Continuous Subcutaneous Hydrocortisone Infusion versus Oral Hydrocortisone Replacement for Treatment of Addison's Disease: A Randomized Clinical Trial

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Context: Conventional glucocorticoid replacement therapy fails to mimic the physiological cortisol rhythm, which may have implications for morbidity and mortality in patients with Addison's disease.

Objective: The objective of the study was to compare the effects of continuous sc hydrocortisone infusion (CSHI) with conventional oral hydrocortisone (OHC) replacement therapy.

Design, Patients, and Interventions: This was a prospective crossover, randomized, multicenter clinical trial comparing 3 months of treatment with thrice-daily OHC vs CSHI. From Norway and Sweden, 33 patients were enrolled from registries and clinics. All patients were assessed at baseline and after 8 and 12 weeks in each treatment arm.

Main Outcome Measures: The morning ACTH level was the primary outcome measure. Secondary outcome measures were effects on metabolism, health-related quality of life (HRQoL), sleep, and safety.

Results: CSHI yielded normalization of morning ACTH and cortisol levels, and 24-hour salivary cortisol curves resembled the normal circadian variation. Urinary concentrations of glucocorticoid metabolites displayed a normal pattern with CSHI but were clearly altered with OHC. Several HRQoL indices in the vitality domain improved over time with CSHI. No benefit was found for either treatments for any subjective (Pittsburgh Sleep Quality Index questionnaire) or objective (actigraphy) sleep parameters.

Conclusion: CSHI safely brought ACTH and cortisol toward normal circadian levels without adversely affecting glucocorticoid metabolism in the way that OHC did. Positive effects on HRQoL were noted with CSHI, indicating that physiological glucocorticoid replacement therapy may be beneficial and that CSHI might become a treatment option for patients poorly controlled on conventional therapy. **(*J Clin Endocrinol Metab* 99: 1665–1674, 2014)**

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Abbreviations: AD, Addison's disease; AddiQoL, AD-Specific Quality-of-Life Questionnaire; AE, adverse event; AUC, area under the curve; BMI, body mass index; BP, blood pressure; CBG, cortisol binding globulin; CI, confidence interval; CSHI, continuous sc hydrocortisone infusion; CTX1, C-terminal crosslinking telopeptides of type 1 collagen; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; HPA, hypothalamus-pituitary-adrenal; HRQoL, health-related quality of life; LDL, low-density lipoprotein; OHC, oral hydrocortisone; PGWBI, Psychological General Well-being Index; P1NP, N-propeptide of type 1 collagen; PSQI, Pittsburgh Sleep Quality Index; SF-36, Short Form 36.

Over the past 60 years, glucocorticoid replacement in Addison's disease (AD) has been virtually unchanged. However, in recent decades a number of reports have shown that AD patients have reduced health-related quality of life (HRQoL) (1, 2), increased cardiovascular risk factors (3, 4), risk of osteoporosis (5–7), and increased mortality (8–10). Conventional replacement therapy includes oral hydrocortisone (OHC) or cortisone acetate twice or thrice daily and the synthetic mineralocorticoid fludrocortisone (11). Although this treatment replenishes the adrenal hormones, it does not restore a normal cortisol biorhythm. In fact, as judged by circulating cortisol levels, this treatment renders the patient overtreated immediately after oral administration and undertreated within a few hours (12). During nighttime and early morning, the glucocorticoid levels on OHC are undetectable, which contrasts the rise seen in healthy individuals (13). The hypothalamus-pituitary-adrenal (HPA) axis is implicated in the regulation of sleep (14, 15). In AD, low nighttime cortisol levels, high ACTH levels, and presumably high levels of CRH might lead to sleep disturbances, although no specific sleep disturbances have been described (16). Studies in patients without AD have shown that normal nighttime cortisol levels are necessary for normal rapid eye movement sleep regulation (17). Compared with estimates of endogenous cortisol production at 5.4–6.1 mg/m^2·d, AD patients on conventional treatment receive too much glucocorticoids (18). Taken together, these concerns have sparked new interest in improving therapeutic regimens.

Efforts have been made to optimize replacement therapy by various strategies (12, 19), but the optimal replacement therapy is still unclear (20). A recent study demonstrated that 24-hour cortisol exposure was reduced by once-daily dual-release hydrocortisone, resulting in a reduction of body weight, blood pressure (BP), and hemoglobin A1c (HbA1c) (21). Although such treatment successfully restored daytime cortisol levels to normal, the late night increase in cortisol was not reestablished. However, restoring the nighttime cortisol surge was obtained by another modified-release hydrocortisone tablet (22, 23).

We previously showed that continuous sc hydrocortisone infusion (CSHI) enables a fine-tuned control of glucocorticoid delivery that allows restoration of the circadian biorhythm (24). Over the last years, we know from clinical experience and personal communication that CSHI has been successfully applied as a last resort treatment option in selected patients with poor functioning. Here we report a clinical trial investigating the effects of imposing a physiological circadian cortisol rhythm on patients with AD. Specifically, we compared CSHI with OHC for effects on hormones in the HPA axis, glucose, lipid and bone metabolism, HRQoL, sleep, and safety.

Materials and Methods

Subjects and design

This multicenter, crossover, randomized clinical trial aimed to compare the effects of 3 months on CSHI with 3 months on thrice-daily OHC in Scandinavian AD patients (Figure 1). The ACTH level, as a marker of overall glucocorticoid effects and regulation, was the primary outcome. Safety and effects on other metabolic parameters, HRQoL, and sleep were secondary end points.

