Comparison of Various Glucocorticoid Replacement Regimens Used in Chronic Adrenal Insufficiency: A Systematic Review

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Keywords

Adrenal · Insufficiency · Glucocorticoid · Outcomes

Abstract

Objective: Patients with adrenal insufficiency require life-long glucocorticoid replacement therapy. Hydrocortisone (15–30 mg/day) and prednisolone (3–7.5 mg/day) are the preferred agents used although there is a lack of consensus among endocrinologists regarding the impact of different steroid regimens on quality of life, bone metabolism, cardio-metabolic outcomes, adrenal crisis and infections. We carried out a retrospective systematic review of the literature to compare the efficacy and side effects of various glucocorticoid replacement regimens in patients with chronic adrenal insufficiency. **Methods:** We searched PubMed, Cochrane Reviews and Google Scholar databases up to March 14, 2019, for studies evaluating various clinical outcomes with glucocorticoid replacement therapy. The abstracts and full studies were appraised and data extracted from the eligible studies. The quality of evidence was evaluated and risk of bias carried out. **Results:** A total of 47 studies including 9 randomised controlled trials (RCTs) and 38 observational studies were evaluated in this systematic review. Prednisolone therapy was observed to be safe as well as efficacious as hydrocorti-

sone although a higher dose was associated with an increased risk of cardiovascular (CV) disease. A lower hydrocortisone dose (15–20 mg/day) was associated with a reduction of blood pressure and improved clinical outcomes although this observation was based on a solitary RCT. Modified release hydrocortisone was observed to reduce the risk of CV disease based upon results from 2 of the RCTs. However, there was no conclusive evidence of benefit of modified release hydrocortisone and continuous subcutaneous hydrocortisone infusion in improving subjective health status. **Conclusion:** Prednisolone therapy remains a safe and efficacious alternative to hydrocortisone although there are concerns of dyslipidaemia and CV disease with higher doses. There is limited level I evidence suggestive of a positive effect of modified release hydrocortisone on CV and metabolic outcomes, particularly weight reduction.

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Introduction

Adrenal insufficiency refers to inadequate production of glucocorticoids/mineralocorticoids by the adrenal cortex [1–3]. It is broadly divided into primary or secondary adrenal insufficiency based on the predominant organ in-

volved in pathogenesis. An adrenocortical pathology leads to development of primary adrenal insufficiency in contrast to pituitary/hypothalamic lesions, which results in secondary adrenal insufficiency [2, 4].

In clinical practice, active glucocorticoids such as hydrocortisone or prednisolone are preferred therapeutic agents in view of a relatively predictable pharmacokinetics compared to their precursors (cortisone acetate and prednisone) [1, 5]. Hydrocortisone is commonly used as glucocorticoid replacement, in 3 quarters of patients with adrenal insufficiency, followed by prednisone/prednisolone and cortisol acetate in 11 and 6% of the patients with adrenal insufficiency, respectively [6]. In recent data compiled from clinics in the UK, 72% of patients are on hydrocortisone, 26% on prednisolone and 2% modified release hydrocortisone [7].

The choice of agent for steroid replacement to use in adrenal insufficiency is paramount as this impacts the health outcomes, including cardiometabolic consequences which are recognised adverse effects of the treatment [2]. Postulated mechanisms for increased cardiometabolic risk in adrenal insufficiency include alteration in physiological cortisol circadian curve and glucocorticoid overreplacement [8]. Selection of glucocorticoid replacement which simulates circadian cortisol rhythm is postulated to be advantageous for metabolic profile in patients with adrenal insufficiency [9]. In contrast, dexamethasone use in adrenal insufficiency is discouraged owing to cushingoid side effects due to improper dose titration [1]. Increase in body weight is a recognised adverse effect associated with most glucocorticoid replacement regimens especially at higher replacement doses. The increase in weight correlates with cardiovascular (CV) risk factors such as worsening of glycaemic control [10]. Quinkler et al. [11] found a statistically significant reduction in both body mass index and glycosylated haemoglobin (HbA_{1c}) with modified release hydrocortisone compared to the conventional hydrocortisone treatment.

Quality of life is impaired in patients with adrenal insufficiency [12]. In evaluating the quality of life in patients with adrenal insufficiency, recognised confounders include patients' perception of their health, mood changes as well as cognitive changes that may occur in adrenal insufficiency [13]. Maintenance of the physiological cortisol circadian levels has an association with improved quality of life in the treatment of patients with Addison's disease [14].

Glucocorticoid replacement in adrenal insufficiency affects bone health with increased risk of osteoporosis

and fractures, especially among patients on higher doses of glucocorticoids exceeding 30 mg of hydrocortisone or its equivalent [15]. The dose-dependent effect of glucocorticoids on bone health was also demonstrated by Schulz et al. [16], who reported that lowering the dose of hydrocortisone resulted in an increase in bone mineral density (BMD) and did not predispose to a higher risk of occurrence of adrenal crisis. There has been variation in bone composition among the patients with adrenal insufficiency treated with various glucocorticoid replacement options with lower scores noted in patients treated with prednisolone [17, 18]. On the other hand, the use of modified release hydrocortisone has been shown to result in improved BMD values [19] although the overall evidence remains conflicting and contentious. A recent study following up patients with primary adrenal insufficiency over 5.5 years showed lower BMD values with prednisolone than hydrocortisone, and no improvement in the values was seen after a change to modified release hydrocortisone [20].

In a systematic review evaluating the glucocorticoid treatment options in adrenal insufficiency, Al Nofal et al. [21] assessed the evidence for differences in various health outcomes in studies published through July 2016. The review included the quality of life of patients, bone health, mortality and acute events, such as adrenal crises. One of the major limitations observed by the reviewers was the lack of high-quality evidence, particularly related to use of relatively newer steroid preparations such as modified release hydrocortisone. Since 2016, there have been multiple further studies which have been carried out to compare conventional hydrocortisone replacement regimens versus prednisolone or modified release hydrocortisone preparations. Our systematic review was aimed to evaluate the efficacy and impact of various glucocorticoid replacement regimens used in patients with adrenal insufficiency. We used objective benchmarks, such as BMD, cardiometabolic outcomes (including blood pressure, blood glucose, lipid profile, body weight, body mass index, waist circumference) apart from rate of infections and adrenal crises with different glucocorticoid replacement doses and regimens.

Objectives

To evaluate and compare the efficacy and safety of various glucocorticoid replacement regimens in patients with adrenal insufficiency (prednisolone, hydrocortisone or modified release hydrocortisone).

To determine the optimum dose for glucocorticoid replacement in patients with adrenal insufficiency.

Fig. 1. PRISMA diagram summarising the search process. PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency.

Materials and Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement which provided a structured overview of the methods recommended to conduct and document the proceedings for the systematic review [22].

