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REVIEW ARTICLE

Why is the management of glucocorticoid deficiency still controversial: a review of the literature

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Summary

All endocrinologists would like to make glucocorticoid replacement therapy for their hypoadrenal patients as physiological as possible. Many would like the reassurance of a method of monitoring such treatment to confirm that they are achieving this aim. Advances in our knowledge of the normal physiology are relevant to our attempts to do this. The cortisol production rate in normal subjects is lower than was previously believed. The normal pattern of glucocorticoid secretion includes both a diurnal rhythm and a pulsatile ultradian rhythm. Glucocorticoid access to nuclear receptors is 'gated' by the 11-β-hydroxysteroid dehydrogenase enzymes, which interconvert active cortisol and inactive cortisone. Such complexities make the target of physiological glucocorticoid replacement therapy hard to achieve. The available evidence suggests that conventional treatment of hypoadrenal patients may result in adverse effects on some surrogate markers of disease risk, such as a lower bone mineral density than age-sex matched controls, and increases in postprandial glucose and insulin concentrations. Although the quality of life of hypoadrenal patients may be impaired, there is no evidence of an improvement on higher doses of steroids, although quality of life is better if the hydrocortisone dose is split up, with the highest dose taken in the morning. Thus the evidence suggests that most patients may safely be treated with a low dose of glucocorticoid (e.g. 15 mg hydrocortisone daily) in two or three divided doses, with education about the appropriate action to take in the event of intercurrent illnesses.

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Introduction

The ideal glucocorticoid replacement therapy would mirror the normal physiological state as closely as possible. In practice, the human glucocorticoid hydrocortisone is commonly given at a dose of about 20 mg daily, in two or three unequal divided doses, such that most of the dose is taken in the morning and less in the afternoon. In this review, we will start with an overview of recent advances in our understanding of the normal physiology in relation to endogenous glucocorticoid production, circulating glucocorticoids and their interconversion, the pattern of glucocorticoid secretion and pregnancy. We will discuss the impact of this knowledge on our attempts to optimize glucocorticoid replacement in hypoadrenal patients, and highlight areas where previously accepted paradigms are challenged. We will then discuss specific studies that have been performed related to optimizing glucocorticoid replacement regimens in patients with hypoadrenalism, including effects on bone, glucose metabolism, cardiovascular function and quality of life. Drawing on these sources of evidence, we will attempt to make some recommendations for clinical practice and future research.

The focus of the review is glucocorticoid replacement therapy for adults with primary and secondary hypoadrenalism. Management of children, patients with congenital adrenal hyperplasia (CAH), acute/emergency management, additional hormone replacement therapy (e.g. fludrocortisone or dehydroepiandrosterone treatment) and treatment with pharmacological doses of glucocorticoids is not included.

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Normal physiology

The normal physiology of cortisol secretion and metabolism has been the focus of much research, the results and limitations of which are of relevance to the consideration of optimal glucocorticoid replacement therapy. They challenge assumptions about the dose and pattern of glucocorticoid replacement, the choice of which glucocorticoid to use, and the use of reference ranges or targets in assessing glucocorticoid replacement therapy in hypocortisolaemic patients. Much of this work has been the subject of a number of expert reviews, which will be summarized here.

Endogenous glucocorticoid production

Using a new analytical procedure (stable isotope dilution thermospray liquid chromatography/mass spectrometry), Esteban *et al.* showed that the cortisol production rate in normal subjects was lower than previously believed.[1] In a study of five men (aged 26·2 ± 5·4 years) and seven women (aged 29·1 ± 5·3 years), they estimated the cortisol production rate to be 27·3 ± 7·5 μmol/day (equivalent to 5·7 mg/m^2/day

or approximately 9·9 mg/day). This result concurs with that obtained by Kerrigan *et al.* using deconvolution analysis, an independent method of determining the cortisol production rate.[2] Deconvolution analysis uses computer modelling based on serial measures of serum hormone concentrations and knowledge of the half-life of the hormone.[3,4] In a study of 18 males in early and late puberty, the estimated average total daily cortisol production rate was also 5·7 ± 0·3 mg/m^2/day.[2] Both results are markedly lower than earlier estimates of 12–15 mg/m^2/day.

Circulating glucocorticoids: cortisol, cortisone and 11-β-hydroxysteroid dehydrogenase

Circulating cortisol in humans is about 90% plasma protein bound mostly to cortisol-binding globulin (CBG).[5] The 'free' cortisol concentration ranges from approximately 1 nmol/l at the diurnal trough to approximately 100 nmol/l at the diurnal peak.[6] Cortisone is an inactive steroid, which circulates at concentrations of around 60 nmol/l, largely unbound to plasma proteins and without marked diurnal variation. The main source of cortisone is 11-β-hydroxysteroid dehydrogenase-type 2 (11-β-HSD-2) in the kidney[6,7] which gates glucocorticoid access to nuclear receptors by a prereceptor mechanism. 11-β-hydroxysteroid dehydrogenase-type 1 (11-β-HSD-1) converts cortisone to cortisol, 'amplifying' the steroid signal in target cells.[8] Tissue-specific pathophysiological changes in local glucocorticoid metabolism with clinical relevance have been reported in adipose tissue, liver, brain and bone. Relevant studies have been recently reviewed[6–9] and will only be summarized here to illustrate some of the implications of this complex system.

