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ORIGINAL

Improvement of health-related quality of life in adult women with 21-hydroxylase deficiency over a seven-year period

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Abstract. Health related quality of life (HRQoL) is impaired in adult patients with 21-hydroxylase deficiency (21-OHD). Up to now, only cross-sectional and no longitudinal studies are available. It is not known if HRQoL can be improved in adult 21-OHD patients. We performed a longitudinal, prospective, single centre, follow-up study over seven years including 15 adult female 21-OHD patients. Two standardized questionnaires (Short Form 12 (SF-12); Hospital Anxiety and Depression Scale (HADS)) were completed in 2003, 2006 and 2010. Adjustment for age and sex was performed by transformation of score values into age- and sex-adjusted Z-scores using data sets from respective normative groups. Data regarding glucocorticoid therapy, clinical and hormonal parameters were assessed. We found that two of eight scales of SF-12 showed a significant improvement and four of eight scales a positive trend to better scores. No significant changes were seen in scores for HADS or for steroid hormone levels. Daily hydrocortisone equivalent dose per body surface significantly decreased over the study period. No changes in BMI were observed over the study period. We conclude that improvement of HRQoL in adult female 21-OHD patients is possible. Several factors might be involved in this improvement including reduced daily hydrocortisone equivalent dose per body surface.

Key words: Congenital adrenal hyperplasia, Hydrocortisone, Prednisolone, Dexamethasone, Short Form 12 (SF-12)

MUTATIONS in the gene encoding 21-hydroxylase cause the most common form of congenital adrenal hyperplasia (CAH) [1, 2]. Clinical management aims at replacement therapy with glucocorticoids and mineralocorticoids to correct hypocortisolism, hypoaldosteronism and to normalize hyperandrogenism, which often results in higher glucocorticoid doses than in primary adrenal insufficiency (PAI) [3]. Physicians face the problem to adjust to ideal dosage of glucocorticoids in order to avoid under- as well as overtreatment [4, 5]. Undertreatment may result in higher risk of adrenal crisis, disturbed pubertal development, reduced final height, infertility, and androgen-driven insulin resistance, however overtreatment results in obesity, impaired glucose homeostasis, infertility and reduced bone mineral density (BMD) [1]. However, the best regimen and approach to monitoring remain elusive. In addition, treatment goals of adults with 21-hydroxylase deficiency (21-OHD) differ from those for children [6]. In the recent years several recommendations advised to reduce the supraphysiological doses of glucocorticoid replacement therapy to reduce glucocorticoid side-effects [3, 6]. No data is available regarding the question if a reduction of glucocorticoid doses also affects health-related quality of life (HRQoL) in adult 21-OHD patients.

Recent studies have found significantly impaired subjective HRQoL in patients with PAI and secondary adrenal insufficiency (SAI) [7-10]. Current data on HRQoL in adult patients with 21-OHD shows conflicting results [11-14], however the most recent studies showed impaired HRQoL also in 21-OHD patients [15-17].

All recent studies on HRQoL in 21-OHD were performed as cross-sectional and not as longitudinal follow-up studies. Therefore, we were interested in the development of HRQoL over time in women with 21-OHD, and performed a prospective longitudinal follow-up study with three visits between 2003 and 2010.

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Methods

Subjects

Participating patients (women with classic form of 21-OHD (SW and SV)) received two standardized questionnaires at their visits to the outpatient clinic of the Endocrine Department of the Charité Campus Mitte, Berlin, Germany, in 2003, 2006 and 2010, which they had to complete without consulting friends or family members, and were asked to return the completed questionnaires. At all three visits the current medication and laboratory results were documented. The underlying diagnosis of 21-OHD was verified by review of the medical records including genetic testing. The study was approved by the ethical committee of the Charité Campus Mitte Berlin (permit no. ES1/037/06), and written informed consent was obtained from all patients prior to participation in 2003.

For medical treatment of 21-OHD standard medications are hydrocortisone (HC), prednisolone (PR) and dexamethasone (DX) [16, 18]. Since those glucocorticoids have a different biological strength, dosage for PR and DX were converted into milligrams of hydrocortisone equivalent (PR was converted 1 to 5 to HC, DX 1 to 70 to HC) [19, 20]. After conversion to the hydrocortisone equivalent dose, the daily total amount of hydrocortisone equivalent in milligrams was calculated as well as the total daily dose per body surface area (mg/m^2). During the study, two experienced endocrinologists were responsible for the treatment and follow-up of the patients. They made every effort to reduce glucocorticoid dosing to as close to physiologic as possible, yet periods of higher doses and more potent steroids might have been necessary to manage androgen excess and to restore fertility, following common practice which were codified officially later as the current guidelines [3, 6].

