Modified-release hydrocortisone decreases BMI and HbA1c in patients with primary and secondary adrenal insufficiency

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Abstract

Objective: Patients with adrenal insufficiency (AI) have impaired health-related quality of life (HRQoL), which is thought to be in part due to unphysiological glucocorticoid replacement therapy. The aim was to compare once-daily hydrocortisone (HC) dual-release tablet (modified-release) with conventional HC therapy regarding clinical data and HRQoL.

Design and methods: We conducted an open, prospective trial at one endocrine center. There were 15 of 26 patients with primary AI, nine of 18 patients with secondary AI, and six congenital adrenal hyperplasia patients switched to modified-release HC therapy by their own decision. We evaluated clinical outcome and disease-specific HRQoL by using AddiQoL questionnaire at baseline and at follow-up (median 202 days (85–498)).

Results: Patients on modified-release HC ($n=30$) showed significant decreases in BMI (26.0 ± 0.75 – 25.6 ± 0.71 , P for change = 0.006) and HbA1c (6.04 ± 0.29 – 5.86 ± 0.28 , P for change = 0.005), whereas patients remaining on conventional HC ($n=20$) showed no change in these parameters (P for interaction = 0.029 and 0.017 respectively). No significant change in AddiQoL score were found in the modified-release HC group (83.8 baseline and 84.9 at follow-up; P for change = 0.629). In the conventional HC group, there was a significant decrease in scores (84.0 baseline and 80.9 at follow-up; P for change = 0.016), with a between-treatment P for interaction of 0.066. The fatigue subscore of AddiQoL showed the same pattern with a significant decrease (P for change = 0.024) in patients on conventional HC therapy (P for interaction = 0.116).

Conclusions: Modified-release HC decreases BMI and HbA1c compared with conventional HC treatment. In addition, it seems to stabilize HRQoL over time.

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Introduction

A life-long, daily medical treatment with glucocorticoids is essential for patients with chronic adrenal insufficiency (AI). Hydrocortisone (HC) is thought to be the best glucocorticoid replacement therapy so far (1, 2). However, a major problem in clinical practice is the management of the total amount of daily HC substitution, the number and the optimal time point of daily doses. Too high HC doses result in supraphysiological blood cortisol levels, and doses too far apart may result in episodes with

insufficient cortisol levels. This is thought to be one of several reasons of impaired health-related quality of life (HRQoL) seen in patients with AI (3, 4). Division or weight adaptation of the daily glucocorticoid dose into several single doses was postulated to improve cortisol profiles during the day and also well-being in small patient groups (5). However, up to now the current replacement strategies are still insufficient to fully restore well-being and daily performance (4, 6).

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Recently, a once-daily dual-release (modified release) HC tablet (Plenadren[®], Viropharma Inc., Exton, PA, USA) has been introduced and shown a more physiological cortisol profile during daytime than conventional treatment in patients with primary AI (PAI) (7), but still lacking the ultradian physiological profile. This treatment proved to be safe and was well-tolerated during 24 consecutive months of therapy in patients with PAI (8). In the initial 3 months trial, this new modified release HC showed an improvement in cardiovascular risk factors, glucose metabolism, and HRQoL in comparison with conventional treatment with trice daily HC (7). However, more than 85% of the patients in the comparator group received daily HC doses of 25 mg or more, more than 77% of patients even received 30 mg or more. These daily doses are regarded nowadays as too high (1, 2), and are related to impaired HRQoL (6). The modified release HC therapy is thought to have a nearly 20% lower serum cortisol AUC than conventional therapy (7). This would result in the case of a switch from 30 mg conventional HC therapy to 30 mg of modified release HC and in an actual dose reduction to 24 mg conventional HC. This indirect dose reduction might have resulted in the positive effects seen in the initial trial.

Therefore, the aim of our study was to detect possible differences in HRQoL in patients switched from conventional HC to modified release HC on an average daily HC dose of 20–22 mg. Secondly, up to now no reports have been published on patients with secondary AI (SAI) or with congenital adrenal hyperplasia (CAH) switched to modified release HC therapy.

