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RESEARCH

Cardiovascular risk profile of low-dose prednisolone and its effect on the quality of life in patients with adrenal insufficiency: the HYPER-AID observational study

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Abstract

Background: Patients with adrenal insufficiency require glucocorticoid replacement therapy either as hydrocortisone in multiple-daily doses or as low-dose prednisolone once daily. Data on the long-term safety, cardiovascular risk, and quality-of-life (QoL) outcomes of prednisolone remain limited.

Methods: In this prospective longitudinal cohort study, patients with adrenal insufficiency underwent a pre-specified switch from multiple-daily dose hydrocortisone to once-daily low-dose prednisolone (2–4 mg) as part of routine clinical care and followed up for at least four months. Cardiovascular risk was assessed using anthropometric and biochemical markers (lipid profile, HbA1c, C-reactive protein, blood pressure, and waist and hip circumference). QoL was evaluated using a modified SF-36 questionnaire. Baseline and follow-up measures were compared using paired *t*-tests or non-parametric equivalents.

Results: Of the 62 enrolled patients, 48 completed follow-up. The mean age was 54.5 ± 13 years; 56% were female; and 83% had secondary adrenal insufficiency. After at least four months on prednisolone, weight decreased significantly (90.6–89.6 kg, $P = 0.007$), accompanied by a reduction in systolic blood pressure (−5 mmHg, $P = 0.032$). Lipid parameters, HbA1c, and CRP remained unchanged ($P > 0.05$). Energy scores improved significantly (+9 points, $P = 0.003$), and patients reported increased treatment convenience ($P = 0.002$).

Conclusion: Low-dose once-daily prednisolone offers comparable cardiovascular risk to hydrocortisone while improving treatment convenience, systolic blood pressure, and SF-36 subjective energy scores. These findings support the use of prednisolone as a potentially preferable alternative in patients with adrenal insufficiency.

Keywords: cardiovascular; prednisolone; hydrocortisone; glucocorticoid replacement therapy

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Introduction

Adrenal insufficiency is a potentially life-threatening condition characterised by inadequate production of glucocorticoids due to primary adrenal disease or hypothalamic–pituitary dysfunction (1). Glucocorticoid replacement therapy is essential and should ideally mimic the physiological diurnal cortisol rhythm (2, 3, 4).

Despite treatment, patients with adrenal insufficiency face an increased morbidity and mortality risk, particularly from cardiovascular disease, osteoporosis, and infections (5, 6). In addition, they report impaired quality of life (QoL), particularly in general health and fatigue domains (7). Chronic over- or underexposure to glucocorticoids may contribute to these outcomes (3, 4, 6).

Current guidelines recommend either multiple-daily doses of hydrocortisone or once-daily low-dose prednisolone for glucocorticoid replacement therapy (8). However, evidence directly comparing their cardiovascular and QOL profiles is limited and mixed (9, 10). Furthermore, it is unclear whether previously reported satisfaction with prednisolone translates into improved QoL (9).

This study aimed to assess cardiovascular risk markers and QoL outcomes in patients switched from multiple-daily dose hydrocortisone to once-daily low-dose prednisolone.

Methods

Study design and participants

This was a prospective, open-label, single-arm, longitudinal cohort study conducted at a UK tertiary centre, as part of the multi-centre HYPER-AID study (https://clinicaltrials.gov/study/NCT03608943). The study evaluated within-participant changes in cardiometabolic and quality-of-life parameters following a pre-specified switch from multiple-daily dose hydrocortisone to once-daily low-dose prednisolone as part of routine clinical care. Patients aged 18–85 years with confirmed adrenal insufficiency, on stable hydrocortisone replacement for at least four months, were eligible. Consecutive patients seen in the endocrine clinic were offered a choice of switching their glucocorticoid replacement regimen. Exclusion criteria included pregnancy and use of the combined oral contraceptive pill.

Study procedures

Participants were switched to prednisolone 2–4 mg once daily, depending on their starting dose of hydrocortisone. Those who were taking a total daily dose of hydrocortisone 20 mg were switched to prednisolone 4 mg once daily, those on 15 mg of hydrocortisone were placed on 3 mg prednisolone, and those taking 10 mg hydrocortisone were switched to prednisolone 2 mg once daily. Dose conversion was based on contemporary pharmacokinetic and clinical outcome data supporting the physiological equivalence and safety of low-dose prednisolone in adrenal insufficiency (11). Participants were reviewed after a minimum of four months on prednisolone. Patients who reverted to hydrocortisone prior to the planned follow-up visit were not included in the primary paired analysis, as they did not complete the intended exposure period. The duration of prednisolone exposure in these individuals varied, and their follow-up data were not analysed.