Eligible patients were identified from a patient registry (Registry of Organ-Specific Autoimmune Diseases) or from the hospital diagnosis registries and invited to participate. The inclusion criteria were verified autoimmune AD and aged 18–70 years. Patients with concomitant diseases were required to be on stable treatment during the study period. Exclusion criteria were diabetes mellitus, cardiovascular or malignant disease, pregnancy, or pharmacological treatment with glucocorticoids or drugs that interfere with cortisol metabolism (antiepileptics, rifampicin, and St Johns wart). The patients should abstain from grapefruit juice during the study period. After signing an informed consent form and attending a screening visit, the patients attended a practical course on pump treatment. The investigators considered withdrawal for safety reasons if a patient had major difficulties managing the infusion pump. Before randomization, the patients then underwent a period of dose adjustments of both treatments (OHC and CSHI) as described below.

The study was approved by regional ethics committees and the National Medicines Agencies in both countries (EudraCT number 2009-010917-61). We conducted the study in accor-

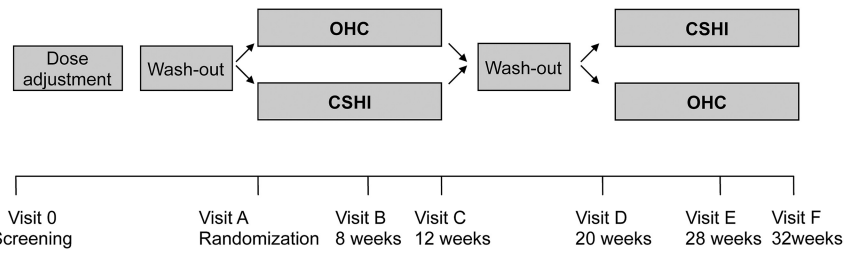

Figure 1. Study design. Patients were screened for participation at visit 0, followed by individual dose adjustment for both OHC and CSHI. After a washout period of a minimum of 1 month, the patients were randomized (visit A) to start with fixed doses of either treatment, lasting 12 weeks. After a washout period of a minimum of 2 months (between visits C and D), the participants shifted to treatment protocol for another 12 weeks. During washout periods, patients were treated with their pretrial replacement therapy.

dance with the principles of good clinical practice (CPMP/ICH/135/95) and the Declaration of Helsinki (1989 version).

Interventions

During CSHI, the patients received hydrocortisone (Solu-Cortef Act-o-Vial; Pfizer Inc) administered by an insulin pump (Dana Diabecare; SOOIL Development Co Ltd). The infusion gear was applied as with an insulin pump. The patients were instructed to clean the injection site with alcohol before needle insertion and replace the hydrocortisone solution and the infusion gear every 3 days. Initial doses were 10.5 mg/m^2·d with the following infusion rate distribution: hours 8:00 AM to 2:00 PM, 0.5 mg/ m^2·h; 2:00–8:00 PM, 0.2 mg/m^2·h; 8:00 PM to 2:00 AM, 0.05 mg/m^2·h; and 2:00–8:00 AM, 1.0 mg/m^2·h. The CSHI doses were adjusted according to salivary cortisol levels (h 6:00–8:00 AM and 11:00–12:00 PM) and morning serum cortisol after 3–5 days. We aimed for a morning salivary cortisol in the middle to upper reference range, a normal morning serum cortisol, and an evening salivary cortisol in the lower reference range.

Oral treatment was weight adjusted and given three times daily as hydrocortisone 5-mg tablets as suggested by Mah et al (12). The oral doses were titrated according to a serum cortisol nomogram 4 hours after the morning dose at days 3–5. We allowed smaller dose adjustments for both treatments based on best clinical judgment during dose titration, whereas all patients were treated with individually adjusted fixed daily doses of both treatments after randomization.

Assays

Fasting blood samples were drawn at 8:00 AM at baseline and after 8 and 12 weeks on each treatment. The samples were stored at −80°C until the end of trial. Salivary cortisol day profiles (obtained at 8:00 AM, 9:30 AM, 11:00 AM, 12:30 PM, 2:00 PM, 3:30 PM, 5:00 PM, 6:30 PM, 7:00 PM, 9:00 PM, 12:00 AM, 3:00 AM, and at 6:00 AM) were sampled at 8 and 12 weeks. The patients were instructed to avoid eating, drinking, smoking, and tooth brushing the last hour before each sampling. Cortisol and cortisone (serum, 24 h urine and saliva) and their metabolites (urine) were analyzed by liquid chromatography-mass spectrometry (25). Salivary steroids were extracted as described by Methlie (26) and tetrahydcortisol-d3 and tetrahydrocortisone-d5 were included as internal standards for the metabolites. Cortisol binding globulin (CBG) in serum was measured by competitive RIA (DIAsource immunoassay). Plasma ACTH was analyzed by chemiluminescent immunometric assay (Immulite 2000; Siemens AG). S-glucose was assayed by UV photometry (Roche Modular). Serum total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and HbA1c were analyzed by standard procedures at Haukeland University Hospital (Bergen, Norway). Samples suited for HbA1c analysis were available only for 14 Norwegian patients. C-terminal crosslinking telopeptides of type 1 collagen (CTX1) was analyzed by immunosorbent assay (ELISA kit; IDS) and N-propeptide of type 1 collagen (P1NP) by competitive RIA (Origon Diagnostica Oy). CBG, CTX1, and P1NP were analyzed at the Hormone Laboratory at Oslo University Hospital. Otherwise, all analyses were performed at Haukeland University Hospital.