Questionnaires

Both questionnaires, the Short Form 12 (SF-12) and the Hospital Anxiety and Depression Scale (HADS) are self-explanatory written multiple-choice self-assessments.

The SF-12, the short form of the SF-36 includes eight multi-item domains: limitations in physical activities because of health problems (physical functioning, PF), limitations in usual role activities because of physical health problems (role functioning physical, RP), bodily pain (BP), general health perception (GH), vitality (energy and fatigue, VT), limitations in social activities because of physical or emotional problems (social functioning, SF), limitations in usual role activities because of emotional problems (role functioning emotional, RE), and general mental health (psychological distress and well-being) (mental health, MH). Scores of the domains range from 0-100 with higher values representing a better subjective health status [21, 22].

The HADS measures in 14 items anxiety and depression in physically ill individuals [23]. 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 cut-off value of 8 is regarded as indicating mild impairment, and a cut-off value of 11 is indicative of severe impairment.

Regarding control group data we calculated the Z-scores by using reference data for SF-12 scores 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 18-65 yr. Reference data for the HADS (n=4410) was obtained from previously performed surveys [24].

Hormonal measurements

At the scheduled visits (2003, 2006 and 2010) blood samples were collected to analyze steroid hormone precursors such as DHEA-S (dehydroepiandrosterone-sulfate), 17-hydroxyprogesterone and androstenedione. For determination of DHEA-S serum levels an assay from DPC Biermann GmbH (Bad Nauheim, Germany) with normal standard values of 0.45-8.38 µmol/L (168-3100 ng/mL) was used. Serum 17-hydroxyprogesterone was measured by using an assay kit from MP Biomedicals GmbH (Eschwege, Germany) with normal standard values of 0.79-8.75 nmol/L (0.26-2.88 ng/mL). The recommended target range of 17-hydroxyprogesterone is 12-36 nmol/L for 21-OHD patients [1]. In 2003 and 2006, serum androstenedione levels were analyzed with a radioimmunoassay kit from Diagnostic Systems Laboratories (Sinsheim, Germany) (normal standard values: 0.91-10.1 nmol/L (0.12-3.31 ng/mL)), where in 2010 an assay from BeckmannCoulter (Krefeld, Germany) was used, however assay differences, which were tested, were negligible. In a further analysis we divided the patients into well and badly biochemically controlled groups (<36 nmol/L *vs* >36 nmol/L) according to the recommended target range [1] and compared HRQoL between these groups.

Statistical analysis

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. Significance was accepted if $p<0.05$. Significance level was adjusted for multiple testing. Analyses were performed using the statistical software package SPSS, version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Study cohort

Nineteen female adult 21-OHD patients from the outpatient clinic were contacted in 2003, and 16 patients (84%) agreed to participate. One patient was excluded from the study due to missing study visit and incomplete questionnaires. Finally, 15 female 21-OHD patients (7 SW and 8 SV) were included into analysis. Clinical parameters across the study period are shown in Table 1. Over the study period height, weight and BMI did not change significantly. Regarding glucocorticoid replacement therapy, the dexamethasone dose was reduced significantly (Table 1).

Most patients (2003: 60%, 2006: 53%, 2010: 60%) received only one type of glucocorticoid (2003: 20% HC, 20% PR, 20% DX; 2010: 26.7% HC, 13.3% PR, 20% DX), while the other patients received a combination of two different glucocorticoids (2003: 6.7% HC+PR, 0% DX+PR, 33.3% HC+DX; 2010: 0% HC+PR, 6.7% DX+PR, 33% HC+DX). The average prescribed daily dosage of HC slightly increased in 2010 compared to 2003 and 2006, whereas the daily dose of PR slightly dropped. The daily dosage of DX was significantly lower at the end of the study period than at the beginning. The calculated daily HC equivalent dose showed a trend to lower doses in 2010 (Table 1). The daily HC equivalent dose per body surface showed a significant reduction in 2010 compared to the two previous study visits (Fig. 1). The same tendency was seen in subgroup analysis regarding SW and SV

Table 1 Clinical parameters in 15 adult female 21-OHD patients.