Routine clinical assessments, including blood pressure, waist/hip circumference, and laboratory tests (lipid profile, HbA1c, C-reactive protein (CRP), full blood count (FBC), and renal, liver, and bone profiles) were performed at baseline and follow-up visits. Blood pressure was measured on a single occasion on arrival to the clinic appointment using a standard automated clinic sphygmomanometer after the participant had been seated for five minutes. A single reading was recorded at each visit in keeping with routine clinical practice. Body weight was measured using calibrated clinic scales with participants wearing light clothing and no shoes.

Concomitant hormone replacement therapies, including thyroid hormone, desmopressin, and fludrocortisone, were recorded at baseline and follow-up. No patients were on DHEA replacement. Cumulative stress-dose glucocorticoid exposure was not systematically recorded. The use of topical, inhaled, or intra-articular glucocorticoids was not quantified.

QoL was assessed using a modified 11-item SF-36 questionnaire (12), grouped into four domains: general health, energy, well-being, and nausea. Scores ranged from 0 to 100, with higher scores indicating a better health status. Average scores are presented for each domain. Methods for calculating the scores are set out in detail by Ware *et al.* (13).

Twelve participants had follow-up HbA1c values remeasured due to a known positive assay bias in the original analyser (Menarini analyser) of up to 5 mmol/mol.

Statistical analysis

Analyses were performed using R 3.5.6. Normality was assessed with the Shapiro–Wilk test. Continuous variables were summarised using means (SD) or medians (IQR). Paired *t*-tests or Wilcoxon signed-rank tests were used for comparisons. $P < 0.05$ was considered statistically significant. Analyses were restricted to participants with complete paired baseline and follow-up data after a minimum of four months on prednisolone; no imputation was performed for missing data.

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Table 1 Baseline characteristics of all included patients.

Variable	Primary AI *n* = 8	Secondary AI *n* = 40	Total *n* = 48
Age (years), mean ± SD	51 ± 4.8	55 ± 14.4	54.5 ± 13.3
Female, *n* (%)	6 (75%)	21 (52.5%)	27 (56.3%)
Glucocorticoid duration (years), median (IQR)	6 (5–14)	10 (4.8–14.8)	9.5 (5–14.8)
On DDAVP, *n* (%)	0 (0)	5 (12.5)	5 (10.4)
Hydrocortisone dose (mg), median (IQR)	20 (20–21.3)	20 (15–20)	20 (15–20)
On thyroxine, *n* (%)	3 (37.5)	27 (67.5)	30 (62.5)
Diabetes, *n* (%)	0 (0)	10 (25)	10 (20.8)
Ischaemic heart disease, *n* (%)	0 (0)	4 (10)	4 (8.9)
≥3 hormone replacements, *n* (%)	0 (0)	11 (27.5)	11 (23)

Baseline characteristics were additionally compared between participants who completed follow-up and those who did not to assess potential selection or attrition bias. As this was an exploratory real-world study embedded within routine clinical care, a formal *a priori* sample size calculation was not performed. The study was designed to generate hypothesis-forming data regarding cardiometabolic safety and patient-reported outcomes following a treatment switch.

Results

Participant characteristics

Baseline characteristics by adrenal insufficiency subtype are presented to describe cohort composition rather than to imply powered comparisons between primary and secondary adrenal insufficiency.

Sixty-two patients were enrolled and underwent baseline assessment while receiving hydrocortisone. Of these, 48 patients (77%) remained on prednisolone for at least four months and completed follow-up assessments, forming the primary analysis cohort (Table 1). Thirteen patients (21%) reverted to hydrocortisone prior to follow-up due to personal preference, and one patient died from acute liver failure secondary to paracetamol overdose, considered unrelated to study treatment. Patients who reverted to hydrocortisone or died were not included in the paired longitudinal analyses.

Baseline characteristics were also compared between participants who completed follow-up and those who did not (Table 2). There were no statistically significant differences between the two groups in age, sex distribution, adrenal insufficiency subtype, duration of glucocorticoid replacement therapy, or baseline anthropometric measures, including weight and body mass index.

Baseline characteristics of the 48 participants who completed the study are shown in Table 1. The mean age was 54.5 ± 13 years; 56% were female; and 17% had primary adrenal insufficiency. Median glucocorticoid exposure was 9.5 (5–14.8) years. The median prednisolone dose for the entire cohort was 4 mg (IQR 4–4 mg). Median doses were similar across adrenal insufficiency types, with both primary and secondary adrenal insufficiency showing a median of 4 mg. Six patients (75% of those with primary adrenal insufficiency) were receiving fludrocortisone at a daily dose of 100 μg, whereas none of the patients with secondary adrenal insufficiency were treated with fludrocortisone.

