CLINICAL STUDY

Impaired subjective health status in chronic adrenal insufficiency: impact of different glucocorticoid replacement regimens

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Abstract

Context: Recent studies have suggested that current glucocorticoid replacement therapies fail to fully restore well-being in patients with adrenal insufficiency (AI).

Objective: To investigate the effect of different glucocorticoid preparations used for replacement therapy on subjective health status (SHS) in AI.

Design and patients: In a cross-sectional study, primary and secondary AI patients were contacted by mail. Individual glucocorticoid replacement regimens, underlying diagnoses and comorbidities were verified by questionnaires and review of medical records. Patients were asked to complete three validated self-assessment questionnaires (Short Form 36 (SF-36), Giessen Complaint List (GBB-24), and Hospital Anxiety and Depression Scale). Results were compared with sex- and age-matched controls drawn from the questionnaire-specific reference cohort.

Results: Of the 883 patients identified, 526 agreed to participate in the study. Completed questionnaire sets were available from 427 patients (primary AI $n = 232$; secondary AI $n = 195$). AI patients showed significantly impaired SHS compared with controls irrespective of the glucocorticoid used for replacement. The only difference in SHS between patients on prednisolone (PR) and hydrocortisone (all patients and sub-analysis for primary AI) was significant higher bodily pain (lower Z-score in SF-36) in patients on PR ($P < 0.05$, $P < 0.01$ respectively). In patients with secondary AI, the PR group showed significantly ($P < 0.05$) less heart complaints (lower Z-score) in the GBB questionnaire compared with the cortisone acetate group.

Conclusions: Glucocorticoid replacement therapy with PR seems to be equivalent to hydrocortisone regarding SHS in patients with AI. However, SHS remains impaired in all patient groups suggesting a need for further improved glucocorticoid replacement strategies.

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Introduction

Patients with chronic primary (PAI) and secondary adrenal insufficiency (SAI) rely on a lifelong, daily medical treatment with glucocorticoids, and in primary AI also with mineralocorticoids (1). Adding DHEA to the replacement regimen in patients with PAI and SAI is still in debate (2). Recently, it has been demonstrated that the patients with PAI and SAI show a significantly reduced subjective health status (SHS), irrespective of age, sex, concomitant disease, and primary or secondary origin of AI (3, 4). Importantly, also increased mortality has been described (5, 6). These observations have renewed the discussion of optimal replacement treatment in AI after about 50 years of almost unchanged regimens. The main focus of this discussion is glucocorticoid replacement as current replacement

strategies lead to cortisol profiles differing profoundly from the physiological diurnal rhythm of serum cortisol.

In clinical practice, several different glucocorticoids are prescribed for hormone replacement therapy. Hydrocortisone (HC) is recommended by most authors as it represents the physiological glucocorticoid (7–9). However, even when given thrice daily, cortisol profiles only partially resemble the circadian profile due to very high peak levels followed by very low trough levels prior to the next oral dose. In PAI, this is also associated with intermittent excess of circulating ACTH. Cortisone acetate (CA), used in the study by Lovas *et al.* (3) in Norway, seems to have a lower serum cortisol peak and a delayed decline of cortisol levels (10, 11). However, cortisol generation may be occasionally affected by an impaired 11 β -hydroxysteroid reductase activity (12).

Prednisolone (PR) is widely used for glucocorticoid replacement, usually given as a single morning dose of 5 mg. It has the advantage of a more sustained action compared with HC and a more convenient administration as a single morning dose. However, long-term side effects and the exact relative potency in humans remain still uncertain. The potency of PR is described to be four to five times higher than HC. Additionally, PR duration of action is 12–36 h compared with 6–10 h for HC. Limited data are available regarding long-term side effects of glucocorticoid replacement therapy (13). The currently available studies might suggest that bone loss is not influenced by the duration or type of steroid treatment (14, 15), but rather by the glucocorticoid dose used for chronic replacement (16). However, none of the studies had included large enough numbers to address this properly.