	2003 (1st visit)	2006 (2nd visit)	2010 (3rd visit)
age (years)	37.2 ± 10.3 (28-62)	40.2 ± 10.3 (31-65)	44.2 ± 10.3 (35-69)
height (cm)	154.4 ± 5.5 (145-169)	154.4 ± 5.3 (145-169)	154.0 ± 5.6 (145-169)
weight (kg)	64.5 ± 12.4 (47-93)	66.8 ± 12.1 (51-92)	67.1 ± 12.7 (49-94)
BMI (kg/m^2)	27.1 ± 5.2 (18.8-39.2)	28.0 ± 4.8 (20.4-39.3)	28.3 ± 4.9 (21.2-39)
daily HC (mg)	11.1 ± 6.5 (5-20)	11.1 ± 7.0 (5-25)	13.1 ± 7.5 (5-22.5)
daily PR (mg)	5.1 ± 2.8 (2-7.5)	4.1 ± 1.4 (2-5)	4.0 ± 1.7 (2-5)
daily DX (mg)	0.44 ± 0.15 (0.25-0.75)	0.40 ± 0.11 (0.25-0.50)	0.31 ± 0.10 (0.19-0.50)*
daily HC equivalent dose (mg)	32.2 ± 13.6 (20-60)	30.8 ± 10.6 (20-55)	25.0 ± 7.0 (13.1-36.3)

Data are means ± SD (range). BMI, body mass index; HC, hydrocortisone; PR, prednisolone; DX, dexamethasone The dose of daily glucocorticoid was converted into milligrams of daily hydrocortisone equivalent (1mg dexamethasone = 14mg prednisolone = 70mg hydrocortisone). *$p<0.05$ compared to 2003.

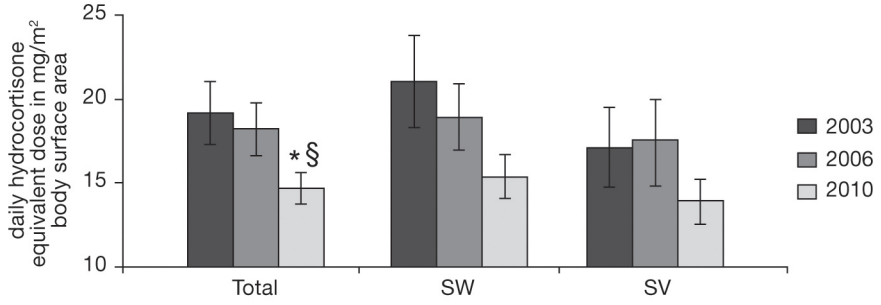

Fig. 1 Daily hydrocortisone equivalent doses (mg/m^2) in patients with 21-hydroxylase deficiency (21-OHD)
The dose of glucocorticoid was converted into milligrams of hydrocortisone equivalent (1mg dexamethasone = 14mg prednisolone = 70mg hydrocortisone). SW, salt-wasting form of 21-OHD; SV, simple-virilizing form of 21-OHD
Means ± SEM *$p<0.05$ compared to 2003; §$p<0.05$ compared to 2006.

patients, however it was not significant (Fig. 1). The daily fludrocortisone dose in SW 21-OHD patients was 104 ± 37 µg (mean ± SD; range 50-150 µg), and did not change over the study period.

HRQoL questionnaires

Female 21-OHD patients showed in the SF-12 questionnaire a significantly better status of mental health (MH) in 2006 compared to 2003 (Fig. 2a). Furthermore, 6 out of the remaining 7 scales indicated a positive tendency in HRQoL from 2003 to 2006. In comparison to 2003 and 2006, HRQoL in 2010 showed significantly less limitations in usual role activities (RP) (Fig. 2a). Furthermore, 6 out of 8 scales indicate a positive ten-

