii) pain, viii) general health perception, and ix) general perception of change in health. Scores are expressed on a 0–100 scale and higher scores indicate a better QoL (27, 28).

The EuroQoL-5D (EQ-5D) assesses current health status reflected in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores are expressed on a 1–3 scale per dimension, with higher scores indicating worse QoL. The questionnaire also includes a visual analog scale (VAS) which comprises a standard vertical 20 cm scale (similar to a thermometer) for recording an individual's rating for their current health-related well-being (29). The VAS score ranges from 0 to 100, with higher scores indicating a better health status.

The Nottingham Health Profile (NHP) assesses general well-being and consists of 38 yes/no questions, which are subdivided into six scales assessing impairments, i.e. pain (eight items), energy level (three items), sleep (five items), emotional reactions (nine items), social isolation (five items), and disability/functioning (eight items). Subscale scores are calculated as a weighted mean of the associated items and are expressed as a value between 0 and 1 (30, 31).

The Physical Symptom Checklist (PSC) assesess 55 physical symptoms that are mentioned in the DSM-III

Table 1 Literature overview of studies reporting on psychological functioning, personality, and QoL, in patients with PAI.

References	*n*	Gender (M/F)	Age (years)	Design	Controls	Domains	Outcomes
(49)	7	3/4	Range, 22–65	Prospective	NA	1	Cortisol levels positivity correlated with well-being
(39)	14	8/6	Range, 32–68	Randomized double-blind crossover	Normative data	1	At baseline, patients scored worse on physical symptoms, mood, psychological activity compared with controls. QoL was influenced by the HC intake scheme, favoring a twice daily instead of a once daily regimen
(8)[a]	110	47/63	Mean±s.d., 41.9±10.6	Observational Cross-sectional	Patients with CFS	1, 5, 6	Patients with AD reported a different structure of illness perceptions compared with patients with CFS
(50)[a]	110	47/63	Mean±s.d., 41.9±10.6	Observational Cross-sectional	Patients with CFS	4, 5	Patients with AD reported different illness perceptions compared with patients with CFS. Disease-related and personal variables were associated with illness perceptions
(51)[a]	110	47/63	Mean±s.d., 41.9±10.6	Observational	NA	1, 5, 6	Illness perceptions seemed to play an important role in physical and psychological functioning
(17, 18)[b]	24	0/24	Mean±s.d., 42±9	Randomized double-blind placebo-controlled	NA	1, 2	Treatment with DHEA resulted in improvement in well-being and sexuality in female patients, but at the end of the study there were no differences between placebo and DHEA
(19)	39	15/24	Mnd (range), 40 (25–69)	Randomized double-blind placebo-controlled cross-sectional	Reference data from controls matched by age and sex	1, 2	There were no differences between patients at baseline and controls. DHEA replacement improved some aspects of psychological function (self-esteem and mood) and fatigue
(36)	33	19/14	Mean±s.d.: men, 43.4±6.55 Women, 51.0±5.44	Observational	Normative data	1	Patients demonstrated reduced GHP and vitality and increased fatigue. Female patients reported reduced physical function
(9)	12	5/7	Range, 24–75	Cross-sectional	Healthy controls Reference values from general population	1	Patients on a 10-5-5 regimen scored worse on a unit designed questionnaire compared with controls. Compared with the general population, patients had worse QoL, regardless of HC regimen. In addition, total QoL score was worse in patients on a 10-5-5 mg regimen, but there were no differences when patients were on a 20-0-10 mg regimen
(52)[c]	20	13/7	Mean±s.d.: men, 45±4.4 Women, 45.8±2.6	Randomized placebo-controlled	NA	1	DHEA administration did not cause any relevant variation in SHS
(16)[c]	989	357/632	Mnd, 51.4	Retrospective Cross-sectional	Patients with osteoarthritis	2	Patients had a 2.68 times greater rate of affective disorders and a 2.12 times greater rate of depressive disorder compared with patients with osteoarthritis