We have recently demonstrated reduced SHS in a large German cohort of patients with primary and secondary AI (4). Inadequate glucocorticoid replacement was suspected as a main cause of this impairment.

The aim of the present study was now to study potential differences in SHS and perceived influences on activities of daily life with regard to different glucocorticoid medications (PR, HC and CA) in this extended large German cohort of patients with PAI and SAI.

Methods

Subjects

Patients with AI from the Federal Republic of Germany and West Berlin with primary or SAI were usually treated with HC, while patients from the former German Democratic Republic (GDR) received PR. This different medical substitution therapy in East- and West Germany has a predominately historical reason, due to former unavailability of HC in the GDR.

All AI patients are currently registered in the outpatient clinics of the Endocrine Departments of the Charité Campus Mitte Berlin and the University Hospital Wuerzburg or private endocrine practices in Berlin ($n=683$), or are registered members of the German self-help network ($n=200$). The patients were asked to participate in a postal survey. The study was approved by the ethical committees of the Charité Campus Mitte Berlin (permit no. ES1/037/06) and the University Hospital Wuerzburg (permit no. 45/04), and written informed consent was obtained from all patients prior to participation. Participating patients received four questionnaires, which they had to complete without consulting friends or family members, and were asked to return the completed questionnaires to the Endocrine Departments. Data regarding SHS from a subgroup of patients (132 patients with PAI and 78 with SAI) from Wuerzburg and the self-helping network have already been published (4).

The underlying diagnosis of AI was verified by review of the medical records. In addition, the following exclusion criteria were applied: AI due to long-term pharmacological glucocorticoid treatment, glucocorticoid doses above 7.5 mg PR equivalent for reasons other than AI, adrenocortical carcinoma, congenital adrenal hyperplasia, adrenoleukodystrophy, and patients with less than 12 months duration of disease.

Questionnaires

Patients were asked to complete three different questionnaires and one self-established general registration form. Psychometric evaluation of patients was performed using three validated self-assessment SHS questionnaires: the social functioning (SF)-36, the brief form of the Giessen Complaint List (GBB-24), and the 'Hospital Anxiety and Depression Scale' (HADS). All three questionnaires are presented as a self-explanatory, multiple-choice self-assessment.

The SF-36 questionnaire is the most widely used generic instrument to assess health-related quality of life (17). It consists of eight multi-item domains representing physical functioning, role functioning physical, bodily pain (BP), general health perception, vitality, SF, role functioning emotional (RE), and mental health (MH), as well as psychometrically based physical and MH summary measures. The domain scores range from 0 to 100 with higher values indicating better quality of life (18, 19). Reference data for SF-36 scores were obtained from the German National Health Survey (Bundesgesundheits Survey 1998, Robert Koch Institut Berlin 2000, Public use file BGS 98) comprising a representative random sample of 7124 subjects from the German population aged between 18 and 79 years (20). Higher -scores indicate less pain or less impaired functioning.

The short form of the GBB-24 questionnaire consists of 24 items defining four subscales (exhaustion tendency (et), gastric symptoms (gs), pain in the limbs (lp), and heart complaints (hc)) each including six items with ratings from 0 to 4. Additionally, a global score of discomfort is calculated by adding up the four subscale scores. The maximum value for each subscale is 24, and the global score 96. Higher scores indicate greater impairment of well-being (21).

The HADS is a 14-item, self-administered rating scale designed to measure anxiety and depression in physically ill individuals (22). Each item is scored as a number, with a maximum score of 21 for each subscale. Higher scores indicate higher levels of anxiety or depression. A cutoff value of 8 correlates with significant impairment and a cutoff value of 11 is indicative of major impairment, e.g. psychiatric disorders like major depression. Reference data for the GBB-24 ($n=2076$) and HADS ($n=2081$) were obtained from surveys performed by Braehler and co-workers (21, 23).