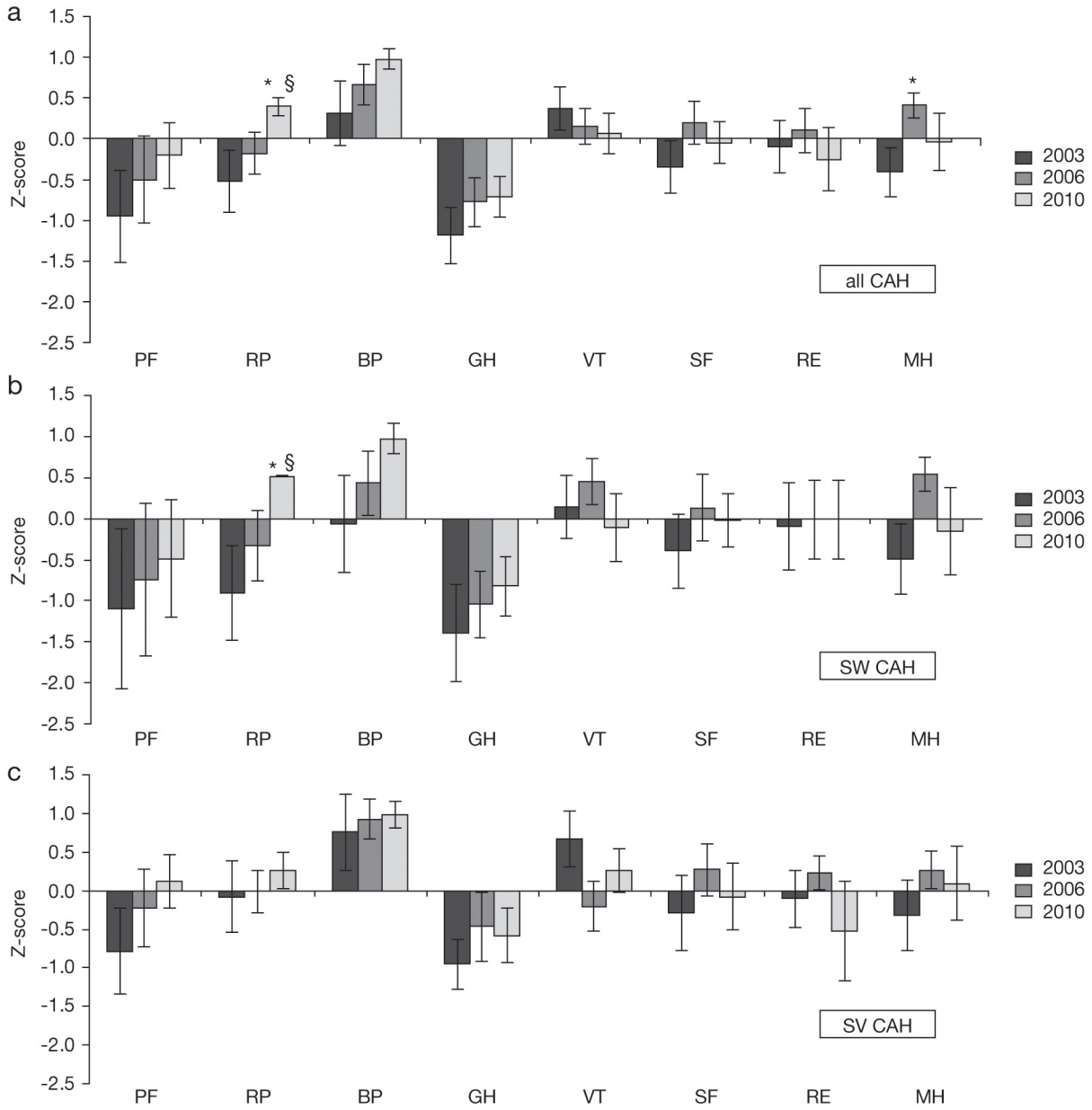

Fig. 2 Z-scores for SF-12 in (a) all patients with 21-hydroxylase deficiency (21-OHD), in (b) patients with salt-wasting form, and in (c) patients with simple-virilizing form of 21-OHD

Higher Z-scores indicate less pain or less impaired functioning. Physical functioning (PF), role functioning physical (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role functioning emotional (RE), mental health (MH). Means ± SEM. * $p<0.05$ compared to 2003; § $p<0.05$ compared to 2006.