Table 1 *Continued*

References	*n*	Gender (M/F)	Age (years)	Design	Controls	Domains	Outcomes
(14)[c]	210	53/157	Mnd (range): PAI: M, 41.5 (20–73) F, 49 (21–76) SAI: M, 54 (22–74) F, 49 (30–74)	Cross-sectional	Sex- and age-matched controls drawn from the questionnaire-specific reference cohort	1, 2	Patients on current standard replacement suffer from impaired QOL, irrespective of origin of disease
(13)	106	44/62	Mnd (range): DHEA, 46 (23–65) Placebo, 46 (22–65)	Randomized double-blind placebo-controlled	Normative data	1	Subscales on psychological well-being were significantly worse in patients compared with the control population. One subscale of the SF-36 (role emotional) improved significantly after DHEA treatment
(10)[c,d]	210	53/157	Mnd (range): PAI: M, 41.5 (20–73) F, 49 (21–76) SAI: M, 54 (22–74) F, 49 (30–74)	Cross-sectional	Sex- and age-matched controls drawn from the questionnaire-specific reference cohort	1, 2	SHS seemed equal regarding different glucocorticoid replacement therapies (HC, prednisone, and cortisone acetate), but was impaired compared with sex- and age-matched controls
(12)	426	153/273	Mean (range), 53 (18–95)	Observational	Normative data	1	QoL is reduced in patients with autoimmune AI, especially in patients with diabetes, whereas thyroid disease did not affect QoL
(20)[c]	14	3/11	Range, 29–70	Prospective	NA	1, 2	Mimicking the physiological rise in cortisol secretion during the night did not affect QoL
(11)[c,d]	210	53/157	Mnd (range): PAI: M, 41.5 (20–73) F, 49 (21–76) SAI: M, 54 (22–74) F, 49 (30–74)	Cross-sectional	Sex- and age-matched controls drawn from the questionnaire-specific reference cohort	1	QoL was impaired in patients. HC dosages above 30 mg/day were associated with worse SHS. Thrice daily intake of HC was not superior to twice-daily intake
(53)[c,d]	216	82/134	Mean ± S.D., mnd (range): PAI, 51 ± 15 48 (20–84) SAI, 57 ± 16 62 (18–81)	Retrospective Cross-sectional	Sex- and age-matched controls drawn from the questionnaire-specific reference cohort	1, 2	Patients showed an impaired SHS compared with controls. Patients who were diagnosed within 3 months showed better SHS
(54)	15	2/13	Mean (range), 34 (20–49)	Observational	NA	2	Patients demonstrated increased levels of anxiety, fear, and over-reaction to stimuli and decreased performance efficacy and need for social contact
(15)	63	18/45	Mnd (range): men, 43 (25–58) Women, 49 (41–56)	Cross-sectional	Patients with congenital adrenal hyperplasia and sex- and age-matched controls from questionnaire-specific reference cohorts	1, 2	Patients with AD showed more QoL impairments compared with patients with CAH

Table 1 *Continued*

References	*n*	Gender (M/F)	Age (years)	Design	Controls	Domains	Outcomes
(40)	15	9/6	Mean (range), 44.6 (21–74)	Randomized double-blind crossover	NA	1	QoL did not differ between patients on a four-dose regimen and patients on a two-dose regimen, but patients on a four-dose regimen tended to report better QoL
(55)[e]	15	9/6	Mean ± S.D., 44.6 ± 15.7	Randomized placebo-controlled double-blind crossover	NA	1	Patients have a dominant Th1 profile that correlates with a reduced QoL
(56)[c]	14	3/11	Mean ± S.D. (range), 63.2 ± 10.0 (47–76)	Crossover Cross-sectional	Reference data from controls matched by age and sex	1	Compared with the control population, patients reported higher fatigue rates at baseline and at 6 months. Modified-release prednisone showed decreased complaints and fatigue compared with standard prednisone treatment
(44)	200	53/147	Mnd (range), 48 (19–90)	Observational	NA	1	QoL was lower in female patients than that in male patients, and it was lower in those with manifestation at older ages and with more autoimmune comorbidities. Latency between first symptoms and diagnosis affected QoL even years after manifestation of disease
(57)	20	8/12	Mnd (range), 49.3 (32–66)	Prospective	NA	1	Reducing over replacement in the evening resulted in a decrease in reported sleep disturbances
Present study	54	21/33	Mean ± S.D., 49.67 ± 11.8	Cross-sectional	Healthy controls matched for age, gender, and education	1, 2, 3	Patients report psychological morbidity and an impaired QoL. Psychological morbidity, impaired QoL, and maladaptive personality traits were associated with higher HC intake