All concomitant medications were recorded both at baseline and at the follow-up appointment. There were no changes in patients' anti-hypertensives, statins, or newly initiated weight loss medications.

Cardiometabolic outcomes

Baseline values refer to measurements obtained while participants were receiving hydrocortisone, and follow-up values refer to measurements obtained after at least four months of prednisolone therapy in the 48 participants who completed follow-up.

Table 2 Baseline characteristics of participants who completed follow-up compared with those who did not.

Variable	Completed follow-up (*n* = 48)	Did not complete follow-up (*n* = 13)
Age, years (mean, SD)	54.5 (13.3)	53.3 (12.8)
Female sex, *n* (%)	27 (56.2)	7 (53.8)
Secondary adrenal insufficiency, *n* (%)	40 (83.3)	9 (69.2)
Duration on steroid replacement, years (mean, SD)	11.4 (8.6)	12.8 (9.9)
Baseline weight, kg (mean, SD)	90.6 (19.4)	85.9 (17.3)
Baseline BMI, kg/m^2 (mean, SD)	31.6 (6.6)	29.2 (5.7)

Baseline refers to measurements obtained while participants were receiving hydrocortisone prior to switching therapy. BMI, body mass index.

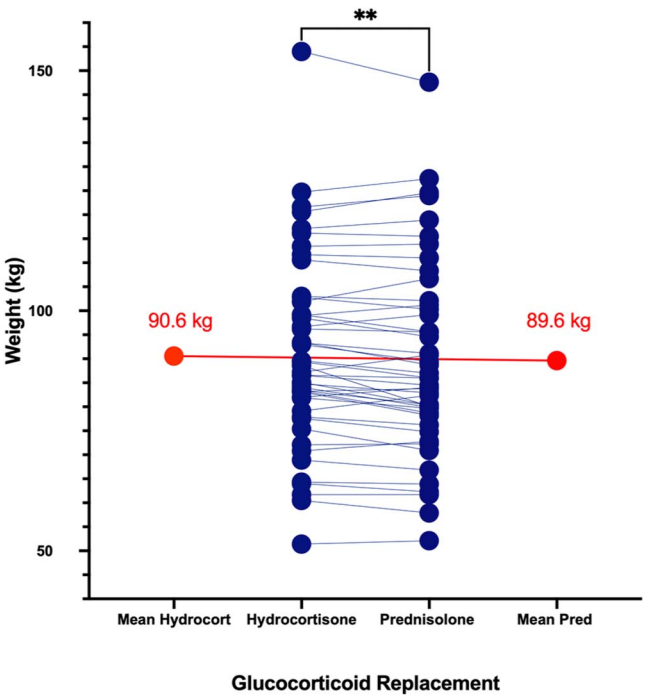

Figure 1

Change in body weight in patients with adrenal insufficiency before and after switching from multiple-daily dose hydrocortisone to once-daily low-dose prednisolone. Individual paired measurements are shown, illustrating within-subject changes over time. Mean body weight for each glucocorticoid regimen is indicated.

At follow-up, weight decreased significantly from 90.6 ± 19.4 to 89.6 ± 20.0 kg (P = 0.007), with a corresponding BMI reduction (31.6 to 31.1 kg/m^2, P = 0.006). Systolic blood pressure reduced by 5 mmHg (P = 0.032), with no change in diastolic pressure (Figs 1 and 2).

No significant changes were noted in total cholesterol, LDL, HDL, triglycerides, CRP, or HbA1c (Table 3).

Quality-of-life outcomes

Modified SF-36 data were available for 40 patients. Energy scores increased significantly from 33 ± 22 to 43 ± 18 (P = 0.003). No significant differences were seen in general health, well-being, or nausea scores (Table 4).

Prednisolone was rated as more convenient than hydrocortisone: 60% reported it as 'very convenient' compared with 25% on hydrocortisone (P = 0.002).

Discussion

This prospective longitudinal cohort study examined within-patient changes in cardiometabolic markers and quality of life following a switch from hydrocortisone to low-dose once-daily prednisolone. As the intervention was not randomised or blinded, the findings should be interpreted in the context of real-world clinical practice rather than as evidence of comparative efficacy.