Subjects and methods

Study participants

Between October 2012 and October 2013, patients with chronic PAI or SAI from the Endocrine Outpatient Clinic of the Charité University Medicine Berlin, who were on stable glucocorticoid replacement therapy for at least 6 months before entering the study, were asked to participate in the study. The patients were recruited in the order they appeared chronologically for their routine visit in the outpatient's clinic. Of the first 53 patients, three patients refused to participate (5.7%). The remaining 50 patients were included into the study. The diagnosis was verified by review of the medical records. All patients had chronic AI with disease duration of at least 2 years. Patients under the age of 18 years, patients with AI due to long-term pharmacological glucocorticoid treatment, and patients with adrenocortical carcinoma were excluded.

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 before participation. The study has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All patients had an emergency kit and a steroid emergency card and received special teaching regarding adrenal crisis.

A total of 50 patients with PAI and SAI were included into the study. The underlying cause of the 26 patients with PAI and the 18 patients with SAI is given in Table 1. Six patients with CAH due to 21-hydroxylase deficiency agreed to participate in the study. The medical treatment of CAH was conventional HC and dexamethasone (DX) (Table 2). As those glucocorticoids have a different biological strength, dosage for DX was converted into milligrams of HC equivalent (DX 1–70 to HC) (9, 10). The fludrocortisone dose in PAI and CAH patients was not changed significantly during the treatment period (Table 2).

Intervention

Once-daily dual-release (modified release) HC (Plenadren[®], Viropharma) is available for the treatment of patients with AI in Germany since October 2012. In this study, patients were offered both treatment regimens (conventional HC or modified release HC) at baseline and they were free to choose which regimen they wanted to have (Fig. 1). Patients who decided to switch to once-daily HC dual-release tablet received the same daily dose of modified release HC as in their previous treatment (or respective equivalent for prednisolone). Recommendations were given to patients who switched to modified release HC including that the dual-release tablet should be taken in the fasting state early in the morning and that in the case of intercurrent illness the daily dose should be doubled (second dose 8 h after the first dose) or tripled (6 and 12 h after the first dose).

Evaluations

Baseline and follow-up evaluations consisted of physical examinations, a disease-specific health questionnaire, and a complete blood analysis (Na, K, Ca, PO₄, creatinine, cholesterol, HDL- and LDL-cholesterol, triglycerides, and HbA1c) performed in the morning before 1000 h. The follow-up visit was scheduled on the day the patient had the next visit at the outpatient clinic (usually every 3–9 months, on average 6 months). In the CAH cohort, we were able to assess questionnaires from a visit in 2011.

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Table 1 Age, duration of disease, underlying diagnosis, and hormone replacement therapy in 50 patients with primary and secondary AI.

	Modified release HC group	Conventional HC group
Primary AI (n)	21	11
Age (years) median (range)	48.0 (34, 83)	54.0 (35, 73)
Duration of disease (years) median (range)	12.0 (6, 25) (n=15)	13.0 (2, 31)
CAH	43.0 (34, 54) (n=6)	
Cause of AI (n)		
Isolated AI	2	4
APS2	10	4
With hypothyroidism	7	4
With diabetes mellitus type 1	4	–
Bilateral adrenalectomy ^a	3	2
Tuberculosis	–	1
CAH salt-wasting/simple-virilizing	4/2	–
DHEA replacement therapy	3	3
Secondary AI (n)	9	9
Age (years) median (range)	51.0 (22, 77)	54.0 (33, 76)
Duration of disease (years) median (range)	6.0 (3, 13)	10.0 (5, 27)
Cause of AI (n)		
pituitary adenoma	5	5
Other tumors ^b	2	3
Idiopathic insufficiency of the anterior pituitary	1	1
Sheehan's syndrome	1	–
Replacement therapy		
L-thyroxine	9	9
Oral contraceptive	–	–
Estrogen replacement	2	2
Testosterone	3	4
Growth hormone	4	1
Desmopressin	2	3

AI, adrenal insufficiency; APS, autoimmune polyglandular syndrome; CAH, congenital adrenal hyperplasia; HC, hydrocortisone.

^aBilateral adrenalectomy for Cushing's disease (n=4) or bilateral pheochromocytoma (n=1).

^bOther tumors: craniopharyngeoma (n=3), sella turcica meningioma (n=1), and intracranial germ cell tumor (n=1).

Disease-specific health questionnaire

To compare patients' complaints and fatigue over the treatment period with different glucocorticoid formulations, patients were asked to complete the newly developed Addison's disease-specific questionnaire (AddiQoL) (11, 12).