Furthermore, a self-established general registration form collected data specifically matched for this survey. We were especially interested in issues concerning the patient's drug consumption (e.g. glucocorticoid use, daily dose), as well as the perceived influence of AI on activities of daily life. In addition, data were collected on duration and cause of AI, further medication, additional endocrine and general health problems, education, and occupational status.

Patients were grouped according to their sex, hormone replacement, as well as primary and secondary AI. Additionally, the duration of treatment and age of manifestation was taken into account. We compared the results of the three standardized questionnaires between the groups.

Statistical analysis

Comparison of quality of life scores between patients and matched controls was performed by Mann–Whitney *U*-test. Before comparison of the subgroups of patients with primary and secondary AI, which were inhomogeneous regarding age and sex distribution, adjustment for age and sex was performed by transformation of score values from patients and controls into age- (decade) and sex-adjusted Z-scores. Calculation of Z-scores was based on the complete data set from the respective normative groups. Differences in Z-scores, age, and body mass index (BMI) were subsequently analyzed by Mann–Whitney *U*-test.

Analyses were performed using the statistical software package SPSS, version 13.0 (SPSS Inc., Chicago, IL, USA). Significance was accepted if $P < 0.05$.

Results

Study cohort

Of the 883 patients contacted, 526 patients (60%) agreed to participate (Fig. 1) in the study. For further analysis of this study, 427 questionnaires were considered.

Data regarding SHS from a subgroup of patients (132 patients with PAI and 78 with SAI) from Würzburg and the self-helping network have already been published (4). However, in the published cohort only 18 patients received CA and one patient PR. The subgroup of patients from Berlin and state Brandenburg included 100 new patients with PAI and 117 with SAI.

Medical substitution

We compared patients with PAI and SAI on treatment with HC, PR, or CA (Table 1).

Comparing all patients on HC versus patients on PR and CA regardless of sex and the cause of AI, the

Figure 1 Flow sheet illustrating the recruitment for the study of 427 patients with adrenal insufficiency (AI).

only significant ($P < 0.05$) difference was a higher BP (lower Z-score) in the SHS (SF-36) in patients on PR (Fig. 2a). The whole group of AI patients showed no considerable differences in anxiety or depression (HADS), or physical complaints (GBB-24; Figs 3a and 4a).

Sub-analysis of PAI patients showed that patients on PR had significantly higher BP (lower Z-score) than those on HC ($P = 0.006$) and CA ($P = 0.008$; Fig. 2b). However, BP was not enhanced compared with controls. No differences were found in regard to anxiety or depression (HADS), or physical complaints (GBB-24) between different glucocorticoid therapy in patients with PAI (Figs 3b and 4b).

In patients with SAI, no difference was found between HC and PR replacement therapies in SHS (Figs 2c, 3c and 4c). The only significant difference ($P < 0.05$) between CA and PR was found in the physical complaints questionnaire (GBB-24) with a lesser heart complaint (lower Z-score) in SAI patients on PR (Fig. 4c).

In a sex-specific sub-analysis, PR and CA were significantly better ($P < 0.05$) than HC with regard to the RE in the SHS (SF-36) in men (data not shown). In women on PR a higher BP ($P < 0.05$) in the SHS (SF-36) was found compared with women on HC (data not shown). Data analysis of the self-established general registration form specifically matched for this survey showed no significant difference between HC and PR (data not shown).

No significant differences in BMI were seen between patients on different glucocorticoid therapy (Table 1). Patients on PR were significantly older and had a longer duration of disease (Table 1). In PAI patients, no difference in the dosage of fludrocortisone therapy was found depending on the different glucocorticoid therapy (Fig. 5).

Table 1 Clinical data on patients with primary (PAI) and secondary (SAI) adrenal insufficiency with regard to their glucocorticoid therapy (HC, hydrocortisone; CA, cortisone acetate; PR, prednisolone).