AD, Addison's disease; CFS, chronic fatigue syndrome; HC, hydrocortisone; SHS, subjective health status; GHP, general health perception; AI, adrenal insufficiency; CAH, congenital adrenal hyperplasia; Mnd, median. Assessed domains: 1, QoL or QoL-related aspects, general well-being, and subjective health status; 2, psychological functioning and psychological morbidity; 3, personality traits; 4, personality-related aspects (i.e. optimism/pessimism and locus of control); 5, illness perceptions; 6, coping strategies.
[a]Duplication of cohort which was previously described by Heijmans *et al*. (8).
[b]Duplication of cohort which was previously described by Arlt *et al*. (18).
[c]Included both patient with PAI and secondary AI.
[d]Duplication of cohort which was previously described by Hahner *et al*. (14).
[e]Duplication of cohort which was previously described by Ekman *et al*. (40).

classification (32). The presence of symptoms is rated on a severity scale from 0 to 3. We excluded the gender-specific items ($n=4$) from the analyses to rule out bias by gender. The total symptom score ranges from 0 to 153. A higher score indicates more (severe) physical symptoms in the preceding week (33).

The Dimensional Assessment of Personality Pathology short form (DAPPs) consists of 136 items to assess personality traits, which are subdivided into 18 subscales: submissiveness, cognitive distortion, identity problems, affective lability, stimulus seeking, compulsivity, restricted expression, callousness, oppositionality, intimacy problems, rejection, anxiousness, conduct problems, suspiciousness, social avoidance, narcissism, insecure attachment, and self-harm. The score for each subscale differs with maxima of 30–40, with higher scores indicating more pronounced maladaptive personality traits (34).

Statistical analysis

Data were analyzed using IBM SPSS Statistics, version 20.0.0 (SPSS, Inc.). All data were presented as mean ± S.D., unless mentioned otherwise. The primary analysis comprised the scores on the questionnaires, comparing between patients with stable treatment for PAI and healthy matched controls. To check the normality of data, the Kolmogorov–Smirnov test was used in addition to histograms and boxplots. Groups were compared using independent samples *t*-test. A Mann–Whitney *U* test was used in case of non-parametric data. χ^2 was used in case of categorical data. Because of multiple comparisons, the level of significance for this analysis was set at $P \leq 0.01$. The secondary analysis comprised the relationship between the scores on the various questionnaires and the mean daily dose of hydrocortisone, using a stepwise linear regression model. We included age and gender as additional independent variables. Because of the exploratory nature of this secondary analysis, adjustment of the level of significance for multiple testing was not performed, and the level of significance was set at $P \leq 0.05$.

Results

Sociodemographic and clinical characteristics

A total of 54 patients with PAI and 54 healthy controls, matched for gender, age, and education, were included. All patients were on stable hydrocortisone and fludrocortisone replacement therapy for a mean duration of 10.1 ± 8.5 years (range, 2–38 years), as prescribed by their individual physicians (mean daily hydrocortisone intake of 25 ± 7 mg (range, 10–50 mg), divided in two to three dosages). Eighty-three percent of the patients also used fludrocortisone in addition to hydrocortisone. Additional medical therapy included DHEA (26% of patients), levothyroxine (46%), anti-hypertensive drugs (13%), and oral contraceptives (9%). Sixty-five percent of female patients were postmenopausal (Tables 2 and 3).