The recently developed AddiQoL for patients with PAI initially included 36 questions (11), and has been validated and reduced to a 30 item questionnaire (12). Items that are positive had scores from 1 to 6; negative HRQoL statements were reversed for questionnaire scoring (6 to 1). The scoring was converted to points: 6=4 points; 5 and 4=3 points; 3 and 2=2 points, 1=1 point. The algebraic sum of points was calculated. Higher points indicate a higher level of HRQoL. The subscale fatigue, which consists of questions 1–5 and 23, 26, and 27, was also calculated.

Statistical analyses

All analyses were performed by Stata/IC version 12.0 (Stata Corp., College Station, TX, USA) software for

Windows. To estimate change in AddiQoL and clinical outcomes from baseline to follow-up, we used linear regression models for repeated measures (i.e., linear mixed effects models). All models defined treatment, time, and treatment-by-time interaction as fixed effects, whereas a random intercept effect was specified to account for the intra-individual correlation. The intra-individual correlation was also directly modeled by using spatial power covariance structure to account for the unequal follow-up time, but this covariance structure did not improve model fit. Follow-up time was modeled as a 30-day incremental time variable and incorporated as continuous term in the regression models. A *P* value for change within treatment groups was obtained directly from regression models by using the margins command (z-test) in Stata. To investigate between-treatment change in AddiQoL and clinical outcomes, we used the likelihood ratio test by comparing the log-likelihood between models with and without the treatment-by-time term. All analyses were adjusted for sex, type of AI, age, and age-by-time interaction. Additional

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Table 2 Patients with AI ($n=50$) at baseline and follow-up (234 ± 132 days) after receiving modified release hydrocortisone or conventional hydrocortisone. Data are medians (min. and max.) or numbers.

	Modified release HC group		Conventional HC group	
	Baseline	Follow-up	Baseline	Follow-up
Female/male	23/7		14/6	
PAI/CAH/SAI	15/6/9		11/0/9	
Age (years)	48 (22, 83)		54 (33, 76)	
PAI/SAI				
HC daily dose (mg)	20.0 (15.0, 30.0) ($n=18$)	20.0 (20.0, 25.0) ($n=24$)	20.0 (10.0, 70.0)	20.0 (12.5, 50.0)
Predni daily dose (mg)	5.0 $\pm$ (4.0, 5.0) ($n=6$)	–	–	–
CAH				
HC daily dose (mg)	10.0 (10.0, 20.0) ($n=4$)	20.0 (20.0, 25.0) ($n=6$)		
Dexa daily dose (mg)	0.25 (0.19, 0.38) ($n=3$)	–		
HC equivalent dose per day	18.8 (10.0, 36.3)	20.0 (20.0, 25.0)		
Fludrocortisone daily dose (mg) ^a	0.10 (0.05, 0.15)	0.10 (0.05, 0.15)	0.10 (0.05, 0.20)	0.10 (0.05, 0.20)

PAI, primary adrenal insufficiency; CAH, congenital adrenal hyperplasia; SAI, secondary adrenal insufficiency; HC, hydrocortisone; Predni, prednisolone.

^afor PAI and salt-wasting CAH.

adjustments were made for glucocorticoid dose and diabetes mellitus where appropriate. All P values were two-sided and values <0.05 were considered statistically significant.

Results

At baseline, there were no differences regarding age (Table 2), BMI, HbA1c, or lipid profile between the two groups (modified release vs conventional HC) (Table 3). In both groups, the HC dose was diminished slightly but not significantly (Table 2). During the treatment period, there was a small but significant decrease in BMI in the modified release HC group (P for change 0.006) and no change in the HC group (P for change 0.887), with a significant between-treatment difference in BMI development during the treatment period (P for interaction = 0.029) (Table 3). In the modified release HC group, HbA1c decreased significantly (P for change 0.005), with a significant between-treatment difference in HbA1c development during treatment (P for interaction = 0.017). Also, there was a small decrease in total cholesterol in the modified release HC group (P for change = 0.036), but without any between-treatment differences (P for interaction = 0.294). No changes were found in either group for HDL, LDL, and triglycerides (Table 3), or for sodium, potassium, calcium, and 25-vitamin D3 (data not shown).

Median time of follow-up visit was 128 days (range 68–429) for the modified release HC group and 338 days (range 98–498) for the HC group, and after adjusting for potential confounding factors, the between-treatment difference in AddiQoL and Fatigue scores was not

significant; P for interaction = 0.066 for AddiQoL and 0.116 for Fatigue scores (Table 3). In the modified release HC group ($n=30$), we found no significant trend for change in AddiQoL and Fatigue scores. However, in the HC group, AddiQoL and Fatigue scores decreased significantly (AddiQoL, P for trend = 0.016 and Fatigue 0.024) (Table 3). This deterioration in HRQoL with conventional treatment showed the lowest scores in the patients with the longest follow-up time (Fig. 2).