	PAI (n=232)						SAI (n=195)					
	Men (n=58; 25%)			Women (n=174; 75%)			Men (n=79; 40%)			Women (n=116; 60%)		
	HC	CA	PR	HC	CA	PR	HC	CA	PR	HC	CA	PR
n	47	7	4	153	5	17	56	2	21	92	5	19
Age (years)	47±2.4	53±4.7	65±10.7*	48±1.1	49±4.7	60±2.5 ^{†,‡}	54±2.2	69±3.5	61±2.7	51±1.5	55±6.9	62±2.5**
Duration of disease (years)	10±1.3	25±6.4	20±4.6*	12±0.8	18±6.4	23±2.5 [†]	9±1.0	26±15.0	19±2.1 [†]	12±1.0	15±7.6	21±2.3 [†]
BMI (kg/m ²)	25.6±0.6	26.4±1.9	25.9±2.3	23.7±0.3	22.1±1.0	25.0±0.9	26.8±0.8	24.4±2.6	27.0±0.7	26.4±0.6	25.7±1.8	28.3±1.4
On DHEA treatment (n=)	2	1	0	56	1	4	3	0	0	26	0	0

Data are given as mean ± s.e.m. **P*<0.05, ***P*<0.005, [†]*P*<0.001 vs HC; [‡]*P*<0.05 vs CA. BMI, body mass index; DHEA, dehydroepiandrosterone.

Figure 2 Z-scores (mean ± s.e.m. scores) for SF-36 in (a) all patients with adrenal insufficiency, (b) patients with primary adrenal insufficiency (PAI), and (c) patients with secondary adrenal insufficiency (SAI) depending on different glucocorticoid therapies. Decade- and sex-adjusted Z-scores were calculated for subgroup analysis. Higher scores indicate less pain or less impaired functioning. HC, hydrocortisone; PR, prednisolone; CA, cortisone acetate; PF, physical functioning; RP, role functioning physical; BP, bodily pain; GH, general health perception; VT, vitality; SF, social functioning; RE, role functioning emotional; MH, mental health; **P*<0.05 compared with HC; ***P*<0.01 compared with HC and CA.

Figure 3 Z-scores (mean $\pm$ S.E.M. scores) for HADS in (a) all patients with adrenal insufficiency, (b) patients with primary adrenal insufficiency (PAI), and (c) patients with secondary adrenal insufficiency (SAI) depending on different glucocorticoid therapies. Decade- and sex-adjusted Z-scores were calculated for subgroup analysis. Higher scores indicate higher levels of anxiety or depression. HC, hydrocortisone; PR, prednisolone; CA, cortisone acetate.

Discussion

Standard replacement therapy for chronic adrenal insufficiency (AI) consists of glucocorticoids (1), which clearly prevent life-threatening adrenal crisis. However, current replacement regimens fail to fully restore health-related quality of life in affected patients (3). An analysis of 989 patients with chronic AI from Denmark revealed a significantly higher rate of affective and depressive disorders compared with a control group of patients with osteoarthritis (24). Moreover, there is preliminary evidence from a large Swedish patient sample indicating that primary AI may even be associated with increased mortality (5), which had been demonstrated previously for patients with hypopituitarism including SAI (6). Recently, we have shown an impaired health-related SHS, irrespective of origin of disease or concomitant disease in 210 patients with primary and secondary AI (4). We hypothesized that non-physiological glucocorticoid replacement is the main cause of reduced health status in these patients.

The present study, which includes the already published subgroup of patients from Wuerzburg (4), confirms our recent findings of reduced SHS in this extended patient cohort of now 427 patients. Although HC, PR, and CA have different pharmacokinetic and also pharmacodynamic properties, SHS and daily performance was not influenced by these different replacement modes in a relevant manner.