Questionnaires

At each visit, the patients completed the two generic HRQoL questionnaires Short-Form 36 (SF-36) (27) and Psychological General Well-being Index (PGWBI) (28), and the AD-Specific Quality-of-Life Questionnaire (AddiQoL) questionnaire, comprising 30 items with scoring algorithms as described elsewhere (29). Higher scores indicate higher level of HRQoL (score range 30–120). To measure subjective sleep quality and disturbances during the past month, the patients completed the Pittsburgh Sleep Quality Index (PSQI) at each visit, which consists of 16 items producing seven component scores and a total index score ranging from 0 to 21 (30). Higher scores indicate more sleeping problems; a score above 5 is indicative of poor sleep.

Sleep registration

The study participants completed a 7-day actigraph recording after 8 weeks on both treatments. The actigraph continuously records information about intensity and frequency of movement. The participants were asked to press a button to indicate time for lights off and lights on. The actigraphs AW4 (Norway), AW7 (Sweden) (Actiwatch, Cambridge Neurotechnology Ltd), and Actiwatch 2 (Sweden) (Respironics/Phillips) were used and were analyzed with the actiwatch sleep analysis (AW4 and AW7) and actiware software (Actiwatch 2). Time in bed, sleep time, wake time, sleep efficiency, sleep-onset latency, sleep bouts, wake bouts, and fragmentation were chosen as parameters for analysis. In parallel with the actigraph recordings, a sleep diary for the period was administered. From the sleep diaries, data on sleep onset latency, total sleep time, number of awakenings, and sleep quality were analyzed.

Statistical analysis

All P values were two sided, and values of $P < .05$ were considered statistically significant. Data are given as percentages, medians, or means together with a variability measure. The area under the curve (AUC) for salivary profiles was calculated by the composite trapezoidal rule and was reported for 24-hour (AUC24h) as well as for daytime (AUC08–24) and nighttime (AUC24–08) for each patient and for each treatment arm. Statistical analysis of paired data (24 h urine) was done by Wilcoxon signed rank test.

To estimate differences in metabolism, HRQoL, and sleep between CSHI and OHC treatments, a linear mixed-effects model for repeated measures was used (31). Our model defined treatment, visit time, treatment sequence, treatment period, and treatment-by-time interaction as fixed effects. To account for the intraindividual correlation between repeated measures, a random effect with patients nested within sequence of treatment was specified. Because of skewed distributions, several variables from the SF-36 domain, glucose, homeostasis model assessment (HOMA) index, and CTX-1 were transformed as recommended (32). To investigate treatment-by-time effects on metabolism, HRQoL, and sleep, we used the likelihood ratio test by comparing the log-likelihood between models with and without the treatment-by-time term. To obtain P for trend in means within treatment groups, the effect of time was included as a linear term in the mixed effect model using the z-test. To obtain P for model-predicted mean differences between treatment groups for different visit time, we performed a post hoc test for pairwise comparisons (z-test).

Results

Participants

Fifty-five patients were screened for participation. Of these, 18 were excluded at screening or during the dose adjustment period. The reasons for exclusion were lack of adherence to the study protocol (n = 6), pregnancy (n = 2), technical difficulty with pump gear (n = 3), plaster allergy (n = 1), lack of time to participate (n = 1), or interference of pump treatment with work or sports activities (n = 3). One patient was excluded because this individual was diagnosed with a chronic neurological disease and another one because of inexplicably low salivary cortisol levels on CSHI, regardless of dose adjustment. Thirty-seven patients were randomized and 32 completed the trial. The investigators withdrew two patients: one became pregnant and one refused to adhere to the prescribed doses (CSHI). Three patients withdrew consent, one because of plaster allergy (CSHI), one because of lack of time for the study (OHC), and one because of technical problems with the pump (CSHI; data from visits A–E were included in the study). Hence, data from 33 patients were included in further analyses (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). The mean age was 48 (SD 12) years, the mean AD duration 12.4 (SD 10.1) years, and 25 patients (75.8%) were female.

Six females received androgen replacement and three estrogen replacement. Fifteen patients (45%) were Swedish and 18 (55%) were Norwegian. The majority were full-time workers (60.6%) and 12.1% did not work. Only 21% did not engage in physical activity, whereas 55% exercised more than 3 hours per week. All the Swedish patients received pretrial glucocorticoid replacement therapy with hydrocortisone; all the Norwegians were treated with cortisone acetate. Most of the patients received glucocorticoids twice (n = 13) or thrice (n = 14) daily and six patients received four or five daily doses. Fourteen patients were treated for hypothyroidism (42%); 24 had other comorbidities. Only hay fever (n = 5), bronchial asthma (n = 2), hypercholesterolemia (n = 3), osteopenia (n = 3), premature ovarian failure (n = 2), and hypertension (n = 2) occurred in more than one patient.

Glucocorticoid levels and effects on the HPA axis and glucocorticoid metabolism

The OHC doses (mean 0.26 mg/kg·d; SD 0.08) were slightly lower than the CSHI doses (mean 0.31 mg/kg·d; SD 0.07); both were lower than the hydrocortisone equivalent pretrial doses (mean 0.36 mg/kg·d, SD 0.13) (see Supplemental Table 1). Morning ACTH levels decreased during CSHI and remained high during OHC (Figure 2A). During CSHI, the morning serum cortisol and cortisone levels were within the reference range (25), in contrast to