Table 2 Clinical characteristics of patients with PAI. Data are noted in mean (S.D.) or number and percentage (%). Patients with PAI and matched controls did not differ on any characteristic.

	PAI ($n=54$)	**Matched controls** ($n=54$)
Gender (M/F)	21/33	21/33
Age (years)	49.67 (11.8)	49.26 (12.5)
Educational level	Low: 10 (19%) Medium: 21 (39%) High: 23 (43%) Unknown: 0	Low: 9 (17%) Medium: 22 (41%) High: 22 (41%) Unknown: 1 (2%)
BMI	26.42 (5.3)	NA
PAI diagnosis	AI: 44 (82%) Non-AI: 5 (9%) BA: 2 (4%) Unknown: 3 (5%)	NA
Hydrocortisone dose[a]	24.90 (7.2)	NA
Florinef	45 (83%)	NA
DHEA	14 (26%)	NA
Levothyroxine[b]	25 (46%)	NA
Oral contraceptive	2 (11%)	NA
Anti-hypertensives	7 (13%)	NA
Menopause	15 (45%)	NA

PAI, primary adrenal insufficiency; NA, not applicable; AI, autoimmune; BA, bilateral adrenalectomy.
[a]Total dose per day.
[b]Hypothyroidism due to Hashimoto's thyroiditis.

Psychological functioning and QoL

Patients with PAI had a higher total score on the Irritability Scale ($P=0.004$) compared with matched controls. Patients also showed higher scores on the somatic arousal subscale of the MASQ-30 ($P=0.003$). Clinically significant apathy and irritability (a score of ≥14 on the Apathy Scale and on the Irritability Scale) was present in 35 and 33% of patients, respectively, and significantly more irritability was observed in patients than in controls ($P=0.01$). On the HADS, 11% of patients had a score of ≥8 on the anxiety subscale and 6% on the depression subscale. This is indicative for the presence of clinically relevant anxiety or depression respectively. There were no significant differences between patients and controls on the depression subscale, anxiety subscale, or total HADS score (Table 4).

Table 3 Clinical characteristics of PAI subjects. Data are noted in mean (s.d.) or number and percentage (%).

	Males with PAI ($n=21$)	Females with PAI ($n=33$)
Age (years)	48.48 (13.1)	50.52 (11.0)
Educational level	Low: 3 (14%) Medium: 9 (43%) High: 9 (43%)	Low: 7 (21%) Medium: 12 (36%) High: 14 (42%)
BMI	26.12 (3.6)	26.62 (6.3)
PAI diagnose	AI: 17 (81%) Non-AI: 2 (10%) BA: 2 (10%) Unknown: 0	AI: 27 (82%) Non-AI: 3 (9%) BA: 0 Unknown: 3 (9%)
Hydrocortisone dose[a]	26.90 (6.8)	23.62 (7.3)
Florinef	16 (76%)	29 (88%)
DHEA	2 (10%)	12 (36%)
Levothyroxine[b]	6 (29%)	19 (58%)
Oral contraceptive	NA	2 (11%)
Anti-hypertensives	3 (14%)	4 (12%)
Menopause	NA	15 (45%)

PAI, primary adrenal insufficiency; NA, not applicable; AI, autoimmune; BA, bilateral adrenalectomy.
[a]Total dose per day.
[b]Hypothyroidism due to Hashimoto's thyroiditis.

Patients scored worse on all subscales of the MFI-20 compared with matched controls, i.e. general fatigue ($P<0.001$), physical fatigue ($P<0.001$), reduced activity ($P=0.003$), reduced motivation ($P=0.006$), and mental fatigue ($P<0.001$). Patients with PAI also scored worse on the physical functioning subscale ($P<0.001$), social functioning subscale ($P=0.001$), role limitation (physical) subscale ($P<0.001$), vitality subscale ($P=0.009$), and general health perception subscale ($P<0.001$) of the SF-36. On the EQ-5D, patients scored worse than matched controls on activity ($P<0.001$) and the VAS ($P<0.001$). Furthermore, patients scored worse on energy ($P<0.001$) and physical ability ($P<0.001$) compared with matched controls as measured with the NHP. Lastly, patients reported more general/neurological symptoms ($P<0.001$), autonomic symptoms ($P<0.001$), genital symptoms ($P=0.002$), and feeling hot/cold ($P<0.001$) on the PSC compared with matched controls.