We could detect no relevant differences in SHS between the glucocorticoid preparations used in our patients. A difference was seen in the overall cohort and in PAI patients with a higher pain perception in patients on PR compared with a decrease in those on CA or HC. However, pain perception in PR users did not differ from pain perception in the reference population. In our previous paper, we hypothesized that the reduced pain perception in patients with PAI might be due to the increased levels of POMC. Thus, a reduction of POMC levels by the longer acting PR might explain the observed differences between the HC and the PR group in the present study. However, no data on morning plasma ACTH concentrations were available to test this hypothesis.

As the mineralocorticoid effect of PR is less compared with HC, higher doses of fludrocortisone were expected in the PR group. However, fludrocortisone doses were largely identical in the two subgroups suggesting different mineralocorticoid availability, which might also participate in the minor differences observed in this study.

The cohorts were slightly inhomogeneous regarding the age and disease duration with older subjects and longer disease duration in the PR group. Nevertheless, patients on PR presented with comparable SHS like patients on HC or CA. Furthermore, our analysis adjusted for age and sex by using Z-scores. We could not further detect a significant difference in BMI between the groups. BMI in the PR cohort was slightly higher but this might be attributed to the higher age.

Figure 4 Z-scores (mean $\pm$ S.E.M. scores) for GBB-24 in (a) all patients with adrenal insufficiency, (b) patients with primary adrenal insufficiency (PAI), and (c) patients with secondary adrenal insufficiency (SAI) depending on different glucocorticoid therapies. Decade- and sex-adjusted Z-scores were calculated for subgroup analysis. Higher scores indicate greater impairment of well-being. HC, hydrocortisone; PR, prednisolone, CA, cortisone acetate; * $P < 0.05$ compared with CA.

Altogether, in chronic glucocorticoid replacement therapy for AI, PR can be regarded as equivalent to HC concerning SHS. This is in contrast to the widely held opinion that long-acting glucocorticoids are inferior and should be avoided in AI. However, it is necessary to

Figure 5 Daily fludrocortisone dose (mg/day) in patients with primary adrenal insufficiency depending on different glucocorticoid therapies (HC, hydrocortisone; CA, cortisone acetate; PR, prednisolone).

point out that this is a cross-sectional study, which shows only observational data. Possible limitations are that the cohort size might still be too small to detect real differences. In addition, we did not investigate long-term effects on other parameters such as bone turnover, metabolic parameters, or overall survival. However, in a small study there were no significant differences between bone mineral density in patients with AI treated with HC and those on PR (15). This indicates the need for prospective clinical trials.

The reason for the consistently impaired SHS in patients with AI remains to be elucidated. While in normal subjects cortisol is secreted in a pulsatile fashion with a clear diurnal rhythm (25, 26), this pattern is profoundly different in patients with AI receiving current replacement regimens (13). In particular, patients take their first HC dose in the morning starting with very low cortisol levels, whereas in normal subjects a steep cortisol rise is found in the hours before waking. Accordingly, patients with PAI typically exhibit increased plasma ACTH concentrations prior to the first morning dose. Thus, the most pronounced difference to normal subjects occurs in the hours between midnight and waking. New timed release glucocorticoid preparations may allow the treatment to better mimic the early morning cortisol rise prior to waking in the patients with AI and may hold the potential to positively affect the quality of life in AI (27). This view is supported by a recent short open-label pilot study in seven patients with Addison's disease. In this study, administration of HC via continuous s.c. infusion successfully re-established the physiological circadian variation and allowed reduction of the glucocorticoid dose. Treatment was well tolerated and led to an improvement of SHS (28). Furthermore, a timed release PR preparation was recently used in patients with rheumatoid arthritis showing that glucocorticoid release prior to waking significantly reduced disease activity compared with an identical morning dose of standard PR (29).

In conclusion, PR is equivalent to HC as glucocorticoid replacement therapy regarding SHS, which is significantly

impaired in AI compared with sex- and age-matched controls. An optimal glucocorticoid replacement awaits the availability of a glucocorticoid formulation that can replicate the normal circadian rhythm and replace physiological cortisol production. Future interventional trials are necessary to explore the role of these more physiological glucocorticoid replacement strategies in AI.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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