Eligibility Criteria

The following were the inclusion criteria for the studies which were evaluated in this systematic review:

- Studies carried out in an adult population with primary or secondary adrenal insufficiency (patients aged >18 years)
- Use of a well-documented steroid replacement regimen (primarily hydrocortisone, prednisolone, dexamethasone) with evaluation of outcomes which included rates of adrenal crises, infections, patient satisfaction, metabolic and CV disease complications (glycaemic control, serum lipids, elevated blood pressure and body weight)

In view of only a limited number of prospective double-blinded randomised control trials (RCTs) which have been carried out in patients with adrenal insufficiency comparing different steroid regimens, observational studies were also included in this systematic review.

Exclusion criteria:

- Case reports
- Studies which were not available in the English language
- All non-original studies.

Data Source and Selection of Studies

The related studies meeting the inclusion criteria were identified through a search of Medline (1948–2019) using the search terms as follows: “adrenal insufficiency,” “Addison disease,” “adrenal hypofunction,” hypoadrenalism*, hydrocortison*, prednisolone,

lone, dexamethasone, “modified release hydrocortisone,” “subcutaneous hydrocortisone,” “quality of life,” “bone density,” fracture*, “adrenal crisis,” infection*, weight*, HbA_{1c}, “body mass index.” We also searched the Cochrane Central Register of Controlled Trials using the above search terms. We conducted the last search on March 14, 2019. A Google search was performed to find any additional studies which may have been omitted in the initial search.

Data Collection and Analysis

The titles of studies obtained by the above-mentioned search methodology were evaluated systematically. The abstracts were reviewed to determine their suitability for this review, using predefined inclusion criteria. The review of abstracts was done by both authors and any discrepancy was resolved by referring to the predefined inclusion criteria. The full texts of all the studies which were deemed relevant were retrieved and assessed to determine eligibility.

Data Extraction

A data extraction form was used to extract data from the selected full texts. The data obtained included the year of study publication and name of the first author, number of study participants, type of adrenal insufficiency (primary or secondary), duration of the study, the numbers allocated to the study arms, the study inclusion and exclusion criteria, the characteristics of the study participants, the types and doses of glucocorticoids administered and documented outcomes. The data on infection, adrenal crises and CV/metabolic outcomes documented were also derived.

Assessment of Quality of Evidence

The risk of bias in the studies included in this review was systematically evaluated. For RCTs, this included the generation of

random sequences, the allocation concealment, and the extent of blinding of the study investigators using the Cochrane tool for risk of bias for randomised trials [23].

Results

The initial search of Medline yielded 6,863 titles. The titles were screened, and 53 abstracts were selected. 49 of these abstracts were eligible for inclusion in this systematic review, and full texts of these 49 studies were evaluated. A further 10 studies were obtained by hand searching of citations from previous reviews and thorough search on Google Scholar, as summarised in Figure 1.

Glucocorticoid Replacement and BMD

A total of 11 previous studies evaluated the effect of glucocorticoids on BMD although none of these studies were RCTs (cohort studies $n = 6$, cross-sectional studies $n = 5$). Interestingly in 3 of these observational studies carried out by Chandy and Bhatia [18], Leelarathna et al. [24] and Ragnarsson et al. [25], there was a lack of association between glucocorticoid dose and BMD. Similarly, Danilowicz et al. [26] reported no change in BMD measured by bone density scan (dual-energy X-ray absorptiometry) at the hip or lumbar regions with a lower hydrocortisone dose of 10–15 mg. In addition, Chikada et al. [27] observed no association between BMD and hydrocortisone dose for patients who were receiving a lower steroid dose of 13.6 mg/m². In contrast, Braatvedt et al. [28] and Schulz et al. [16] noted an improved BMD with lower doses of steroid therapy.

The type of steroid regimen influenced bone density-related outcomes as reported by Koetz et al. [17], Chandy and Bhatia [18] and Frey et al. [20]. The use of prednisolone was associated with a lower BMD. Frara et al. [19] observed an increased BMD after a switch from hydrocortisone to modified release hydrocortisone.

The studies on glucocorticoid replacement and BMD are shown in Table 1.

Glucocorticoid Replacement and CV/Metabolic Outcomes

A total of 17 studies were identified which evaluated the effect of glucocorticoids on CV and metabolic outcomes. Thirteen of these studies were observational studies (cohort studies $n = 9$, cross-sectional studies $n = 4$). Three of the 4 randomised trials assessed effects of various types of glucocorticoids on CV and/or metabolic out-

comes whereas 1 RCT evaluated the effect of glucocorticoid dose on CV and metabolic outcomes.

The effect of the dose of glucocorticoid replacement on CV and metabolic outcomes was assessed in 6 of the studies. Filipsson et al. [29], Danilowicz et al. [26] and Staufienbiel et al. [30] observed anthropometric benefits of lower doses of glucocorticoid replacement including lower body mass index, body weight and abdominal fat. It was reported that for patients on lower doses of glucocorticoid replacement (20.5 mg hydrocortisone) CV outcomes including lipid profile, glycosylated haemoglobin (HbA_{1c}), blood pressure and fasting glucose were comparable to controls that were not on glucocorticoid replacement [25]. Reduction in blood pressure (up to 5 mm Hg) was seen with a lower dose of glucocorticoid replacement [31, 32].

The CV and metabolic outcomes on different glucocorticoid replacement options were assessed in 11 of the studies. The CV outcomes with modified release hydrocortisone in an RCT by Johannsson et al. [33] included weight reduction of 0.9 kg with up to 5.5 mm Hg blood pressure reduction and a statistically significant decline in HbA_{1c}. However, there was also a statistically significant increase in serum triglycerides and a decrease in high-density lipoprotein (HDL) cholesterol. Similarly, Giordano et al. [14] observed a significant decrease in waist circumference, HbA_{1c} and low-density lipoprotein (LDL) cholesterol with modified release hydrocortisone. Frara et al. [19] reported reduction in fasting glucose with modified release hydrocortisone treatment over 2 years. Mongioi et al. [34] also reported improved HbA_{1c} and lipid profile in individuals with primary adrenal insufficiency treated with modified release hydrocortisone.

In a randomised trial, Isidori et al. [10] reported a weight reduction benefit of 4 kg over 24 weeks with modified release hydrocortisone compared to the standard treatment group in addition to a significant reduction in HbA_{1c}.