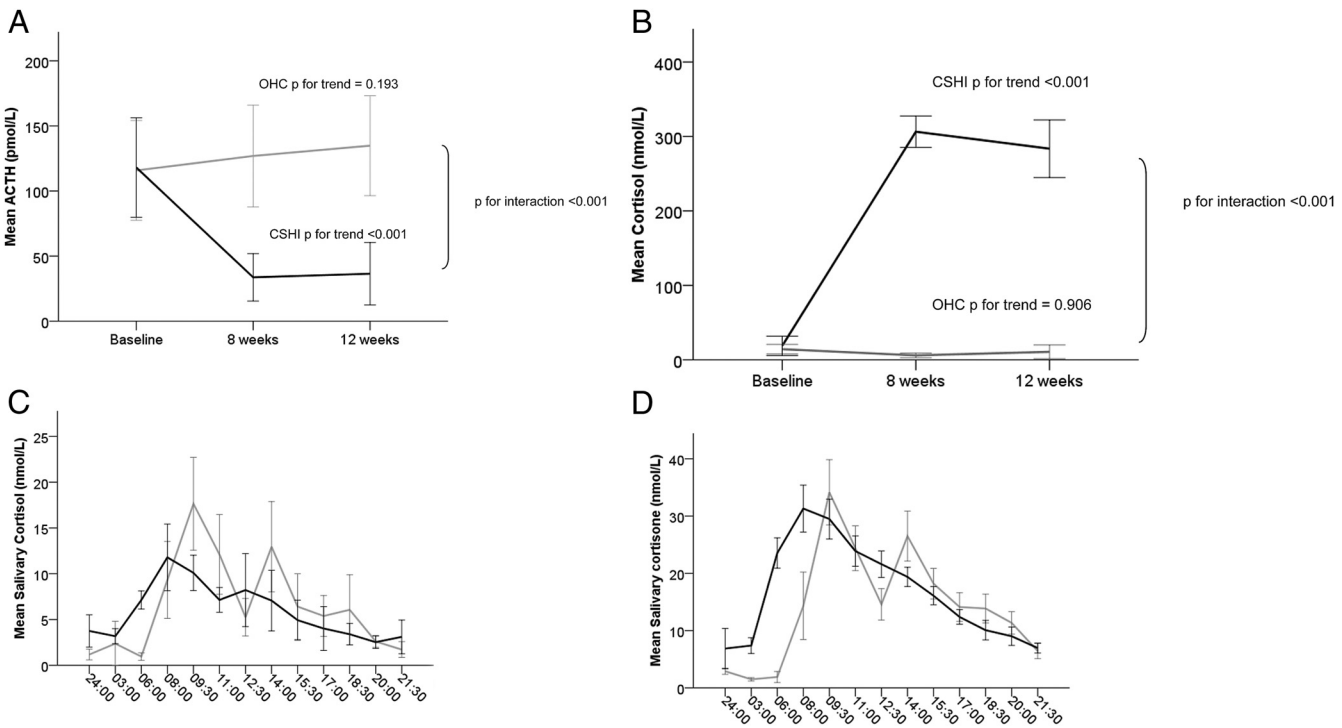

Figure 2. Treatment effects on the HPA axis. A, Morning ACTH levels. B, Morning cortisol levels. C, Twenty-four-hour salivary cortisol curves. D, Twenty-four-hour salivary cortisone curves. The black line represents CSHI, and the gray line represents OHC. Error bars represent 95% CIs. For AUC results, see Supplemental Figure 1.

the low levels found on OHC (Figure 2B). The salivary cortisol and cortisone day curves are presented in Figure 2, C and D. No between-treatment difference was seen in the AUC_{24h} for salivary cortisol, but the daytime AUC_{08-24} was higher for OHC and nighttime AUC_{24-08} was higher for CSHI (Supplemental Figure 1). The AUC_{24h} for salivary cortisone was higher for CSHI than for OHC. Furthermore, nighttime salivary cortisone AUC was higher with CSHI treatment, but no difference was found between the treatments during daytime.

Urine metabolites and calculated enzyme indices are shown in Table 1. Both 24-hour urinary excretions of cortisol and cortisone were significantly higher during CSHI than during OHC, whereas no between-treatment differences were found in total cortisol metabolites. Estimated enzyme indices of 5α-reductase, 5β-reductases, and CYP3A4 were elevated in OHC compared with CSHI as well as when compared with healthy controls in a previous study (33) (Figure 3).

Effects on metabolism

No significant differences between treatments in weight, waist to hip ratio, or BP were observed, although there was a tendency toward an increase in weight and body mass index (BMI) with CSHI (Table 2). No between-treatment differences were found in insulin, insulin C-peptide, or HOMA index; however, there was a trend toward an increased HOMA index with CSHI. Morning glucose levels increased with CSHI and were significantly higher on CSHI than on OHC ($P = .004$). HbA1c (n = 14) decreased over time in both treatments (both P for trend = .019). There were no significant differences in levels of cholesterol, HDL, LDL, and triglycerides. Both CTX1 and P1NP declined during CSHI treatment, whereas on OHC treatment, CTX1 was stable and P1NP increased. The levels were within the reference range and the differences small (Table 2).

Effects on HRQoL

The HRQoL scores remained unchanged during OHC treatment (Supplemental Table 2). During CSHI, the AddiQoL scores increased significantly and were better than the AddiQoL scores with OHC (Figure 4). The AddiQoL short version scores displayed a similar pattern. Of the other HRQoL indices, the PGWBI vitality score and (total) index increased significantly with CSHI, and only the vitality score was significantly different between treatments. The SF-36 physical function score was better with CSHI than with OHC.