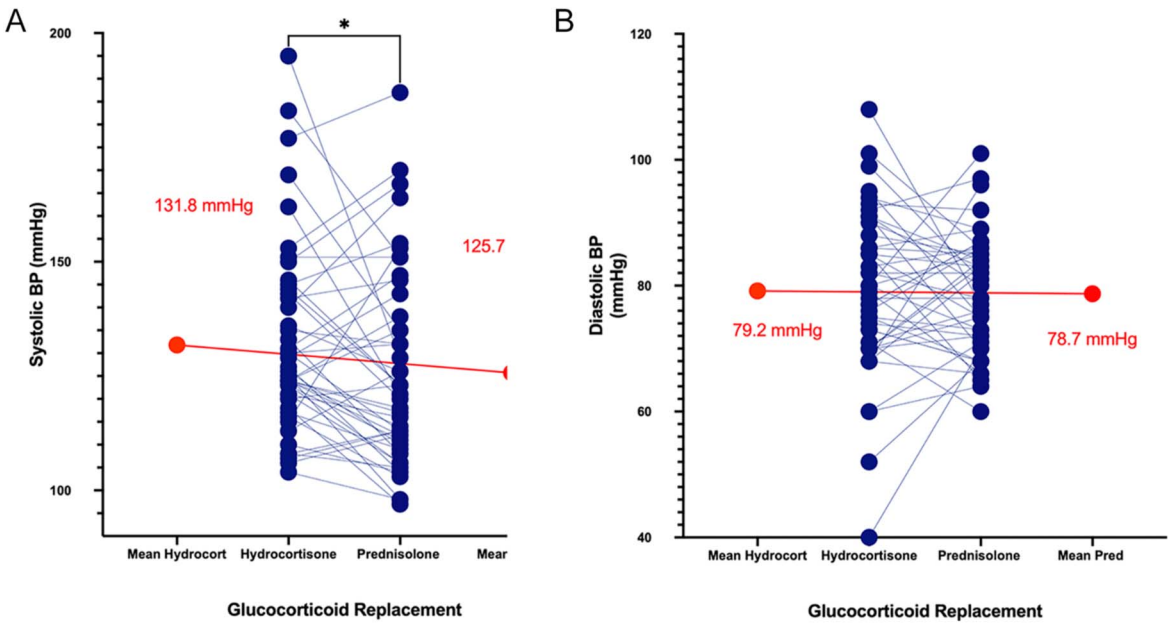

Figure 2

(A) Change in systolic blood pressure before and after switching from hydrocortisone to once-daily low-dose prednisolone. Paired clinic measurements are shown for individual participants to illustrate within-subject changes. (B) Change in diastolic blood pressure before and after switching from hydrocortisone to once-daily low-dose prednisolone. Individual paired clinic measurements are shown to demonstrate within-subject variation over time.

Table 3 Cardiometabolic outcomes in all patients following switching from multiple-daily dose hydrocortisone to once-daily low-dose prednisolone.

Measure	Baseline	Follow-up	Difference	*P* value
Weight (kg), mean ± SD	90.6 ± 19.4	89.6 ± 20	−1.20	**0.007**
BMI (kg/m^2), mean ± SD	31.6 ± 6.6	31.1 ± 6.8	−0.40	**0.006**
Waist-to-hip ratio, mean ± SD	0.93 ± 0.07	0.94 ± 0.08	0.01	0.36
Systolic blood pressure (mmHg), median (IQR)	125 (120–143)	120 (110–137)	−5.0	**0.032**
Diastolic blood pressure (mmHg), median (IQR)	79 (71–87)	79 (71–85)	0.00	0.722
HbA1c (mmol/mol), median (IQR)	39 (37–43)	40 (37–44)	1	0.430
Total cholesterol (mmol/L), mean ± SD	5.0 ± 1.3	4.9 ± 1	−0.02	0.860
Triglycerides (mmol/L), median (IQR)	1.7 (1.2–2.5)	1.6 (1.1–2.4)	−0.05	0.201
HDL cholesterol (mmol/L), median (IQR)	1.5 (1.3–1.9)	1.5 (1.3–1.9)	0.00	0.311
LDL cholesterol (mmol/L), median (IQR)	2.4 (2–3)	2.6 (2–3)	0.20	0.426
CRP (mg/L), median (IQR)	2.6 (1.1–6.9)	2.35 (1.5–5.6)	−0.25	0.606

Bold indicates statistical significance, $P < 0.05$. Baseline values represent measurements on hydrocortisone prior to treatment switch. Baseline and follow-up values include only participants who completed ≥4 months of prednisolone therapy (n = 48).