The CV safety of prednisolone was observed in a cross-sectional study by Smith et al. [35], who observed no differences in waist circumference, body weight, HbA_{1c}, blood pressure, total and LDL cholesterol between hydrocortisone and prednisolone treatment. However, in this study, patients in the prednisolone group were on much lower doses of equivalent glucocorticoid replacement than in the hydrocortisone group. These results are in contrast with the observations made by Quinkler et al. [36], patients in the prednisolone arm had a higher dose, hydrocortisone equivalent 20 mg, than in the study by Smith et al. [35]. Quinkler et al. [36] reported a significant

Table 1. Glucocorticoid replacement and bone mineral density

Year of publication/ type of study	First author	Duration of study	Patients, <i>n</i>	Gender Age	Types of glucocorticoid	Mean dose of glucocorticoid (HCE)	Sites of measurement	Z score/T score
1999, cross-sectional, PAI [28]	Braatvedt	–	29	19 M 10 F	Most HC/CA 2 PN 1 Dexa	M 26 mg HC F 23 mg HC	Lumbar spine Femur neck Femur trochanter Left radius	21% had Z scores >2 SD below normal age-matched control
2004, cohort, 10 PAI, 5 SAI [27]	Chakida	104 months	15	7M 8 F 54.9 years	7 hydrocortisone 6 HC + Dexa 2 PN	12 ≤13.6 mg/m ² HC 3 >13.6 mg/m ² HC	Lumbar spine	66% of those on HC >13.6 mg/m ² HC had Z score <80% of age-matched control
2008, cohort, SAI [26]	Danilowicz	6–12 months	11	2 M 9 F	Hydrocortisone	Reduce HC dose to 10–15 mg/day	Hip Spine	Baseline 1.038 Final 1.035 Baseline 0.898 Final 1.014
2009, cross-sectional, PAI [15]	Lovas	–	292	106 M 186 F	185 CA 99 HC 7 PN 1 Dexa	Norway: 32.1 mg UK/New Zealand: 26.5 mg	Femur neck Lumbar spine	Reduced –0.21 to –0.28 Reduced –0.17 to –0.57
2010, retrospective, cohort, PAI [24]	Leelarathna	–	48	17 M 31 F	44 HC 2 CA 2 PN	HC dose 24 mg	Spine Hip	7.4% Z score <–2.5 37% Z score <–1 (osteopenia) None Z score <–2.5 18.5% Z score <–1
2012, cross-sectional, PAI [17]	Koetz	–	81	23 M 58 F	54 HC 26 PN 1 PN + Dexa	HC dose 21.9 mg or 11.9 mg/m ²	Lumbar spine Femur neck	F Z score –0.98 M Z score –0.6 F Z score 0.07 M Z score –0.23
2012, cross-sectional, SAI [25]	Ragnarsson	–	204	108 M 96 F	173 CA 31 HC	20.5 mg HC	Lumbar spine Neck of femur	1.134 g/cm ² 0.923 g/cm ² 22% Z score <–2.5 61% Z score <–1 (osteopenia)
2016, cross-sectional, PAI [18]	Chandy	–	41	31 M 10 F 50.9 years	All PN	HCE 13.0 mg/m ²	Lumbar spine Neck of femur	Male –0.42 Z score Male –0.50 Significantly lower than reference population for males
2016, cohort, PAI [16]	Schulz	24 months	57	15 M 42 F	39 HC 18 PN	HC 25.3 mg 13.9 mg/m ²	Lumbar spine Neck of femur	Baseline –0.42 Z score Follow-up –0.31 (small but significant increase in lumbar Z scores during the follow-up) Baseline –0.21 Follow-up –0.21

Table 1 (continued)

Year of publication/ type of study	First author	Duration of study	Patients, <i>n</i>	Gender Age	Types of glucocorticoid	Mean dose of glucocorticoid (HCE)	Sites of measurement	Z score/T score
2018, cohort, PAI/CAH [20]	Frey	5 years	44	-	12 modified release HC 19 HC 13 PN	21.1 mg Modified release HC 24.2 mg HC 32.7 mg HCE PN group	Femur neck	Z scores -0.30 modified release HC 0.26 HC -0.71 PN Significantly reduced BMD (femur neck/total hip/ trochanter with PN)
2018, cohort, SAI [19]	Frara	2 years	14	4 M 10 F 55 years	Modified release HC for 2 years	20 mg HC Median dose	Lumbar spine	Baseline T score median -1.4 2-year follow-up -1.1 Baseline T score -1.1 2-year follow-up -0.9

HC, hydrocortisone; CA, cortisol acetate; PN, prednisolone; Dexa, dexamethasone; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; CAH, congenital adrenal hyperplasia; HCE, hydrocortisone equivalent; BMD, bone mineral density.

Table 2. Glucocorticoid replacement and cardiovascular outcomes

Year of publication/ type of study	First author	Duration of study	Patients, <i>n</i>	Gender Age	Type of glucocorticoid	Mean dose of glucocorticoid (HCE)	Cardiovascular/metabolic outcomes
2006, cohort, SAI [29]	Filipsson	1 year	1,707	43.1 years	1,186 HC 487 CA 52 PN/Dexa	HC group 24.1 mg CA group -24.4 mg PN group 26.8 mg	HCE doses >20 mg/day had higher BMI, TC, LDL-C and triglycerides HCE doses <20 mg/day had same metabolic en points as controls PN/Dexa group had increased waist/hip ratio as compared with controls Cortisol acetate group had lower HbA _{1c} than the HC group
2008, cohort, SAI [26]	Danilowicz	6-12 months	11	2 M 9 F	HC	Reduce HC dose to 10-15 mg/day	Reduced HC dose (10-15 mg) resulted in loss of 7.1 kg of total body fat and 4.1 kg of abdominal fat Significant decrease in TC and triglyceride concentrations
2010, retrospective, cohort, PAI [24]	Leelarathna	-	48	17 M 31 F	44 HC 2 CA 2 PN	HC dose 24 mg	65% overweight with BMI >25 and 23% were obese with a BMI >30 19% were hypertensive 65% had TC >5.0 mmol/L, and 15% of the sample had a TC >6.0 mmol/L

Table 2 (continued)

Year of publication/ type of study	First author	Duration of study	Patients, <i>n</i>	Gender Age	Type of glucocorticoid	Mean dose of glucocorticoid (HCE)	Cardiovascular/metabolic outcomes
2012, cross- sectional, SAI [25]	Ragnarsson	–	204	108 M 96 F	173 CA 31 HC	20.5 mg HC	Lower fasting glucose among patients on glucocorticoid replacement compared to those not on replacement No difference in serum lipids, HbA _{1c} , systolic and diastolic BP, metabolic syndrome among those on glucocorticoid replacement compared to those not on replacement The low mean HCE dose accounts for this
2012, randomised trial, PAI [33]	Johannsson	24 weeks	63 47 years	37 M 26 F	HC Modified release HC	–	0.7 kg weight reduction over 12 weeks with OD HC 0.9 kg weight reduction over 24 weeks with OD HC 5.5 mm Hg decrease in systolic BP, 2.3 mm Hg reduction in diastolic BP over 12 weeks with OD HC 0.1% (statistically significant) reduction in HbA _{1c} with no change in fasting glucose 0.1 mmol/L decrease in HDL cholesterol, 0.2 mmol/L increase in triglycerides with OD HC
2014, randomised trial, PAI [37]	Øksnes	12 weeks	37 48 years	–	31 HC 29 CSHI	HC group: 0.26 mg/kg/day CSHI group: 0.31 mg/kg/day	No difference in waist-to-hip ratio or BP noted Tendency toward an increase in weight and BMI with CSHI Statistically significant increase in fasting glucose with CSHI No significant differences in levels of cholesterol, HDL cholesterol and triglycerides CSHI had small but significantly higher LDL cholesterol
2015, cross-sectional, PAI/SAI [30]	Staufenbiel	–	132 54 years	52 M 80 F	HC	M 21.5 mg F 20.3 mg	Higher BMI in patients with adrenal insufficiency compared to healthy controls Significant correlation between BMI and cortisol hair levels for the male patients with adrenal insufficiency Waist-to-hip ratio and waist circumference were related to HC dose in mg/kg
2015, cohort, PAI/SAI [11]	Quinkler	202 days	50	13 M 37 F	30 modified release HC 20 HC	20 mg HC	Significant decrease in BMI and HbA _{1c} and TC with modified release HC No change in triglycerides, LDL and HDL cholesterol
2015, cross-sectional, PAI/SAI [31]	Castinetti	–	201	–	HC	22.9 mg	PAI: HC dose was slightly but significantly higher in those with dyslipidaemia than in those without SAI: there was a significant association between HC dose and dyslipidaemia and high BP vs. normal BP
2016, randomised trial, SAI [32]	Buning	10 weeks	47	29 M 18 F	HC	0.2–0.3 mg/kg vs. 0.4–0.6 mg/kg	Higher HC dose increased systolic BP of 5 mm Hg, increased diastolic BP of 2 mm Hg Body weight increased by 0.5 kg and BMI increased by 0.2 with higher-dose HC
2016, cohort, PAI [14]	Giordano	12 months	19	4 M 15 F 47.3 years	Modified release HC	20 mg	Significant difference was observed in waist circumference, HbA _{1c} , TC and LDL-C levels after 12 months of modified release HC treatment