Effects on sleep

We found no significant between-treatment difference by actigraphy. Data from the sleep diaries suggested shorter sleep time with CSHI than with OHC, but this finding was not verified by actigraphy (Supplemental Table 3). The PSQI global score increased during CSHI treatment [baseline mean 4.8, confidence interval (CI) 3.7, 5.8 vs a 12-wk mean of 5.6 (CI 4.5, 6.7), P for interaction = .016 when compared with OHC]. Examining the seven underlying PSQI component scores, only self-reported

Table 1. Twenty-Four-Hour Urinary Excretion of Cortisol Metabolites and Calculated Enzyme Indices

	OHC (n = 31)		CSHI (n = 29)		Wilcoxon Signed Rank *P* Value
	Median	Range	Median	Range	
Free cortisol	73.5	22.4, 814	453.7	196.0, 1822	<0.001
Free cortisone	230.8	86.3, 913	414.7	238.2, 1029	<.001
6β-Hydroxycortisol	529.4	103.8, 2879	471.9	75.8, 1340	.452
THF	9216	4056, 20 712	10 940	5695, 20 849	.002
AlloTHF	6149	584.0, 13 463	4715	331.7, 10 281	<.001
THE	15667	7696, 33 494	16 772	7091, 29 603	.285
Total metabolites	30852	15 318, 57 899	34 805	16 978, 62 454	.219
11β-HSD2 activity[a]	3.45	0.81, 7.61	0.95	0.42, 2.19	<.001
CYP3A4 activity[b]	6.88	2.20, 14.15	1.03	0.10, 3.21	<.001
Overall 11β-HSD activity[c]	0.95	0.49, 1.70	0.96	0.40, 1.70	.285
5α-Reductase activity[d]	85.7	7.0, 529.0	8.5	0.91, 19.9	<.001
5β-Reductase activity (cortisol)[e]	117.7	25.5, 612.8	24.3	11.4, 44.0	<.001
5β-Reductase activity (cortisone)[f]	56.6	21.6, 184.2	36.4	16.8, 62.0	<.001

Abbreviations: alloTHF, allo-tetrahydrocortisol; THE, tetrahydrocortisone; THF, tetrahydrocortisol. All values are given as nanomoles per 24 hours.

[a] Cortisone to cortisol calculated ratio.

[b] 6β-Hydroxycortisol to cortisol calculated ratio.

[c] (THF + a-THF) to THE calculated ratio.

[d] a-THF to cortisol calculated ratio.

[e] THF to cortisol calculated ratio.

[f] THE to cortisone calculated ratio.

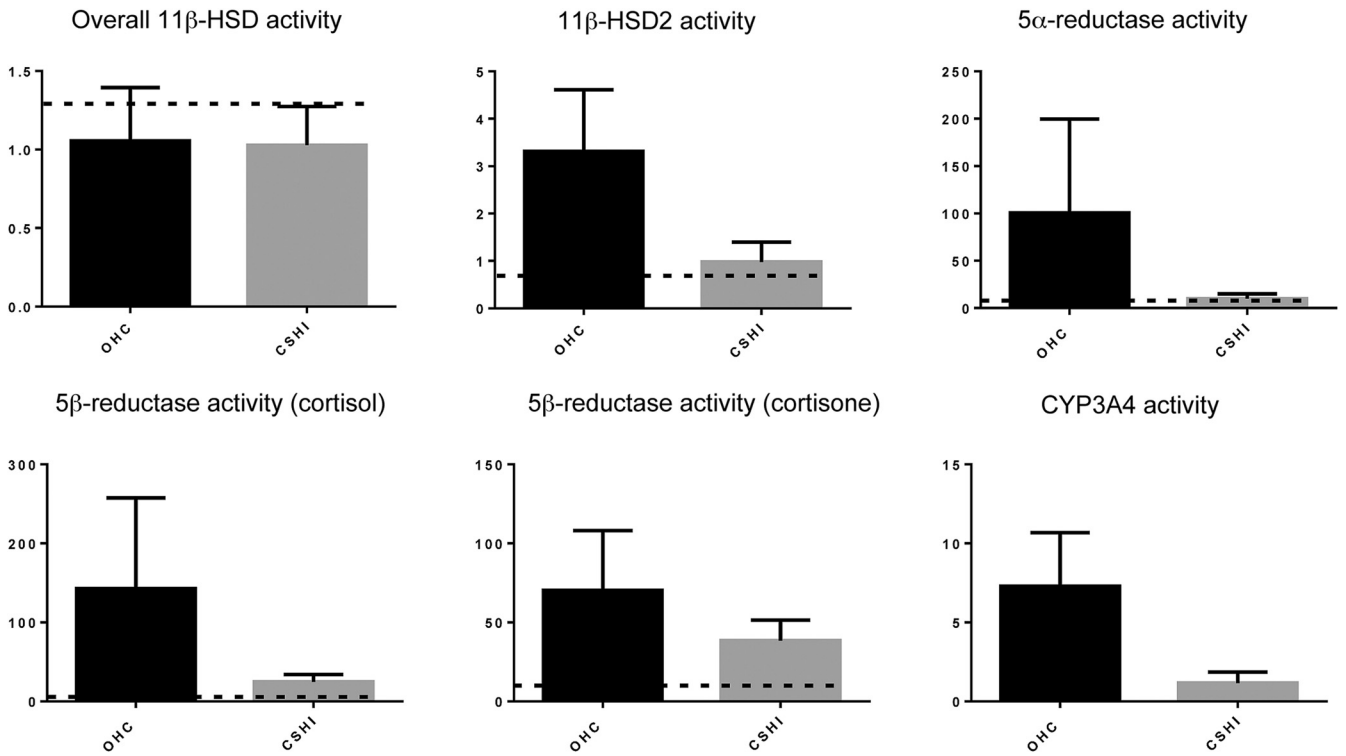

Figure 3. Cortisol metabolism. Enzyme indices were estimated from 24-hour urine cortisol metabolites. Overall HSD activity included (THF+ allo-THF)/THE. HSD2 activity included cortisone to cortisol ratio. 5α-Reductase activity included allo-THF/cortisol. 5β-Reductase activity (cortisol) included THF/cortisol. 5β-Reductase activity (cortisone) included THE/cortisone. CYP3A4 activity included 6β-cortisol/cortisol. The black columns represent CSHI, and the gray columns represent OHC. Error bars represent 95% CIs. The broken line (F) indicates levels from healthy controls in a recent study from Boonen et al (33). HSD2, hydroxysteroid dehydrogenase type II; THF+allo-THF/THE, tetrahydrocortisol plus allotetrahydrocortisol to tetrahydrocortisone.

sleep length and self-reported time in bed scores increased during CSHI.