Personality traits

The scores of the patients on the DAPPs personality traits were not different from those of the matched controls.

The association with daily hydrocortisone intake

Higher hydrocortisone intake was associated with lower psychological well-being, more maladaptive personality traits, and more impaired QoL. More specifically, a higher dose of hydrocortisone was associated with more depressive symptoms (HADS Depression subscale, $\beta=0.282$, $P=0.038$), as well as decreased physical functioning ($\beta=-0.365$, $P=0.008$), more physical role limitations ($\beta=-0.329$, $P=0.015$), and more pain ($\beta=-0.272$, $P=0.047$) (all SF-36 subscales). Moreover, the SF-36 subscale vitality was negatively associated with gender ($\beta=-0.284$, $P=0.039$), indicating that females reported less vitality. Furthermore, a higher hydrocortisone intake was associated with worse scores on mobility ($\beta=0.345$, $P=0.011$) and the VAS ($\beta=-0.335$, $P=0.013$) of the EQ-5D. Lastly, a higher hydrocortisone intake was associated with several maladaptive personality traits, including more cognitive distortion ($\beta=0.288$, $P=0.037$), identity problems ($\beta=0.474$, $P=0.000$) (Fig. 1), compulsivity ($\beta=0.302$, $P=0.029$), restricted expression ($\beta=0.277$, $P=0.042$), callousness ($\beta=0.376$, $P=0.005$), oppositionality ($\beta=0.291$, $P=0.035$), rejection ($\beta=0.282$, $P=0.043$),

Table 4 Psychological functioning, QoL, and personality in patients with PAI. Data are noted in mean (s.d.); only significant results are listed.

	PAI ($n=54$)	Matched controls ($n=54$)	*P* value
Irritability scale			
Total score	11.32 (7.0)	7.78 (5.3)	0.004
Score ≥ 14, *n* (%)	18 (33%)	7 (13%)	0.010
MASQ-30			
Somatic arousal	15.49 (7.0)	12.00 (2.6)	0.003
MFI-20			
General fatigue	12.15 (5.5)	7.21 (3.5)	<0.001*
Physical fatigue	11.04 (5.1)	6.83 (2.6)	<0.001*
Reduced activity	9.72 (4.1)	7.40 (3.3)	0.003
Reduced motivation	8.67 (3.5)	6.87 (3.0)	0.006
Mental fatigue	11.08 (4.4)	7.38 (2.9)	<0.001*
SF-36			
Physical functioning	80.29 (19.6)	94.15 (7.7)	<0.001*
Social functioning	77.12 (24.5)	91.27 (14.6)	0.001
Role limitation (physical)	65.28 (43.8)	93.75 (17.8)	<0.001*
Vitality	48.21 (9.8)	52.92 (8.5)	0.009
General health perception	54.06 (26.1)	77.31 (15.5)	<0.001*
EQ-5D			
Activity	1.35 (0.5)	1.06 (0.2)	<0.001*
VAS	72.66 (15.9)	84.12 (10.2)	<0.001*
NHP			
Energy	0.29 (0.4)	0.03 (0.1)	<0.001*
Physical ability	0.09 (0.1)	0.01 (0.0)	<0.001*
PSC			
General/neurological	0.73 (0.5)	0.35 (0.2)	<0.001*
Autonomic symptoms	0.53 (0.4)	0.16 (0.2)	<0.001*
Genital symptoms	0.29 (0.4)	0.11 (0.2)	0.002
Feeling hot/cold	0.79 (0.7)	0.27 (0.3)	<0.001*

Level of significance was set at *$P\leq 0.01$, adjusting for multiple testing.