Table 2 (continued)

Year of publication/ type of study	First author	Duration of study	Patients, <i>n</i>	Gender Age	Type of glucocorticoid	Mean dose of glucocorticoid (HCE)	Cardiovascular/metabolic outcomes
2017, cohort, PAI [42]	Nilsson	5 years	71	36 M 35 F 48.2 years	Modified release HC	28–29 mg/day	Small but significant increases in mean fasting plasma glucose (0.4–0.7 mmol/L) were observed at 12, 36 and 60 months No significant change in mean HbA _{1c} from baseline to 5 years but small significant increases were observed at 12 and 36 months (0.6 and 1.1 mmol/mol, respectively) Small significant increases from baseline were observed for TC and LDL-C at 36 months. No significant change in BP, body weight, BMI
2017, cross-sectional, PAI/SAI [35]	Smith	–	146	63 M 83 F 55 years	82 HC 64 PN	HC group 20.5 mg PN group 14.8 mg (HCE)	There was no significant difference in TC, LDL levels, waist circumference, weight, BMI, HbA _{1c} , systolic/diastolic BP between HC and PN patients
2017, cohort, PAI/SAI [36]	Quinkler	2 years 9 months	188	73 M 115 F 59.5 years	141 HC 47 PN	HC group 21.5 mg PN group 20 mg	Significantly higher mean TC and LDL-C levels in PN group HbA _{1c} , high-density lipoprotein and triglyceride levels, BMI, systolic and diastolic BP and waist circumference were not significantly different
2018, cohort, SAI [19]	Frara	2 years	14	4 M 10 F 55 years	Modified release HC for 2 years	20 mg HC Median dose	During 2 years of follow-up, significant decrease in fasting glucose; no significant change in HbA _{1c} , TC, HDL cholesterol or triglycerides
2018, randomised trial, PAI/SAI [10]	Isidori	24 weeks	89	47 M 42 F	17 HC 26 CA 46 modified release HC	Standard treatment group 18 mg/m ² /day Switched group 16 mg/m ² /day	Body weight reduction was superior in patients in the once-daily HC group (lost 2.1 kg) compared with those in the standard treatment group (gained 1.9 kg) Significant difference in BMI (–1.7) and waist circumference (–2.5 cm) between the 2 groups Significant difference in HbA _{1c} (–0.3%) between the 2 groups Significantly lower HDL in the switch treatment group at 24 weeks
2018, cohort, PAI/SAI [34]	Mongioi	12 months	19	12 M 7 F	Modified release HC	24.7 mg/day HC	Improved lipids and HbA _{1c} with modified release HC for patients with PAI Higher triglycerides observed with modified release HC in SAI

HC, hydrocortisone; CA, cortisol acetate; PN, prednisolone; Dexa, dexamethasone; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; HCE, hydrocortisone equivalent; BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA_{1c}, glycosylated haemoglobin; BP, blood pressure; OD, once daily; HDL, high-density lipoprotein; CSHI, continuous subcutaneous hydrocortisone infusion.

Table 3. Glucocorticoid replacement and rate of adrenal crises

Year of publication/ type of study	First author	Duration of study	Patients, <i>n</i>	Gender Age	Type of glucocorticoid	Mean dose of glucocorticoid (HCE)	Effect on rate of adrenal crises
2008, cohort, SAI [26]	Danilowicz	6–12 months	11	2 M 9 F	HC	Reduced HC dose from 20–30 to 10–15 mg/day	The reduction in dose of HC resulted in no incidences of adrenal crises (no fatigue/ weakness symptoms, blood pressure remained normal; normal energy levels)
2010, cross-sectional, PAI and SAI [39]	Hahner	–	444	140 M 304 F	353 HC 19 CA 67 PN 12 Dexa	20–25 mg HC group 20 mg PN group (median)	There was no association between glucocorticoid dose/body surface area and incidence of adrenal crises
2015, cohort, PAI and SAI [38]	Hahner	2 years	364	141 M 282 F	375 HC 16 CA 28 PN 4 Dexa	25–30 mg HC group 20 mg PN group (median)	There was no significant variation in incidence of adrenal crisis between HC, CA and PN groups There was no association between the glucocorticoid dose (mg/day) and incidence of adrenal crises
2016, retrospective, cohort, PAI and SAI [40]	Smans	21 years	458	241 M 217 F 58 years	342 HC 82 CA	20 mg HC	CA was associated with a significantly reduced risk for adrenal crisis, with risk ratio 0.62 There was no association between the glucocorticoid dose and incidence of adrenal crisis
2019, cohort, PAI and SAI [7]	Iqbal	7 years	2,648	52.9 years	1,912 HC 691 PN 45 modified release HC	–	Proportion of patients with one or more episodes of adrenal crisis since the first prescription was 5.4% in the HC cohort, 5.9% in the PN cohort and 6.7% in the modified release HC cohort Mean number of adrenal crises per patient per year after the first prescription was 0.02, 0.03 and 0.03 for the HC, PN and modified release HC cohorts, respectively There was no significant variation in incidence of adrenal crisis between the 3 cohorts

HC, hydrocortisone; CA, cortisol acetate; PN, prednisolone; Dexa, dexamethasone; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; HCE, hydrocortisone equivalent.