dency in 2010 compared to 2003. Analyses of SW and SV patients showed the same positive tendency for HRQoL from 2003 to 2006 and 2010 (Fig. 2b and 2c). SW patients showed a significant improvement in usual role activities (RP) in 2010 compared to the previous visits (Fig. 2b). The HADS questionnaire showed no significant differences during the seven-year follow up period, neither in the whole cohort, nor in subgroup analysis of SW and SV patients (Fig. 3a-c)

Hormonal data

Mean serum levels of androstenedione (2003: 7.9 ± 2.4nmol/L; 2006: 6.7 ± 1.5nmol/L; 2010: 8.1 ± 2.4nmol/L) and DHEA-S (2003: 0.91 ± 0.2µmol/L; 2006: 0.75 ± 0.1µmol/L; 2010: 0.89 ± 0.3µmol/L; means ± SEM) were within the normal reference range and showed no increase even when the glucocorticoid dose was lowered. However, several patients showed increased androstenedione levels (Fig. 4a and 4b). The mean serum levels of 17-hydroxprogesterone were above the recommended target range of 12-36 nmol/L [1] and showed a tendency towards higher levels in 2010 under the reduced glucocorticoid dose (2003: 70.1 ± 28.5nmol/L; 2006: 64.7 ± 18.3nmol/L; 2010: 124.4 ± 48.5nmol/L; means ± SEM). Only two patients showed very high 17-hydroxyprogesterone levels (Fig. 4c). We did not find any significant differences in HRQoL between the groups of well and badly biochemically controlled patients.

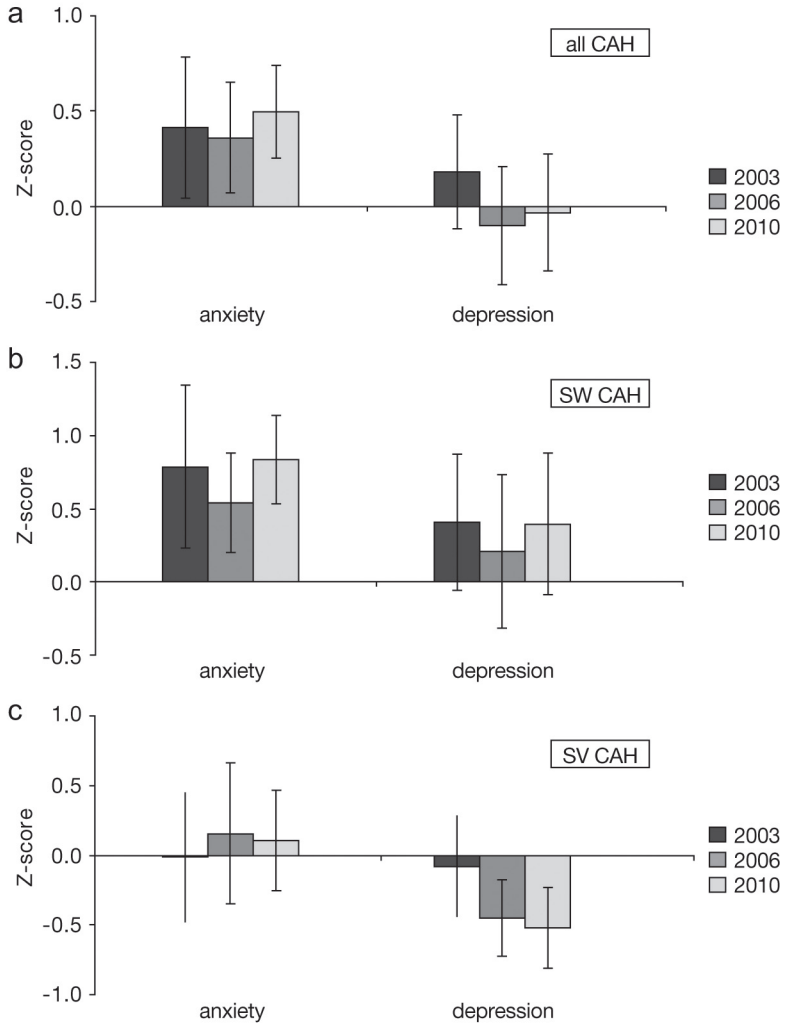

Fig. 3 Z-scores for HADS in (a) all patients with 21-hydroxylase deficiency (21-OHD), in (b) patients with salt-wasting form, and in (c) patients with simple-virilizing form of 21-OHD. Higher scores indicate higher levels of anxiety or depression. Means ± SEM.