Adverse events

During OHC 22 adverse events (AEs) were reported, of which one was probably related to the study drug (nausea indicating insufficient dosage) and four as possibly related: mild headache (n = 1), orthostatism (n = 1), and fatigue (n = 2). One serious AE was recorded, ie, hospitalization because of gastroenteritis. During CSHI treatment, 24 AEs were registered, of which four probably related to the treatment: rubor and itching at injection site (n = 3) and fatigue (n = 1). Later it was discovered that the fatigue was due to technical problems with the pump gear, leading to periods without active infusion of the study drug. No patients in the CSHI treatment had any serious AEs.

Discussion

This study shows that CSHI can safely reestablish the circadian cortisol rhythm and normalize morning ACTH levels in AD patients, which is in sharp contrast to the typical daytime cortisol peaks and troughs and elevated morning ACTH seen with OHC treatment. Notably, OHC yielded major alterations in the pattern of glucocorticoid metabolites and metabolic enzyme activities, whereas CSHI restored glucocorticoid metabolism close to normal.

There is no optimal biomarker for follow-up of AD patients in glucocorticoid replacement therapy. ACTH measurement is not useful on OHC because elevated morning ACTH levels are inevitable because of the nighttime cortisol pause. However, with CSHI or other physiological therapies the ACTH levels might become a useful biomarker for individualization of doses. Whether there is any benefit in normalizing ACTH levels apart from improving pigmentation is not known. However, recent research on the melanocortin receptor system has demonstrated that ACTH and other proopiomelanocortin-derived metabolites have multiple effects (eg, regulation of appetite and behavior, immune modulation, and modulation of lipolysis) (34–36). Thus, normalization of ACTH could have important albeit not-yet-defined effects on AD patients.

Because hydrocortisone is administered differently with CSHI and OHC, we could not assume equal daily doses with the two treatments. Notably, the doses were reduced from before inclusion in both treatment arms. The esti-

Table 2. Overall Treatment Effect From Mixed Models and Comparisons at Each Time Point for Metabolic Parameters

	OHC		CSHI				
Parameters	**Patients, n**	**Observed Mean Value (95% CI)**	**Patients, n**	**Observed Mean Value (95% CI)**	**Predicted Mean Difference (95% CI)[a]**	***P* for Difference[b]**	***P* for Interaction[c]**
Glucose							
Baseline	33	4.8 (4.6, 5.0)	32	4.7 (4.5, 4.8)	−0.10 (−0.29, 0.09)	.303	.004
12 wk	33	4.8 (4.6, 4.9)	32	5.0 (4.9, 5.2)	0.27 (0.76, 0.46)	.006	
P for trend[d]		0.831		0.001			
HbA1c							
Baseline	14	5.2 (5.1, 5.3)	14	5.3 (5.1, 5.4)	0.039 (−0.034, 0.11)	.298	1.00
12 wk	14	5.1 (5.0, 5.2)	14	5.2 (5.0, 5.3)	0.039 (−0.034, 0.11)	.298	
P for trend[d]		0.019		0.019			
Cholesterol							
Baseline	33	5.1 (4.8, 5.4)	32	5.3 (5.0, 5.7)	0.29 (0.03, 0.54)	.026	.966
12 wk	33	5.3 (5.0, 5.6)	32	5.5 (5.1, 5.8)	0.24 (−0.01, 0.49)	.064	
P for trend[d]		0.179		0.344			
HDL							
Baseline	33	1.7 (1.5, 1.9)	32	1.7 (1.5, 2.0)	0.02 (−0.08, 0.12)	.655	.242
12 wk	33	1.7 (1.5, 1.9)	32	1.8 (1.5, 2.0)	−0.24 (−0.12, 0.07)	.633	
P for trend[d]		0.261		0.839			
LDL							
Baseline	33	3.2 (2.9, 3.5)	32	3.3 (3.0, 3.6)	0.13 (−0.87, 0.34)	.246	.528
12 wk	33	3.2 (2.9, 3.5)	32	3.4 (3.1, 3.7)	0.28 (0.07, 0.50)	.009	
P for trend[d]		0.966		0.144			
Triglycerides							
Baseline	33	1.0 (0.9, 1.1)	32	1.1 (0.9, 1.3)	0.17 (0.02, 0.32)	.028	.060
12 wk	33	1.1 (0.9, 1.2)	32	1.0 (0.8, 1.2)	−0.04 (−0.19, 0.11)	.583	
P for trend[d]		0.698		0.973			
Insulin C-peptide							
Baseline	31	0.7 (0.5, 0.8)	32	0.7 (0.6, 0.9)	0.03 (−0.09, 0.15)	.604	.283
12 wk	32	0.6 (0.5, 0.8)	31	0.8 (0.6, 1.0)	0.13 (0.02, 0.25)	.027	
P for trend[d]		0.385		0.417			
Insulin							
Baseline	31	8.1 (5.0, 11.3)	32	9.5 (5.6, 13.3)	1.21 (−2.50, 4.92)	.523	.524
12 wk	32	9.6 (5.9, 13.3)	31	11.3 (5.2, 17.4)	1.71 (−1.97, 5.41)	.362	
P for trend[d]		0.440		0.303			
HOMA index							
Baseline	31	1.8 (1.1, 2.5)	32	2.0 (1.2, 2.8)	0.20 (−0.74, 1.13)	0.678	.186
12 wk	32	2.1 (1.2, 3.0)	31	2.6 (1.2, 4.0)	0.45 (−0.48, 1.39)	0.340	
P for trend[d]		0.490		0.011			
Waist to hip ratio							
Baseline	33	0.9 (0.8, 0.9)	33	0.8 (0.8, 0.9)	−0.007 (−0.02, 0.01)	0.360	.242
12 wk	32	0.8 (0.8, 0.9)	32	0.8 (0.8, 0.9)	0.003 (−0.01, 0.02)	0.667	
P for trend[d]		0.535		0.463			
BMI							
Baseline	33	25.4 (24.2, 26.7)	33	25.7 (24.3, 27.0)	0.26 (−0.004, 0.52)	0.054	.085
12 wk	33	25.3 (24.0, 26.6)	32	25.8 (24.5, 27.2)	0.67 (0.41, 0.94)	<.001	
P for trend[d]		0.291		0.037			
Weight							
Baseline	33	74.3 (69.8, 78.8)	33	75.1 (70.1, 80.1)	0.84 (0.05, 1.64)	.04	.114
12 wk	33	73.9 (69.3, 78.5)	32	75.8 (70.8, 80.7)	2.01 (1.21, 2.81)	<.001	
P for trend[d]		0.345		0.05			
Systolic BP							
Baseline	33	111.6 (107.6, 115.6)	33	113.1 (109.0, 117.2)	1.56 (−2.37, 5.49)	.437	.731
12 wk	33	115.5 (112.0, 119.1)	32	114.6 (110.8, 118.4)	−0.65 (−4.59, 3.30)	.747	
P for trend[d]		0.040		0.336			
Diastolic BP							
Baseline	33	75.1 (72.9, 77.3)	33	75.2 (72.7, 77.6)	−0.06 (−2.52, 2.40)	.962	.940
12 wk	33	75.7 (73.6, 77.8)	32	75.2 (73.1, 77.2)	−0.49 (−2.96, 1.98)	.697	
P for trend[d]		0.698		0.973			
P1NP							
Baseline	33	60.0 (51.0, 69.0)	32	64.1 (54.1, 74.0)	5.34 (−0.24, 10.93)	.061	<.001
12 wk	33	68.5 (58.8, 78.3)	33	53.2 (44.5, 62.1)	−15.19 (−20.71, −9.67)	<.001	
P for trend[d]		0.002		<0.001			
CTX1							
Baseline	33	0.46 (0.4, 0.5)	32	0.44 (0.4, 0.5)	−0.85 (−1.93, 0.24)	.746	.007
12 wk	33	0.49 (0.4, 0.6)	33	0.42 (0.3, 0.5)	0.62 (−0.45, 1.70)	<.001	
P for trend[d]		0.104		0.024			