Table 4. Glucocorticoid replacement and infections

Year of publication/ type of study	First author	Duration of study	Patients, <i>n</i>	Gender Age	Type of glucocorticoid	Mean dose of glucocorticoid (HCE)	Effect on infections
2014, randomised trial, PAI [41]	Nilsson	27 months	64	37 M 27 F 47.3 years	32 HC 32 modified release HC with cross-over	20–40 mg	No significant difference in mean number of intercurrent illness (including nasopharyngitis, gastroenteritis, pyrexia) episodes per patient, mean number of days per episode between modified release HC and thrice daily HC
2017, cohort, PAI [42]	Nilsson	5 years	71	36 M 35 F 48.2 years	Modified release HC	28–29 mg/day	Number of intercurrent illness episodes (including nasopharyngitis, gastroenteritis) remained stable over 5-year treatment with DR-HC
2018, randomised trial, PAI/SAI [10]	Isidori	24 weeks	89	47 M 42 F	17 HC 26 CA 46 modified release HC	Standard treatment group 18 mg/m ² /day Switched group 16 mg/m ² /day	Patients in the modified release HC group had more normal immune cell profiles, reduced susceptibility to infections

HC, hydrocortisone; CA, cortisol acetate; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; HCE, hydrocortisone equivalent; DR-HC, dual release hydrocortisone.

Table 5. Glucocorticoid replacement and patients' satisfaction

Year of publication/ type of study	First author	Duration of study	Patients, <i>n</i>	Gender Age	Type of glucocorticoid	Mean dose of glucocorticoid (HCE)	Effect on patient satisfaction
1993, randomised trial, PAI [50]	Riedel	3 weeks	14	8 F 6 M 45 years	7 HC 7 CA	30 mg HC 37.5 mg CA	Basler Befindlichkeits-Skala (mood/psychological) and Beschwerde-Liste (physical symptoms) questionnaires used; also, Addison questionnaire was used Results were significantly better patient well-being with twice daily HC replacement than once daily
2007, cohort, PAI [51]	Lövås	3 months	7	5 F 2 M 44.7 years	CSHI	37.4 mg HC	SF-36 questionnaire used to assess the subjective health status This was observed to improve with CSHI treatment; significant improvement documented for physical functioning and vitality
2007, cross-sectional, PAI and SAI [44]	Hahner	–	210	157 F 53 M	191 HC 18 CA	–	SF-36, Giessen Complaint List, Hospital Anxiety and Depression Scale were used to monitor subjective health status Higher glucocorticoid doses associated with severe impairment of subjective health status, including physical functioning on SF-36 score
2008, cross-sectional, PAI and SAI [49]	Bleicken	–	427	290 F 137 M	348 HC 19 CA 61 PN	–	PN was equivalent to HC in subjective health status in adrenal insufficiency

Table 5 (continued)

Year of publication/ type of study	First author	Duration of study	Patients, <i>n</i>	Gender Age	Type of glucocorticoid	Mean dose of glucocorticoid (HCE)	Effect on patient satisfaction
2010, cross-sectional, PAI and SAI [45]	Bleicken	–	334	49.7 years	HC	–	SF-36, Giessen Complaint List, Hospital Anxiety and Depression Scale were used to monitor subjective health status Patients on doses >30 mg/day HC showed a significantly impaired subjective health status (SF-36)
2012, cross-sectional, PAI and SAI [6]	Forss	–	1,245	–	934 HC 137 PN 75 CA 49 Dexa	–	A higher proportion of those treated with prednisone/PN were worried about long-term side effects than those treated with HC 40% reported multiple dosing of glucocorticoid replacement to have impact on their subjective health status with mental/physical energy fluctuations
2012, randomised trial, SAI [46]	Benson	12 weeks	18	10 F 8 M 52 years	HC (10–0–5–0 mg) (10–5–0–5 mg) PN	17.1 mg HC	SF-36 physical function scores were significantly higher for HC (b.i.d.) compared with prednisone (o.d.) Patients on 15 mg HC replacement had better physical quality of life than on 20 mg HC replacement, with significantly better SF-36 physical sum scale
2013, cross-sectional, PAI [52]	Meyer	–	200	147 F 53 M	192 HC 8 PN 4 CA	25 mg HC group (median)	There was no significant correlation between the daily dose of HC replacement and the quality of life (AddiQoL scores)
2013, cohort, PAI and SAI [53]	Langenheim	6 months	14	11 F 3 M	Modified release prednisone Standard PN	20 mg (HCE)	Significant improvement in global score of discomfort after 3 months of modified release prednisone Treatment with modified release prednisone for 3 months resulted in significantly lower scores in Multidimensional Fatigue Inventory which increased again after switching to PN Improved AddiQoL scores with modified release prednisone
2014, randomised trial, PAI [48]	Gagliardi	10 weeks	10	8 F 2 M 49.6 years	CSHI	21.7 mg HC	CSHI does not improve subjective health status in PAI patients with good baseline subjective health status Double-blinded hence less chance for bias
2014, randomised trial, PAI [37]	Øksnes	32 weeks	33	25 F 8 M 48 years	CSHI HC	CSHI 0.26 mg/kg HC 0.31 mg/kg	Open-label design, hence was prone to bias Improvement in HRQoL vitality indices with use of CSHI as well as improved AddiQoL score, with diminished fatigue Similarly, SF-36 physical function score was better with CSHI
2014, cross-sectional, PAI [54]	Kluger	–	107	84 F 23 M 49.8 years	HC	HC 22 mg	HRQoL (measured by SF-36) was significantly impaired in adrenal insufficiency compared with the general population despite use of recommended HC doses (15–25 mg) Smaller HC dose did not restore impaired HRQoL

Table 5 (continued)

Year of publication/ type of study	First author	Duration of study	Patients, <i>n</i>	Gender Age	Type of glucocorticoid	Mean dose of glucocorticoid (HCE)	Effect on patient satisfaction
2014, cross-sectional, PAI [12]	Tiemensma	–	54	33 F 21 M 50 years	HC	HC 24.9 mg	Significant positive association between the daily HC dose and prevalence of maladaptive personality traits, psychological morbidity (depression measured on HADS), impaired general health perception, physical functioning and vitality (assessed using SF-36)
2014, retrospective, cohort, SAI [47]	Ragnarsson	1 year	1,750	792 F 44.7 years	1,355 HC 395 CA	HC treated 22.3 mg CA treated 23.6 mg (HCE)	Increasing HCE dose was associated with worse QoL. Patients on HCE <10 mg had the best and patients receiving >25 mg demonstrated the poorest QoL.
2016, randomised trial, SAI [43]	Buning	20 weeks	47	18 F 29 M 51 years	HC	HC 0.2–0.3 vs. 0.4–0.6 mg/kg body weight	Patients receiving the higher dose of HC reported significantly fewer symptoms of depression, less general and mental fatigue, increased motivation, better physical functioning and fewer pain symptoms
2016, cross-sectional, PAI [55]	van der Valk	–	328	223 F 105 M	243 HC 85 CA	HC group 25.1 mg	No correlation was found between physical activity and glucocorticoid dose. Patients on a thrice daily HC regime were found to have higher fatigue and lower SF-36 scores
2016, cohort, PAI [14]	Giordano	12 months	19	4 M 15 F 47.3 years	Modified release HC	20 mg	Improvement in AddiQoL total score with modified release HC. However, there was an insignificant increase in fatigue scores with modified release HC
2016, cross-sectional, PAI and SAI [56]	Andela	–	120	74 F 46 M 55 years	HC	HC 21.1 mg	Higher HC intake was associated with significantly greater impairment in physical functioning, less vitality, greater decrease in perceived health and more limitation in daily activities
2016, cross-sectional, PAI and SAI [57]	Harbeck	–	14	11 F 3 M 51.5 years	HC	20.8 mg	There was no difference in QoL between those on higher or lower equivalent doses of HC
2017, cohort, PAI [42]	Nilsson	5 years	71	36 M 35 F 48.2 years	Modified release HC	28–29 mg/day	QoL total scores were unchanged over 5 years of modified release HC, but significant worsening physical functioning was reported
2018, randomised trial, PAI/SAI [10]	Isidori	24 weeks	89	47 M 42 F	17 HC 26 CA 46 modified release HC	Standard treatment group 18 mg/m ² /day Switched group 16 mg/m ² /day	QoL was significantly improved with modified release HC in switch treatment group, assessed by AddiQoL questionnaire
2018, cohort, PAI/SAI [34]	Mongioi	12 months	19	12 M 7 F	Modified release HC	24.7 mg/day HC	Improved well-being with modified release HC, with stable AddiQoL scores over 12 months of follow-up