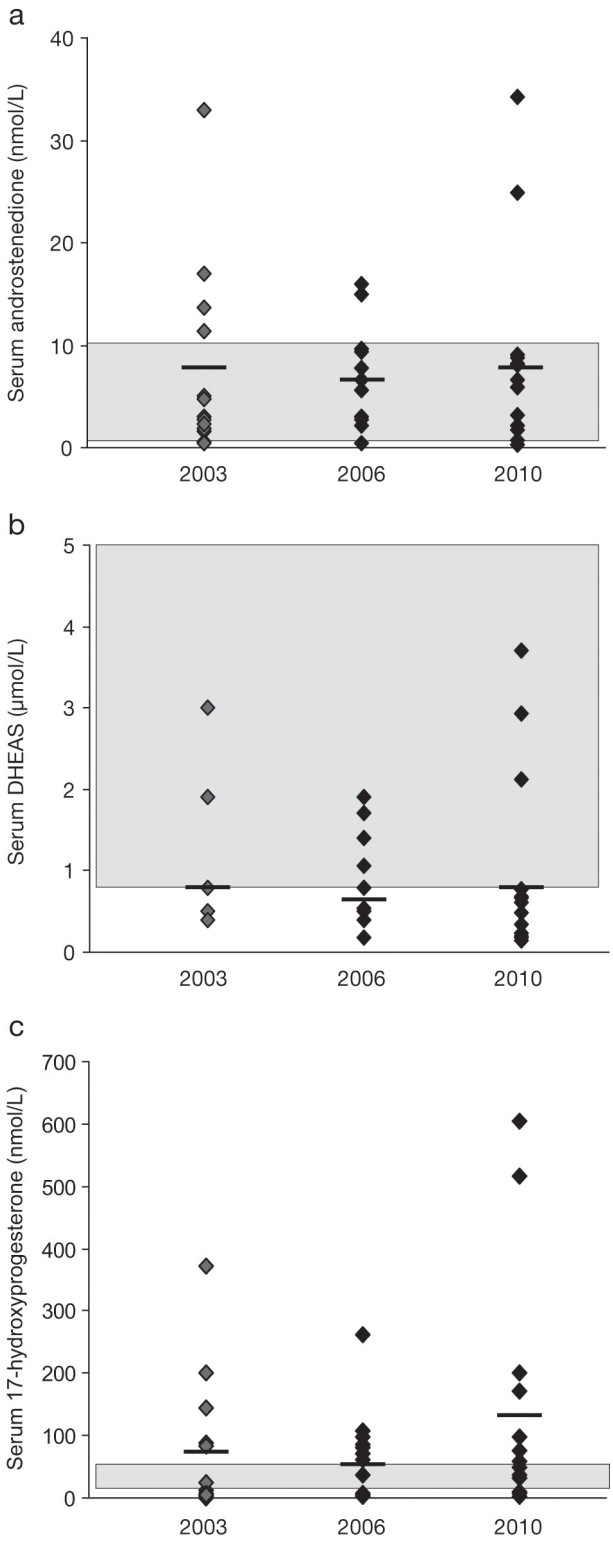

Fig. 4 Serum levels of (a) androstenedione, (b) dehydroepiandrosterone sulfate (DHEAS), and (c) 17-hydroxyprogesterone in patients with 21-hydroxylase deficiency (21-OHD) Individual values are shown. The black bar indicates the mean; the box indicates the area of recommended values.

Discussion

In the British cross-sectional CaHASE study [15], subjective HRQoL showed significant impairment across all eight SF-36 domains in three 21-OHD subgroups. In a Norwegian population-based survey, the subjective health status of adult 21-OHD patients was also impaired [17]. In a German cross-sectional study, we recently found in 81 adult 21-OHD patients mild impairment in HRQoL compared to healthy controls and the 21-OHD patients had better scores in the questionnaires than PAI patients [16]. Most likely the cause of the impaired subjective health perception is complex, including the hormonal disturbances and the steroid treatment as well as psychological issues. For the first time the present study demonstrates that HRQoL can be improved in adult 21-OHD women. The strength of the current study is that it is the first longitudinal study in female adult 21-OHD patients regarding HRQoL. Secondly, it focuses on subjective health status and depression, with the advantage of employing validated questionnaires and comparison to age- and sex-matched reference cohorts.