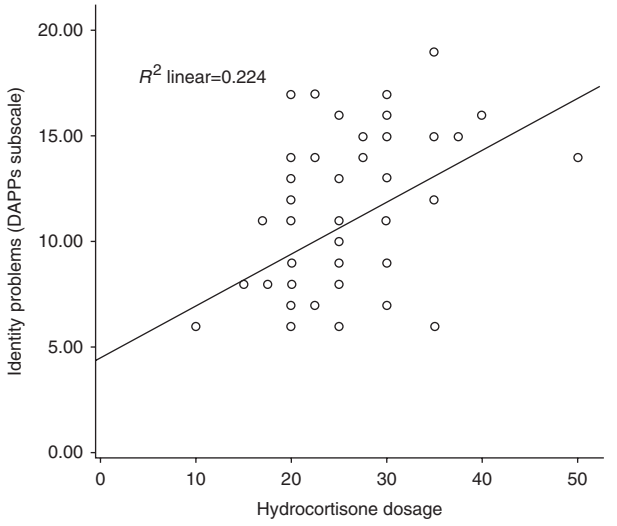

Figure 1
Association between hydrocortisone dosage and identity problems.

social avoidance (β=0.316, P=0.021), and narcissism (β=0.273, P=0.036). Moreover, narcissism (β=−0.337, P=0.010) was negatively associated with age and self-harm was positively associated with age (β=0.324, P=0.017). Female patients reported more conduct problems (β=−0.358, P=0.008; Table 5).

Discussion

This study demonstrates that patients with stable treatment for PAI suffer from more psychological morbidity with irritability and somatic arousal, in addition to impairments of QoL compared with matched healthy controls. However, personality traits were not different between patients and controls, which indicates that personality traits in patients with PAI, in contrast to psychological functioning, are not sensitive to the effects of a chronic disease, such as PAI and its pharmacological treatment in contrast to psychological morbidity. To our knowledge, this is the first study on personality traits in patients with PAI. Interestingly, there was a strong and consistent association between the mean daily hydrocortisone dose and the prevalence of maladaptive personality traits, such as cognitive distortion, identity problems, and compulsivity, and also with restricted expression, callousness, oppositionality, rejection, social avoidance, and narcissism. Furthermore, there was a strong positive relation between the mean daily hydrocortisone intake and reported psychological morbidity (i.e. depression) and QoL impairments (i.e. several measures of physical functioning and pain).

Previous studies by our group have shown similar results with regard to psychological functioning and QoL in patients in long-term remission of Cushing's disease, though patients in remission of Cushing's disease also showed more maladaptive personality traits than their matched controls (3, 4, 5, 35). These observations suggest that psychological functioning and QoL indeed follow the inverted u-shape dose–response curve of cortisol exposure related to MR and GR activation, whereas this is not the case for personality traits and lower cortisol levels. Intriguingly, higher daily hydrocortisone intake seemed to be strongly associated with maladaptive personality traits, indicating that hydrocortisone intake does have a considerable effect on personality traits in patients with AI.

Our findings regarding QoL are in line with the results of previous studies on decreased QoL in patients with AI (9, 14, 36, 37) and the self-reported impact of the disease or treatment on subjective health status (38). In addition,

Table 5 Influence of daily hydrocortisone dosage, age, and gender on dimensions in the questionnaires. There were no significant associations between daily hydrocortisone dosage, age and gender, and scores on the Apathy scale, Irritability scale, MAQ-30, MVI-20, NHP, and PSC.

	Hydrocortisone dosage	Age	Gender
HADS			
Depression	β=0.282*		
SF-36			
Physical functioning	β=−0.365†		
Role limitation (physical)	β=−0.329*		
Vitality			β=−0.284*
Pain	β=−0.272*		
EQ-5D			
Mobility	β=0.345*		
VAS	β=−0.335*		
DAPP			
Cognitive distortion	β=0.288*		
Identity problems	β=0.474†		
Compulsivity	β=0.302*		
Restricted expression	β=0.277*		
Callousness	β=0.376*		
Oppositionality	β=0.291*		
Rejection	β=0.282*		
Conduct problems			β=−0.358†
Social avoidance	β=0.316*		
Narcissism	β=0.273*	β=−0.337*	
Self-harm		β=0.324*	