(*Continued*)

Table 2. Continued

Parameters	OHC		CSHI				
	Patients, n	Observed Mean Value (95% CI)	Patients, n	Observed Mean Value (95% CI)	Predicted Mean Difference (95% CI)[a]	*P* for Difference[b]	*P* for Interaction[c]
CBG							
Baseline	33	1095.9 (1025.8, 1165.9)	32	1105.9 (1036.6, 1175.2)	12.8 (−34.9, 60.6)	.598	.844
12 wk	33	1093.2 (1022.1, 1164.2)	33	1116.3 (1031.1, 1201.6)	19.6 (−27.6, 66.7)	.416	
P for trend[d]		0.910		0.869			

Baseline indicates start of each treatment type.

[a] Predicted mean difference was obtained by using linear mixed-effect models with a random intercept.

[b] *P* for difference was obtained by post hoc test for pairwise comparisons.

[c] *P* for interaction was obtained by the likelihood ratio test.

[d] *P* for trend within treatment groups was obtained by incorporating visit time visit time as a continuous model term in the regression model.

mated enzyme indices were significantly higher in OHC than in CSHI and in healthy controls (37). This difference indicates major enzyme induction when hydrocortisone is administered orally, which is avoided when administered parenterally. The OHC doses were slightly lower than CSHI doses, but the salivary cortisol AUC_{24h} was similar on both treatments. However, salivary cortisone might reflect free serum cortisol levels in serum better than salivary cortisol (38). Salivary cortisone AUC_{24h}, and 24-hour urine cortisol were significantly higher and indicate higher hydrocortisone bioavailability on CSHI than on OHC. There were, however, no differences in the total level of urinary glucocorticoids and their metabolites on the two treatments. Furthermore, there was a trend toward a minor increase in BMI on CSHI, albeit no significant between-treatment difference; and morning glucose levels were significantly higher with CSHI.

Likewise, there was a significant trend toward higher morning HOMA index on CSHI but no between-treatment difference. Otherwise, HbA1c levels decreased with both treatments and no changes were found in other parameters such as waist to hip ratio, BP, or lipids. Taken together, the results suggest that the CSHI starting dose might have been even lower and closer to the estimated normal production (18, 39). Based on this and the analyses of 24-hour glucocorticoid profiles in a subgroup (manuscript in preparation), we have revised the dosing algorithm with the highest dosing interval delayed by 1 hour, producing a 9% reduction of the start dose. The revised CSHI dosing algorithm (8:00 AM to 2:00 PM 0.5 mg/m^2·d, 2:00–8:00 PM 0.2 mg/m^2·d, 8:00 PM to 3:00 AM 0.05 mg/m^2·d and 3:00–8:00 AM 1 mg/m^2·d) reduces the starting dose from 10.5 to 9.6 mg/m^2·d.