HC, hydrocortisone; CA, cortisol acetate; PN, prednisolone; Dexa, dexamethasone; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; HCE, hydrocortisone equivalent; CSHI, continuous subcutaneous hydrocortisone infusion; SF-36, 36-item Short Form Health Survey; AddiQoL, Addison's disease-specific quality-of-life questionnaire; HRQoL, health-related quality of life; HADS, Hospital Anxiety and Depression Scale; QoL, quality of life.

increase in LDL and total cholesterol among patients on prednisolone.

Regarding CV outcomes with cortisol acetate, a study by Filipsson et al. [29] reported lower HbA_{1c} with cortisol acetate treatment compared to hydrocortisone. Additionally, the cardiometabolic consequences of continuous subcutaneous hydrocortisone infusion were assessed by Øksnes et al. [37], who observed an increase in fasting glucose, weight/body mass index compared to patients on conventional hydrocortisone, however with no reported variation in lipid profile (including HDL and LDL cholesterol and triglycerides), insulin or homeostasis model assessment index (other than a trend to an increase in the latter with continuous subcutaneous hydrocortisone infusion). These outcomes are summarised in Table 2.

Glucocorticoid Replacement and Rate of Adrenal Crises

We identified 5 observational studies which evaluated the effect of glucocorticoid dose/regimen on the rate of adrenal crises. The effect of the dose of glucocorticoid replacement on the rate of adrenal crises was assessed in 4 out of these 5 studies. None of these studies reported a significant association between the dose of glucocorticoid and the rate of adrenal crisis. Danilowicz et al. [26] reported no difference in the incidence of adrenal crisis with a lower dose of hydrocortisone (10–15 mg). Similarly, Hahner et al. [38, 39] and Smans et al. [40] observed no association between the participants' dose of glucocorticoid and the rate of adrenal crisis.

Three of the studies evaluated the impact of the type of steroid therapy on the development of adrenal crises. Iqbal et al. [7] reported the mean incidence of adrenal crisis per patient of 0.02, 0.03 and 0.03 among patients on hydrocortisone, prednisolone and modified release hydrocortisone, respectively, with no significant difference among the 3 cohorts. Hahner et al. [38] found no association between type of glucocorticoid (hydrocortisone, cortisol acetate or prednisolone) and adrenal crisis.

This contrasts the findings of Smans et al. [40], who observed an association of cortisol acetate with a significantly lower risk of adrenal crisis (risk ratio 0.62). These results are summarised in Table 3.

Glucocorticoid Replacement and Infections

We identified 3 studies which evaluated the impact of glucocorticoid regimen (modified release hydrocortisone) on the rate of development of infections. In a randomised trial, Nilsson et al. [41] compared patients on modified release hydrocortisone and immediate release

hydrocortisone and found a similar number of intercurrent illnesses (such as nasopharyngitis, gastroenteritis, febrile episodes) between the 2 groups. During a 5-year follow-up on modified release hydrocortisone, the rates of intercurrent illness remained stable [42]. Isidori et al. [10] found reduction in the occurrence of infections in the patients allocated to modified release hydrocortisone, as measured by a total infection score, with a decrease in flu episodes compared to conventional glucocorticoid replacement. These findings are shown in Table 4.

Glucocorticoid Replacement and Patients' Satisfaction

We identified a total of 22 studies (RCTs $n = 7$, observational studies $n = 15$) which evaluated the effect of glucocorticoids on patients' satisfaction and their quality of life. Ten of the studies assessed the impact of glucocorticoid dose on the patients' satisfaction and quality of life. Only 1 of the studies reported a subjective improvement in symptoms with higher doses of steroid therapy. On the other hand, 5 of the studies reported worsening of the symptoms while 4 of the studies reported no change in patient satisfaction with higher steroid dose.

Buning et al. [43] observed patients on higher doses of hydrocortisone to have better well-being, physical functioning and motivation with reduced pain and fatigue symptoms. This contrasts the findings of Hahner et al. [44], Bleicken et al. [45], Benson et al. [46], Tiemensma et al. [12], Ragnarsson et al. [47], who showed deterioration in subjective health status as well as physical functioning and vitality with higher doses of glucocorticoids.

Ten studies evaluated patients' satisfaction and quality of life on various glucocorticoid replacement regimens. Løvås and Husebye [51] and Øksnes et al. [37] reported improvement in patients' subjective health status, with continuous subcutaneous hydrocortisone infusion. In contrast, Gagliardi et al. [48] found no change in patients' subjective health status with continuous subcutaneous hydrocortisone infusion, provided that the baseline health status was good. Regarding the effect of prednisolone on patients' satisfaction, Bleicken et al. [49] reported a similar patients' report of health status between those on prednisolone and hydrocortisone. Four studies analysed the effect of modified release hydrocortisone on patients' subjective health status. Giordano et al. [14], Mongioi et al. [34] and Isidori et al. [10] reported an improvement in Addison's disease-specific quality-of-life questionnaire scores with modified release hydrocortisone. On the other hand, Nilsson et al. [42] noted some deterioration in physical function over 5 years of use of modified release hydrocortisone. These findings are shown in Table 5.

Key : ■ High risk ■ Unclear risk ■ Low risk	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Reporting bias)
Riedel et al. [50], 1993, Germany	■	■	■	■	■	■
Johannsson et al. [33], 2012, Sweden, USA, UK	■	■	■	■	■	■
Benson et al. [46], 2012, Germany	■	■	■	■	■	■
Øksnes et al. [37], 2014, Norway, Sweden	■	■	■	■	■	■
Gagliardi et al. [48], 2014, Australia	■	■	■	■	■	■
Nilsson et al. [41], 2014, Sweden	■	■	■	■	■	■
Buning et al. [32], 2016, the Netherlands	■	■	■	■	■	■
Buning et al. [43], 2016, the Netherlands	■	■	■	■	■	■
Isidori et al. [10], 2018, Italy	■	■	■	■	■	■

Fig. 2. Risk of bias assessment. The red shade represents high risk, with green showing low risk and yellow shade representing unclear risk.