When examining results by disease group, there were only small differences in scores between PAI and SAI. In the modified release HC group, patients with PAI ($n=15$) had a mean AddiQoL score of 83.3 (10.8) at baseline and 85.5 (11.7) at follow-up, and Fatigue scores of 22.9 (4.3) and 22.7 (5.4) respectively. The nine SAI patients in the modified release HC group had mean AddiQoL score 84.2 (10.5) at baseline and 84.9 (10.5) at follow-up, and mean Fatigue score 20.9 (2.8) and 22.2 (3.2) respectively. In the HC group, patients with PAI ($n=11$) had decreasing mean

Figure 1
Study design.

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Table 3 AddiQoL scores and metabolic parameters in patients with adrenal insufficiency ($n=50$) at baseline and follow-up after receiving modified release hydrocortisone or conventional hydrocortisone.

Outcome	Baseline		Follow-up		Estimated change per 30 days ^a			
	No. of patients	Observed mean $\pm$ S.E.M.	No. of patients	Observed mean $\pm$ S.E.M.	$\beta \pm$ S.E.M.	P change	Adjusted $\beta \pm$ S.E.M. ^b	Adjusted P change
AddiQoL								
Modified release HC	30	83.8 $\pm$ 1.81	30	84.9 $\pm$ 1.95	0.157 $\pm$ 0.167	0.348	0.081 $\pm$ 0.167	0.629
Conventional HC	20	84.0 $\pm$ 2.11	20	80.9 $\pm$ 2.50	-0.299 $\pm$ 0.130	0.021	-0.305 $\pm$ 0.127	0.016
interaction ^c					0.031		0.066	
Fatigue								
Modified release HC	30	22.4 $\pm$ 0.68	30	22.6 $\pm$ 0.81	0.047 $\pm$ 0.064	0.464	0.017 $\pm$ 0.064	0.793
Conventional HC	20	21.1 $\pm$ 0.66	20	19.9 $\pm$ 0.85	-0.108 $\pm$ 0.050	0.030	-0.110 $\pm$ 0.049	0.024
interaction ^c					0.057		0.116	
BMI								
Modified release HC	30	26.0 $\pm$ 0.75	30	25.6 $\pm$ 0.71	-0.057 $\pm$ 0.019	0.003	-0.056 $\pm$ 0.020 ^d	0.006
Conventional HC	20	25.7 $\pm$ 1.14	20	25.8 $\pm$ 1.08	0.002 $\pm$ 0.015	0.887	0.000 $\pm$ 0.015 ^d	0.985
interaction ^c					0.015		0.029 ^d	
HbA1c								
Modified release HC	27	6.04 $\pm$ 0.29	28	5.86 $\pm$ 0.28	-0.020 $\pm$ 0.008	0.014	-0.023 $\pm$ 0.008 ^e	0.005
Conventional HC	20	5.63 $\pm$ 0.13	18	5.72 $\pm$ 0.15	-0.0002 $\pm$ 0.006	0.975	0.001 $\pm$ 0.006 ^e	0.807
interaction ^c					0.049		0.017 ^e	
Cholesterol								
Modified release HC	30	213.8 $\pm$ 7.97	29	200.1 $\pm$ 7.57	-1.835 $\pm$ 0.760	0.016	-1.655 $\pm$ 0.787	0.036
Conventional HC	19	221.8 $\pm$ 10.8	19	210.9 $\pm$ 13.1	-0.586 $\pm$ 0.604	0.332	-0.605 $\pm$ 0.608	0.320
Interaction ^c					0.198		0.294	
HDL								
Modified release HC	30	65.4 $\pm$ 3.5	29	62.7 $\pm$ 3.3	-0.302 $\pm$ 0.231	0.190	-0.317 $\pm$ 0.240	0.188
Conventional HC	19	62.5 $\pm$ 4.3	19	61.2 $\pm$ 5.0	-0.187 $\pm$ 0.183	0.306	-0.177 $\pm$ 0.186	0.340
interaction ^c					0.696		0.647	
LDL								
Modified release HC	30	127.2 $\pm$ 7.6	29	121.4 $\pm$ 7.0	-0.912 $\pm$ 0.485	0.060	-0.716 $\pm$ 0.496	0.149
Conventional HC	19	133.9 $\pm$ 9.1	18	128.4 $\pm$ 11.1	0.037 $\pm$ 0.388	0.925	0.010 $\pm$ 0.385	0.980
interaction ^c					0.127		0.251	
Triglycerides								
Modified release HC	30	115.7 $\pm$ 11.9	29	120.9 $\pm$ 11.3	0.944 $\pm$ 1.828	0.605	1.571 $\pm$ 1.889	0.406
Conventional HC	19	149.3 $\pm$ 16.4	19	173.4 $\pm$ 26.7	0.333 $\pm$ 1.462	0.820	0.376 $\pm$ 1.471	0.798
interaction ^c					0.794		0.619	