Although this study did not have statistical power and the proper design to reach firm conclusions on HRQoL and sleep effects, the observed improvement of AddiQoL scores suggests that CSHI diminishes fatigue in AD. The generic questionnaires demonstrated significant HRQoL improvement only in the vitality (PGWBI) and the physical function (SF-36) subscales. This finding indicates superior responsiveness of AddiQoL over generic questionnaires and suggests that it might detect changes over time better than those two generic questionnaires. Thus, our results indicate that replicating the circadian cortisol pattern by CSHI might improve HRQoL. The effects on HRQoL in the current study were not as striking as in the pilot trial (24), but whereas the pilot study included only patients with poor functioning, the present study included patients, regardless of HRQoL status. Patients who are functioning well with OHC may perceive CSHI as complicated and disturbing, whereas patients with poor functioning may experience significant gain and readily accept CSHI treatment. The sleep diaries and the PSQI suggested reduced sleep time with CSHI, but this was not verified by actigraphy. Furthermore, sleep time for both treatments were similar to findings in a Norwegian reference population (40), and the PSQI scores were better in both treatment groups than in a healthy control group in another study (41). Finally, it is an interesting observation that the reduction from the pretrial doses both in the CSHI and OHC arms did not adversely affect HRQoL.

The open-label crossover design implies important limitations to the interpretation of the treatment effects. Most likely, the primary outcome ACTH and the metabolic parameters are not severely affected by placebo effects. The washout period of 2 months cannot completely exclude carry-over effects between the treatments, but this might be attenuated by the randomization of treatment sequence. However, caution is required when interpreting effects on subjective HRQoL and sleep scores. The variation of the outcome parameters in AD and the expected effects of CSHI were not known prior to this study, rendering power calculation difficult. The limited number of participants implies low statistical power and risk of type II error when effect sizes are small. Furthermore, although it is not surprising that some of the screened patients withdrew from

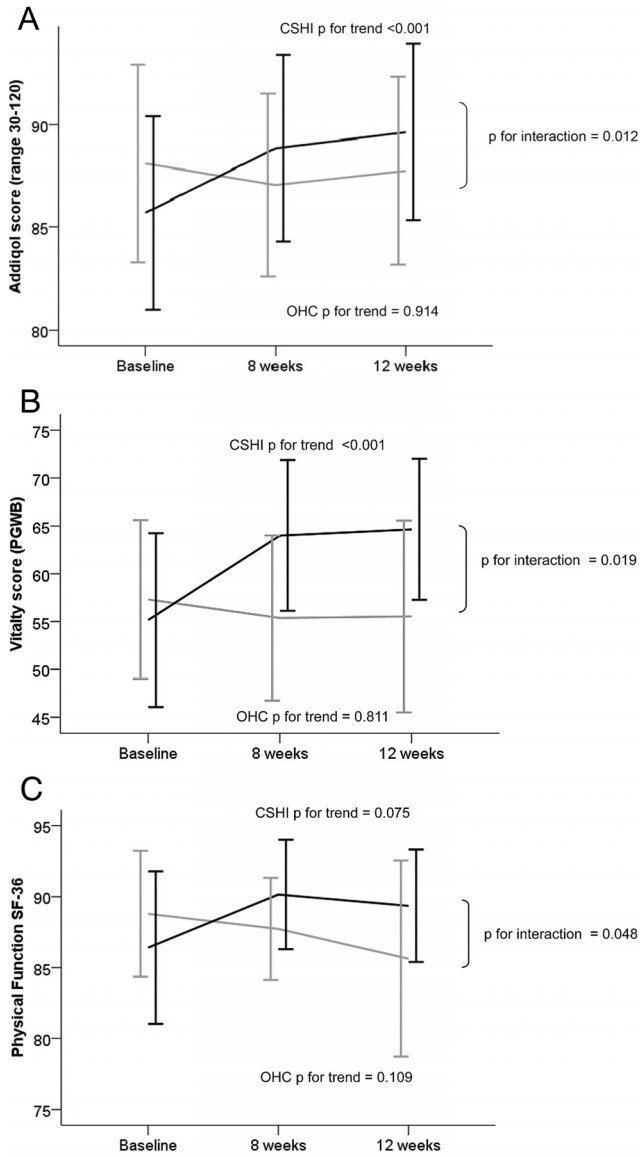

Figure 4. Treatment effects on HRQoL. A, AddiQoL scores. B, PGWB vitality scores. C, SF-36 physical function scores. The black line represents CSHI, and the gray line represents OHC. Error bars represent 95% CIs. For results on all HRQoL variables, see Supplemental Table 1.

the study prior to randomization considering experience with insulin pump treatment (42), this could suggest selection bias. However, the mean baseline HRQoL scores in the randomized patients were better than the scores in previous cross-sectional studies (1, 2). Both in AD and diabetes mellitus, pump treatment requires a capable and willing patient, and proper patient education and follow-up are mandatory. Most importantly and despite any limitations associated with the study design, the study demonstrates that CSHI is a safe and reliable mode of glucocorticoid replacement and thus an attractive treatment option in selected patients.

In conclusion, CSHI produced a more physiological circadian cortisol biorhythm than conventional therapy and induced normalization of morning ACTH and cortisol levels, restoration of nighttime cortisol levels, and changes in glucocorticoid metabolism resembling healthy individuals. CSHI proved safe and may eventually become a treatment option for selected patients with adrenal insufficiency that function poorly on conventional therapies. Furthermore, the modified-release oral therapies and the current CSHI dosing schedule may create a smooth circadian cortisol profile, but the normal biorhythm also includes an ultradian rhythm superimposed on the circadian profile (43). Future CSHI trials should aim at replicating the full ultradian rhythm, which could possibly further improve outcome for AD patients.

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