Risk of Bias

All the 9 randomised trials included in this review had random allocation of participants, which reduced the risk of selection bias. In 5 of these trials, blinding of the study participants was done to reduce the risk of performance bias in these randomised trials. There were incomplete outcome data in 3 of the studies due to attrition. This is shown in Figure 2.

Discussion

There is a lack of consensus among endocrinologists regarding optimum glucocorticoid dose and regimen with the majority of patients with adrenal insufficiency either receiving hydrocortisone (15–30 mg/day) or prednisolone (3–7.5 mg/day) based on regional/local practices. The evaluation of an adequate steroid replacement dose/regimen relies on symptom control, clinical examination (volume status, postural drop of blood pressure, features of underreplacement such as buccal and mucosal pigmentation or overreplacement such as proximal myopathy, easy bruisability and purple stria on abdomen) and biochemical parameters (serum electrolytes, urea, etc.). The cortisol day curve which was used previously for steroid dose titration has been shown to be non-reliable and used infrequently in clinical practice. In addition, the synthetic steroid preparations are unable to rep-

licate the synchronised circadian alteration of cortisol levels under physiological states. Considering these limitations, we carried out a systematic review of published evidence related to the impact of various glucocorticoid regimens and doses on BMD, CV and metabolic parameters, incidence of adrenal crisis, infection rate and patient satisfaction.

Our systematic review shows conflicting results on the impact of the dose of glucocorticoid replacement on BMD. A higher steroid dose was shown to lead to reduced BMD in 3 of the studies in contrast to 1 study which showed an improved BMD with a higher dose while 4 of the studies reported no differential impact of glucocorticoid dose on BMD [16–18, 24–28]. The major limitation with all of these 8-studies includes an observational design which is clearly an inferior level of evidence as compared to well-designed RCTs. In addition, the study population was heterogeneous with confounding factors which could have impacted the final results.

Prednisolone use was reported to be associated with a reduced BMD in 3 of the observational studies although the limitations reported include a small sample size of studies, the impact of prior glucocorticoid therapy before commencement of the study and the lack of randomisation [17, 18, 20]. One recent study reported an increase in BMD with modified release hydrocortisone. It was postulated that modified release hydrocortisone reversed the excessive control of bone turnover by supraphysiological

Table 6. Cardiovascular outcomes from randomised trials on modified release hydrocortisone

Parameter	Johannsson et al. [33]	Isidori et al. [10]
Body weight	Weight reduction 0.7 kg difference compared to standard glucocorticoid treatment over 12 weeks	Weight reduction 4 kg difference compared to standard glucocorticoid treatment in 24 weeks
Body mass index	–	Reduction by 1.7 with modified release HC over 24 weeks
Waist circumference	–	Reduction in waist circumference by 2.5 cm with modified release HC
HbA _{1c}	Reduction in HbA _{1c} by 0.1% with 0.6% reduction in patients with DM at 12 weeks	Reduction in HbA _{1c} by 0.3% at 24 weeks
LDL cholesterol	No significant difference with the treatment	No significant difference with the treatment
Triglycerides	Reduction in triglycerides by 0.2 mmol/L at 12 weeks	No significant change with the treatment
HDL cholesterol	Reduction in HDL cholesterol by 0.1 mmol/L at 12 weeks	Reduction in HDL cholesterol by 0.23 mmol/L at 24 weeks
Systolic blood pressure	Difference of –5.5 mm Hg compared to standard treatment	–
Diastolic blood pressure	Difference of –2.3 mm Hg compared to standard treatment	–

HC, hydrocortisone; HbA_{1c}, glycosylated haemoglobin; DM, diabetes mellitus; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

conventional cortisol replacement. However, this study had a small sample size, and the participants were enrolled retrospectively [19].

Well-recognised CV and metabolic adverse effects of exogenous glucocorticoids include weight gain, hypertension and impaired glucose tolerance [35]. Out of the 6 studies which evaluated the effect of steroid dose on CV risk factors, 5 were observational studies and 1 an RCT. The RCT reported a reduced blood pressure of up to 5 mm Hg apart from a decrease in body weight with a lower dose of hydrocortisone (0.2–0.3 mg/kg body weight) [32]. The results from the 5 observational studies were also consistent with RCT results. Use of a lower dose of corticosteroids was associated with CV benefit including lower weight, body mass index, abdominal fat, waist circumference, waist-hip ratio, HbA_{1c} and blood pressure [25, 26, 29–31]. The improved CV and metabolic outcomes with a lower dose of glucocorticoids is not surprising considering the historical preference for a relatively higher dose of steroid replacement in patients with adrenal insufficiency. The advances in the measurement of cortisol have shown a daily cortisol production of 5.7–7.4 mg/m²/day which equates to 9.5–10.0 mg/day of cortisol for an average individual under physiological conditions [58].

We could identify only 3 RCTs which compared CV and metabolic outcomes with different glucocorticoid replacement options. Two of these RCTs assessed CV out-

comes with modified release hydrocortisone while one of the RCTs evaluated the effects of continuous subcutaneous hydrocortisone infusion. A significant reduction in body weight and HbA_{1c} was noted with the use of modified release hydrocortisone; however, there was also a significant decrease in HDL cholesterol in both these trials [10, 33]. In the study by Isidori et al. [10] there was a significantly higher reduction in body weight with modified release hydrocortisone among patients with secondary adrenal insufficiency. Table 6 sums up the cardiometabolic outcomes observed with the use of modified release hydrocortisone tablets.

The cardiometabolic effects of subcutaneous hydrocortisone infusion were evaluated in an RCT by Øksnes et al. [37], who reported a mild increase in weight and fasting sugars with continuous subcutaneous hydrocortisone infusion with no effect on blood pressure. It was speculated that the findings might have been attributed to a higher hydrocortisone dose resulting in elevated urine cortisol and salivary cortisone in the continuous subcutaneous hydrocortisone infusion group compared to individuals receiving oral hydrocortisone.