There might be several reasons for the observed improvement in HRQoL over the seven-year study period.

a) Effort to reduce the glucocorticoid replacement dose to minimize glucocorticoid side effects

Glucocorticoid overtreatment is a possible contributor to the adverse metabolic profile, the higher rate of osteoporosis [15, 25, 26], and the reported lower HRQoL [27] in 21-OHD, PAI and SAI. This has brought a change towards a reduction in glucocorticoid doses in the last years [5] to minimize glucocorticoid side effects. In the present longitudinal follow-up study, the total amount of hydrocortisone equivalent given was significantly reduced during the study time. This had no negative effect on the patient's HRQoL as one might suggest, e.g. due to increasing androgen levels. In addition, the anxiety and depression scores remained in the same range. However, we observed a significantly improved HRQoL in parts of the SF-12 questionnaire items in the follow-up visits. This might be due a change in androgen precursor levels; however, we did not observe a significant increase in androstenedione due to changes in medical treatment. Only 17-hydroxyprogesterone levels were even more variable, and several patients had levels higher than the

recommended 36 nmol/L [1] at the end of the study. However, recently it was discussed if 17-hydroxyprogesterone levels are suitable to monitor 21-OHD with the current therapy regimens [27].

Another explanation for improvement in HRQoL might be the diminished glucocorticoid dose itself. Higher daily glucocorticoid doses are associated with an impaired HRQoL in patients with PAI and SAI [7]. However, it is not evident from the latter study, if the patients had initially a worse HRQoL and then received more glucocorticoids by their physicians, or received initially more glucocorticoids, which resulted then in a worse HRQoL. The results from the present study may be interpreted in favour for the latter hypothesis that a reduced daily glucocorticoid dose results in a better HRQoL. Recently, it was shown in male patients with SAI that a reduction in the daily hydrocortisone dose did not significantly compromise HRQoL [28].

b) Influence of changing from long-acting versus shorter acting glucocorticoids

Recently, we investigated the possible impact of different glucocorticoid replacement therapies on HRQoL in patients with PAI and SAI [9]. Prednisolone seemed to be equivalent to hydrocortisone as glucocorticoid replacement therapy regarding HRQoL in PAI and SAI [9]. However, no data is available regarding longitudinal data so far, but it is hypothesized that longer-acting glucocorticoids might have negative effects over a longer period. Effects on BMD might reflect those effects, and our recent data indicate that glucocorticoid replacement therapy with prednisolone is likely to have a selective adverse impact on bone relative to hydrocortisone therapy in PAI patients [25]. In our present study, a gradual switch from longer to shorter acting glucocorticoids was observed. Especially, the dexamethasone dose was reduced significantly and the hydrocortisone dose increased. This could have had an influence on the improved HRQoL in our cohort. At the study start 21-OHD patients with SW had higher glucocorticoid doses and a poorer HRQoL than 21-OHD patients with SV, which might explain that improvement in HRQoL was more pronounced in 21-OHD patients with SW over the study period.

c) Influence of body mass index

An increased body fat index, respectively BMI, due to hypercortisolism was found in former studies with 21-OHD patients [15, 29, 30]. It is known that BMI normally increases in age, is related to worse physical conditions and results in a decrease of HRQoL [31]. However, in the present study we can rule out any effect of BMI on HRQoL, because the patient's BMI remained unchanged.

d) Influence of age

Age correlates with better HRQoL in both sexes in 21-OHD patients indicating a possible adaptation to the chronic disease [16]. This is most likely indicative of better disease acceptance and improved coping strategies over lifetime, which is in line with previous published data in PAI and SAI [8], and might have influenced our results.

e) Influence of specialized centres

All 21-OHD patients in this study were treated in a tertiary care centre with a special interest in CAH. During the study, two endocrinologists were responsible for the treatment and follow-up of the patients. This specialized care might have influenced the HRQoL data in this study. However, social support and visiting intervals (every 6 months) did not change during the study period. In addition, there might be a selection bias in that healthier patients participated in the study and were perhaps more motivated to improve their well-being.

In conclusion, we showed that improvement of HRQoL in adult female 21-OHD patients is possible in a reasonable time span. Several factors might be involved in this improvement including reduced daily hydrocortisone equivalent dose per body surface.

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