Switching from multiple-daily dose hydrocortisone to once-daily low-dose prednisolone was associated with significant improvements in weight, systolic blood pressure, and patient-reported energy. These findings support earlier data, suggesting prednisolone's metabolic neutrality when used at physiological doses (9, 14). The small number of participants with primary adrenal insufficiency precluded meaningful subgroup analyses of cardiometabolic or quality-of-life outcomes by aetiology.

One study comparing hydrocortisone with prednisolone in paediatric patients with congenital adrenal hyperplasia demonstrated better clinical and hormonal control with prednisolone, permitting a reduction in the replacement dose. The authors found that the schedule used suggested a hydrocortisone to prednisolone bioequivalence ratio of 6–8:1 (15).

Previous studies have raised concerns over a less favourable impact on lipid profiles with prednisolone; however, these have been with higher doses and therefore greater glucocorticoid exposure (10). Our findings align with studies using 2–4 mg/day, showing no adverse effects on lipid profiles, weight, or glycaemia (4, 9, 16).

Patient-reported outcomes were favourable. Increased energy and improved treatment convenience reflect a meaningful enhancement in QoL. Unlike prior cross-sectional studies, this prospective design supports a temporal relationship (9, 17). The observed improvement in subjective energy may relate to pharmacokinetic and pharmacodynamic differences between prednisolone and hydrocortisone (18). Prednisolone has a longer biological half-life and higher affinity for the glucocorticoid receptor, which may result in more sustained receptor activation over the day (11). In contrast to multiple-dose hydrocortisone regimens, once-daily prednisolone may provide smoother glucocorticoid exposure with fewer peaks and troughs, potentially reducing periods of relative under-replacement that can contribute to fatigue. While speculative, these mechanisms offer a plausible biological explanation for the improved energy scores observed in this cohort.

Limitations include the lack of a comparator due to the real-world observational study design, and the potential for selection and attrition bias given that participants were not randomised and some reverted to hydrocortisone prior to the follow-up visit. Thirteen patients switched back to their original glucocorticoid replacement regimen due to personal preference and were not included in the paired analyses, which may have resulted in survivor bias; however, baseline characteristics did not differ significantly between participants who completed follow-up and those who did not (Table 2), mitigating but not eliminating this

Table 4 Mean (SD) scores for each domain of the modified SF-36 questionnaire at baseline (on hydrocortisone) and at follow-up after switching to prednisolone in patients with adrenal insufficiency. Higher scores indicate a better health status.

Domain	Baseline mean (SD)	Follow-up mean (SD)	Mean difference	*P* value
General health	39 (22)	44 (21)	5	0.118
Energy	33 (22)	43 (18)	9	**0.003**
Well-being	66 (18)	68 (17)	2	0.420
Nausea	89 (21)	93 (13)	4	0.263
Total scores	228 (56)	248 (48)	20	**0.025**

Bold indicates statistical significance, $P < 0.05$.

concern. Reliance on single-point clinic blood pressure measurements rather than repeated or ambulatory assessments reflects the pragmatic clinic-based design and may have introduced measurement variability.

As this was a paired pre–post study in which each participant acted as their own control, adjustment for fixed covariates, such as age and sex, was not required; however, the modest sample size precluded reliable multivariable or stratified analyses, and residual confounding by unmeasured time-varying factors cannot be excluded. Although no changes occurred in antihypertensive therapy, lipid-lowering medication, or initiation of weight-loss treatments during follow-up, several potential confounders were not fully captured, including cumulative lifetime glucocorticoid exposure, frequency of stress-dose use, and exposure to non-oral glucocorticoid preparations. These factors may have influenced cardiometabolic and quality-of-life outcomes.

The small proportion of patients with primary adrenal insufficiency is representative of patients seen in our department. It is thought that hydrocortisone has greater mineralocorticoid activity compared with prednisolone; however, no patients with primary adrenal insufficiency who were switched to prednisolone required an increase in their fludrocortisone dose.

The absence of a formal *a priori* power calculation and the relatively small sample size limit the ability to detect modest effects and increase the risk of type II error. Consequently, the findings should be considered exploratory and hypothesis-generating rather than definitive.

Future prospective randomised trials are needed to confirm these findings and to evaluate longer-term outcomes.

Conclusion

Once-daily low-dose prednisolone compared to multiple-daily hydrocortisone in adrenal insufficiency was associated with no adverse cardiometabolic changes and modest improvements in weight, systolic blood pressure, and patient-reported energy over short-term follow-up.

Declaration of interest

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

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Ethics

The study was approved by the Yorkshire and the Humber-Bradford Leeds Research Ethics Committee (REC Ref: 18/YH/0128). All participants provided written informed consent.

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