The safety of a glucocorticoid replacement regimen has been of paramount importance in patients with adrenal insufficiency especially considering an increased mortality in this cohort [59]. We identified 5 observational studies which evaluated the effect of glucocorticoid on the incidence of adrenal crises. None of these

Table 7. Impact of type of glucocorticoid on subjective health status

Study	Study design	Patients, <i>n</i>	Main results regarding subjective health status
Lovas et al. [51], 2007	Cohort study	7	CSHI associated in improvement in subjective health status over 12 weeks, particularly physical function and vitality assessed with SF-36
Gagliardi et al. [48], 2014	Randomised trial	10	No improvement in subjective health status with CSHI in patients with good baseline status
Øksnes et al. [37], 2014	Randomised trial	33	Improvement in vitality and physical function scores seen with CSHI over 3 months
Bleicken et al. [49], 2008	Cross-sectional study	427	Higher body pain symptoms reported with prednisolone than with hydrocortisone; prednisolone equivalent to hydrocortisone in the other aspects
Forss et al. [6], 2012	Cross-sectional study	1,245	Greater concern on adverse effects of treatment among patients on prednisolone than on hydrocortisone
Langenheim et al. [53], 2013	Cohort study	14	Modified release prednisolone associated with lower fatigue, better motivation and higher AddiQoL scores than with prednisolone over 6 months
Giordano et al. [14], 2016	Cohort study	19	Improved AddiQoL scores with 12 months' use of modified release hydrocortisone; however, insignificant increase in fatigue scores
Nilsson et al. [42], 2017	Cohort study	71	No change in Fatigue Impact Scale and Psychological General Well-Being over 5 years of modified release hydrocortisone, but lower physical function noted
Isidori et al. [10], 2018	Randomised trial	89	Improvement in AddiQoL scores with modified release hydrocortisone for 24 weeks
Mongioi et al. [34], 2018	Cohort study	19	Improved well-being with modified release hydrocortisone, with stable AddiQoL scores over 12 months of follow-up

CSHI, continuous subcutaneous hydrocortisone infusion; SF-36, 36-item Short-Form Health Survey; AddiQoL, Addison's disease-specific quality-of-life questionnaire.

studies reported an increase in the risk of development of adrenal crisis with a lower glucocorticoid dose. A lower hydrocortisone dose (10–15 mg/day) was observed to be equally safe as compared to the historically used higher dose as far as the incidence of adrenal crises [26] was concerned. We also observed no conclusive evidence for the superiority of a particular glucocorticoid regimen in lowering the incidence of adrenal crises (including modified release hydrocortisone, prednisolone and hydrocortisone), except for cortisol acetate which was reported in one observational study to have a significant reduction in risk of adrenal crisis (relative risk 0.62). The study had limitations including a retrospective design, lack of randomisation, low number of adrenal crisis overall and insufficient number of participants on longer-acting glucocorticoids to draw a meaningful inference for this subgroup [40].

The majority of adrenal crises are precipitated by infections (gastroenteritis, respiratory and urinary tract in-

fections, and viral infections) [38, 40]. The infection risk in patients with adrenal insufficiency is increased with over- or underreplacement with glucocorticoid replacement therapy considering the immunosuppressive effects of the treatment per se [10]. We identified 2 RCTs and 1 observational study which evaluated the effects of glucocorticoid replacement (modified release hydrocortisone) on the rate of development of infection. The largest of these studies ($n = 89$) reported a normal immune profile with reduced infection scores with modified release hydrocortisone tablets [10].

In hypoadrenalism, the impairment in patients' subjective health status is attributable, at least in part, to the intrinsic shortcomings of glucocorticoid replacement therapy [12]. In a systematic review and meta-analysis, Al Nofal et al. [21] reported improved quality of life with modified release hydrocortisone and continuous subcutaneous hydrocortisone infusion compared to immediate release hydrocortisone.

We included 6 RCTs which assessed the effect of the type or dose of glucocorticoid replacement on quality of life of the patients with adrenal insufficiency. The results of these 6 RCTs presented conflicting observations pertaining to the impact of glucocorticoid dose on subjective quality of life and patients' satisfaction. Buning et al. [43] reported benefits of a higher dose to include lower fatigue, higher motivation and better physical function. This contrasts with the findings of Benson et al. [46], who reported improved physical function with a lower dose of hydrocortisone. The effect of various glucocorticoid treatment options on patients' subjective health status as seen in the randomised trials was also conflicting, particularly for continuous subcutaneous hydrocortisone infusion, with no increase in patient satisfaction with continuous subcutaneous hydrocortisone infusion reported by Gagliardi et al. [48] whereas Øksnes et al. [37] found improved physical function and reduced fatigue with this treatment. The reasons behind this difference were postulated to be due to the good baseline subjective health status among patients studied by Gagliardi et al. [48]; in addition, the trial carried out by Øksnes et al. [37] was not blinded hence was prone to bias. In a randomised trial by Isodari et al. [10], improvement in patients' quality of life by up to 9 points of Addison's disease-specific quality-of-life questionnaire scores was reported. One of the flaws which could be identified for these studies includes that the study participants were not masked (single-blinded study) which predisposes the participants to recollection bias. These results are shown in Table 7.

Our systematic review has several strengths and limitations. We carried out a comprehensive search using multiple databases and included a wide source of publications. We included 47 studies to carry out systematic review and followed the PRISMA statement. A predefined proforma helped analyse and compare the studies while an independent observer screened the studies for potential commercial bias. The major limitations of this systematic search remains a dearth in high-quality RCTs which could have compared the various glucocorticoid regimens prospectively. The majority of the studies which have been carried out in this field are observational with the majority of these being uncontrolled and/or having a cross-sectional design with a relatively short follow-up duration. This itself leads to an inferior quality of evidence. This was a significant constraint related to the evidence which was available from the literature search. Also, we did not evaluate the impact of fludrocortisone and androgen replacement such as dehydroepiandrosterone sulphate on the subjective health status of patients with adrenal insufficiency.

One of the key observations of our systematic review (based on the evidence from a single RCT and multiple observational studies) suggests a lower dose of glucocorticoid replacement associated with improved CV outcomes apart from lower blood pressure, body weight, HbA_{1c} and waist circumference [25, 30–32]. In addition, evidence from relatively short duration trials suggests that modified release hydrocortisone is efficacious in lowering CV risk [10, 33]. However, there is a need for longer-duration studies to assess further whether these cardiometabolic benefits could be sustained over a period of time. From a single randomised trial, continuous subcutaneous hydrocortisone infusion provided no benefit in the reduction of CV risk factors [37].

Based on our systematic review, we observed no difference in the risk of adrenal crises based on regimen and dose of glucocorticoid used. Furthermore, a reduction in BMD (from 1 cross-sectional study and 2 cohort studies) and elevation of total lipoprotein and LDL was noticed with the use of higher doses of prednisolone [16, 28, 36]. Prednisolone has an established role in the management of adrenal insufficiency with the ongoing debate regarding its efficacy as compared to hydrocortisone in patients with primary as well as secondary adrenal insufficiency. Based on our systematic review, prednisolone use can be deemed safe and efficacious in patients with adrenal insufficiency. In addition, prednisolone therapy offers a more economical alternative to hydrocortisone which offers long-term health-economic benefits; however, where generic medications are available, the price difference may not be significant.

Most of the evidence in the current systematic review was obtained from short-term follow-up randomised trials and observational studies. There is a need for long-term follow-up double-blinded randomised trials to assess the effects of the type of glucocorticoid on subjective quality of life, CV factors, BMD, adrenal crises and infections in patients with adrenal insufficiency.

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