Normal cholesterol, <200 mg/dl (5.17 mmol/l); LDL-cholesterol, <160 mg/dl (4.14 mmol/l); HDL-cholesterol, >35 mg/dl (0.91 mmol/l), triglycerides, and <180 mg/dl (2.06 mmol/l).

^aBy linear mixed effect models including a random intercept and the following fixed factors: treatment group, follow-up time, and treatment-by-time interaction. Follow-up time was transformed to time per 30 days and modeled as a continuous term.

^bAdjusted for sex, type of adrenal insufficiency, age, and age-by-time interaction.

^cOverall P value for treatment-by-time interaction (z-test).

^dAdditionally adjusted for glucocorticoid dose.

^eAdditionally adjusted for diabetes mellitus.

AddiQoL score from 83.3 (10.2) at baseline to 80.1 (11.1) at follow-up, with mean Fatigue scores of 21.8 (3.1) and 20.2 (4.1) respectively. In the SAI HC group ($n=9$), AddiQoL scores decreased from 85.0 (8.9) to 81.9 (11.9) and Fatigue scores from 20.3 (2.6) to 19.4 (3.5) from baseline to follow-up. For the six patients with CAH, all included in the modified release HC group, mean AddiQoL score were 84.5 (s.d. 7.8) at baseline and 83.3 (9.7) at follow-up, and mean Fatigue scores 23.5 (s.d. 3.3) and 22.5 (4.2) respectively. Two years before baseline, these six patients had a mean AddiQoL score of 88.5 (s.d. 14.9) and Fatigue

score of 23.3 (5.2), suggesting a gradual decline in HRQoL scores over time in this group.

Post hoc analysis without the six CAH patients showed the same pattern and did not substantially alter the results for the various outcome parameters compared with whole group analysis.

Discussion

Our study showed that modified-release HC decreases BMI and HbA1c compared with conventional HC treatment.

Figure 2

Scatter plots of differences in AddiQoL scores over follow-up time in patients on modified release hydrocortisone (A) and conventional hydrocortisone (B). The differences in Fatigue scores showed a similar pattern (data not shown).

In a previous study, modified release HC treatment reduced 24-h glucocorticoid exposure by nearly 20%, particularly in the afternoon, resulting in reduced body weight and HbA1c in a subgroup of patients with diabetes mellitus (7). In our study, HC equivalent doses were only slightly reduced in both treatment groups (although not statistically significant), and the mean HC daily dose in both treatment arms were lower (20–22 mg) than that in previous studies. Because the modified release HC group included five diabetic patients and the HC group three, statistical results on HbA1c were adjusted for the presence of diabetes. Furthermore, because glucocorticoid dose has an impact on weight and BMI, results obtained for BMI

were adjusted for daily dose. Nevertheless, modified release HC reduced both BMI and HbA1c significantly when compared with conventional treatment, although absolute changes were small. Plat *et al.* (13) have previously found that elevation of plasma cortisol in the evening when the hypothalamus–pituitary–adrenal (HPA) axis is normally quiescent has more deleterious metabolic effects than a similar elevation in the morning when the HPA axis is maximally activated. Possibly, the reduction in HbA1c levels results from reduced afternoon cortisol exposure with modified release HC. Accordingly, the reduction in 24-h HC exposure with modified release HC may explain the reduction in BMI.