Only associations that reached statistical significance (*P<0.05 and †P<0.01) are depicted.

several QoL studies demonstrated that inadequate hydrocortisone replacement dosages and, especially, high hydrocortisone dosages negatively affected QoL (11, 37, 39, 40). Accordingly, we found negative effects of high hydrocortisone intake on QoL in patients with PAI. Intriguingly, we also found a negative effect of high hydrocortisone intake on psychological morbidity and the prevalence of maladaptive personality traits.

In healthy individuals, cortisol is secreted in a pulsatile fashion with a superimposed circadian rhythm. It is actually impossible to mimic this normal pattern of hormonal secretion by hydrocortisone replacement. These imperfections in pharmacotherapy are, at least in part, associated with persistent vague complaints and a decreased QoL (9). The importance of mimicking the circadian rhythm of cortisol secretion in patients with AI is supported by a study of Johannsson *et al*. (41), which demonstrated that in patients treated with once-daily dual-release hydrocortisone tablets, a more circadian-based cortisol profile and more favorable scores on questionnaires assessing psychological well-being and fatigue were observed, compared with patients treated with conventional hydrocortisone treatment. Furthermore, both Løvås & Husebye (42) and Oksnes *et al*. (43) reported that continuous hydrocortisone infusion in patients with PAI resulted in cortisol and ACTH levels toward normal circadian levels and positively affected QoL. These two studies suggest that the physiological profile might be related to QoL outcomes.

A previous study by Thomsen *et al*. (16) reported an increased risk for developing affective disorders (e.g. depression, bipolar disorder) in hospitalized patients with AI. In our cohort of patients with stable PAI, we did not find differences in depressive symptoms between patients and healthy controls. However, considering the fact that we did find other psychological morbidity (i.e. irritability and somatic arousal), we postulate that even after correction of hypocortisolism, patients with PAI remain vulnerable for developing psychological and, in particular, mood symptoms.

Recently, gender, manifestation at older age, more autoimmune comorbidities, and latency between first symptoms and diagnosis have been found to negatively affect QoL in patients with AI (44). Our data indicate that the amount of daily hydrocortisone intake should also be included as a potential influencing factor of QoL. Nevertheless, because of the exploratory nature of our study, future research is needed to provide more insights into predictors of reduced QoL in patients with AI and to further distinguish whether the QoL impairments are caused by the disease itself or its treatment. In addition to the focus on research about somatic predictor variables, researchers should pay attention to potential psychological contributing factors, such as negative illness perceptions and ineffective coping strategies, because recent data have indicated that negative illness perceptions were related to a decreased QoL in patients in long-term remission of Cushing's diseases (45).

A possible limitation of this study is the cross-sectional design, which does not preclude that maladaptive personality traits and QoL impairments were already present before the onset of the disease. Furthermore, we cannot simply conclude that high hydrocortisone intake causes a decreased QoL, because it might be that high hydrocortisone dosages were prescribed because patients suffered from psychological symptoms or a decreased QoL. Therefore, future studies should use a longitudinal design to enable the evaluation of the course of psychological functioning, QoL, and personality, and of the influence of adaptations in hydrocortisone intake on these three domains over time. A longitudinal design might also elucidate the interesting discrepancy between our finding that personality traits of patients with PAI do not differ from healthy controls, whereas higher daily hydrocortisone intake is significantly associated with maladaptive personality traits in patients with PAI.

In summary, patients with stable treatment for PAI report psychological morbidity and impaired QoL. There is a positive association between the daily hydrocortisone intake and the presence of psychological morbidity, maladaptive personality traits, and QoL impairments. These results point toward the possibility to intertwine psychosocial parameters in care for patients with endocrine replacement in general, and for patients with AI specifically. This approach would open the area of self-management research in this patient category, which has already been shown to have positive effects on QoL in patients with other chronic somatic diseases (46, 47, 48).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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