Our study shows for the first time that differences in HRQoL using the disease-specific AddiQoL in patients with AI switched from conventional HC to modified release HC on an average daily HC dose of 20–22 mg compared with patients remaining on conventional HC. Secondly, up to now this is the first report on patients with secondary AI or with CAH switched to modified release HC therapy. The underlying cause of reduced HRQoL in AI has yet to be elucidated. Some authors have suggested that the lack of DHEA could be a causative factor (14), although the largest placebo-controlled randomized study detected only minor HRQoL benefits of DHEA in AI (15). Another theory is that the autoimmune state in itself will compromise HRQoL, given that HRQoLs are affected in several autoimmune conditions (16, 17, 18). A recent study in patients on thyroid replacement therapy has compared SF-36 scores between patient with autoimmune hypothyroidism and postoperative hypothyroidism, demonstrating lower scores in patients with anti-thyroid peroxidase antibodies (19), which supports this theory. Insufficient replacement therapy is suspected to be a major cause of reduced HRQoL in AI, despite the fact that evidence has been lacking (2, 3). Therefore, efforts are being made to provide the most physiological cortisol replacement possible. There is a possible relation between daily dose and HRQoL, as too high dosage chronically could result in a slow decline in HRQoL scores over time, similar to the findings in mild Cushing's syndrome (20). Similarly, too low doses can lead to fatigue and a higher frequency of adrenal crisis, deteriorating HRQoL (21). A recent retrospective cross-sectional study in SAI patients has found that higher HC doses were associated with worse HRQoL, and that patients with doses lower than 10 mg/day had the best HRQoL and patients receiving more than 25 mg/day the poorest HRQoL (22). Another study found that AI patients with doses higher than 30 mg/day have lower HRQoL levels than patients with

lower doses (6). AI patients also have a higher risk of acquiring additional autoimmune disease over time, possibly with an impact on HRQoL levels, although studies on the impact of additional autoimmune disease have been inconsistent (3, 23).

In this study, we could not detect any HRQoL improvement with modified release HC, possibly due to low numbers and low statistical power. Another possible explanation for the fact that HRQoL remained impaired might be that modified release HC is a nonphysiological glucocorticoid replacement in the hours before waking. However, we did find that HRQoL deteriorated with conventional treatment, with the lowest scores in the patients with the longest follow-up time, raising suspicion that HRQoL deteriorates over time in AI with conventional therapy. The largest HRQoL studies in AI have all been cross-sectional, and our results highlight the need for long-term HRQoL follow-up data regardless of replacement therapy strategy. Disease-specific HRQoL questionnaires can be more sensitive for detecting HRQoL changes over time in specific patient groups (24), but they should not be used in a normal population to provide Z-scores to take account of QoL deterioration with aging. Therefore, all statistical analyses in the current study were adjusted for sex, type of AI, age, and age-by-time interaction. The Addison's disease-specific AddiQoL questionnaire was previously applied in a large cross-sectional study, showing that HRQoL scores were lower in the oldest age groups (12), but the impact of AI duration was not investigated. This study was of short duration, and it is unlikely that the scores would deteriorate significantly because of the increasing age during the study.

In this study, no differences in scores were found between patients with isolated AI and patients with autoimmune polyglandular syndrome. Longitudinal data could possibly also provide clues to why HRQoL is reduced in Addison's disease, for instance by investigating the association between HRQoL change and dose, additional comorbidity, adrenal crisis frequency, antibody titer, etc.

There are limitations to this study, foremost the open nonrandomized design in which the patients themselves decided whether they wanted to change to modified release HC or to stay on conventional HC. Nonetheless, despite lack of randomization, there were only small differences in baseline characteristics between treatment groups and these were adjusted for in regression analyses. Furthermore, no treatment preference was presented to the patients by the physician. We can statistically correct for the lack of standardized study visit intervals. The low number of patients in each disease group increases the risk

of type 2 error and makes it difficult to conclude on between-group differences in scores and AddiQoL validity in SAI and CAH. However, the strength of this study lies in the similarity to conventional clinical practice. A single group short-term clinical trial may not be completely representative for the broad spectrum of patients followed long term by most endocrinologists. In our field, most clinical trials present nonblinded short-term HRQoL data (3, 4, 12, 25), which may increase the risk of placebo effects. Presumably, long-term results are more important for the patients. We therefore believe that longitudinal HRQoL data are needed in AI.

In conclusion, we showed that modified release HC decreases BMI and HbA1c and seems to stabilize HRQoL, whereas conventional HC treatment seems to be accompanied by a decrease in HRQoL over time.

Declaration of interest

M Quinkler worked as a consultant for ViroPharma and had received honoraria for talks. M Øksnes, R M Nilsen, K Zopf, and M Ventz have nothing to disclose.

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