In rodent models of obesity, there is increased 11-β-HSD-1 activity in adipose tissue, which may facilitate glucocorticoid-induced adipocyte differentiation. There is reduced activity of hepatic 11-β-HSD-1, interpreted as a compensatory attempt to reduce glucocorticoid-induced hepatic gluconeogenesis.[8] Transgenic mice over-expressing 11-β-HSD-1 in fat model the principal features of the metabolic syndrome, while 11-β-HSD-1 knockout mice have features of a 'cardioprotective' metabolic phenotype.[8] Translational studies in humans reveal a more complex situation: some studies have found that 11-β-HSD-1 activity in fat declines with increasing body mass index[9] while others have not.[7] In the brain, high levels of 11-β-HSD-1 are found in the cerebellum, hippocampus and cortex, such that cortisone and cortisol are equipotent in stimulating excitatory amino acid neurotoxicity.[8] 11-β-HSD-1 knockout mice resist the development of age-associated cognitive impairment. Carbenoxolone (a nonselective 11-β-HSD inhibitor) has been shown to increase verbal fluency in healthy elderly men and to increase verbal memory in older subjects with type 2 diabetes.[10] In bone, 11-β-HSD-1 has been identified within osteoblasts. Expression of 11-β-HSD-1 in bone increases with advancing age, and is positively regulated by pro-inflammatory cytokines.[7,9] Individuals with the highest levels of 11-β-HSD-1 levels may be more susceptible to the adverse effects of glucocorticoid treatment on bone.[7,9] Although this is clearly a complex system that is not fully understood, particularly in man, it does emphasize the need to understand the tissue-specific roles of circulating cortisol and cortisone in mediating normal physiological glucocorticoid effects. This also implies the need to take cortisol: cortisone ratios into account when considering optimal replacement therapy.

The normal pattern of glucocorticoid secretion: diurnal and ultradian rhythmicity

It is well-recognized that the natural cortisol peak in humans occurs early, prior to awakening, and falls progressively during the day to reach low levels in the evening.[2,11] In addition to the circadian rhythm of glucocorticoid secretion, automated frequent blood sampling techniques have revealed a pulsatile ultradian rhythm throughout the 24-h cycle[12]. The pulses vary in amplitude throughout the day, with the amplitude generally decreasing during the diurnal trough. Models suggest that the 'pulsatile' and 'circadian' components are separable secretory modes and can be independently regulated.[13] Ultradian rhythmicity has been shown in rats,[14] monkeys[15] and humans.[2,11,16,17]

Some of the implications of these observations have recently been reviewed,[13] and will be summarized here. A practical consequence of the pulsatility is that when sampling is infrequent and/or conducted over a short period of time, the underlying pattern of spontaneous pulses in not seen: instead, we see a tremendous variation in baseline cortisol levels, particularly at the diurnal peak, which may either be dismissed as 'noise' in the system and concealed in mean data, or misinterpreted as being causally related to an unintentional stressor. A theoretical consequence of the pulsatility is that it may be another way to achieve tissue specificity: as the two glucocorticoid receptors (MR and GR receptors) have different affinities, they will be differentially occupied and activated depending on the circulating level of ligand. Pulsatility will have a particularly significant effect on occupancy of the lower affinity GR receptors. Thus the relative balance of activation between the two receptor types may change rapidly over the course of a cortisol pulse, such that differences in receptor distribution could allow pulses to carry different information to different tissues.[13] There is evidence that continuous, prolonged *vs.* intermittent, short exposure to glucocorticoids may have different effects on steroid-responsive hepatic enzymes, such as tyrosine aminotransferase (TAT), which catalyses the first step in tyrosine catabolism. While *in vitro* exposure to glucocorticoid results in sustained high levels of TAT activity,[18] *in vivo*, after an early rise, TAT activity starts to decline despite continuous high levels of glucocorticoid, suggesting down-regulation in response to nonphysiological patterns of exposure.[19] *In vitro* experiments show significant down-regulation of GR on prolonged exposure to glucocorticoids, with rapid recovery during withdrawal periods, and effective induction of GR target genes following short pulses of glucocorticoid treatment.[20]

Pregnancy, 11-β-hydroxysteroid dehydrogenase type 2 and foetal programming

In a normal pregnancy, maternal cortisol-binding globulin levels rise, and free cortisol concentrations are higher in the last trimester. Two-thirds of circulating foetal cortisol originates from the foetal adrenals (which can be distinctly identified from week 8), with trans-placental transfer of maternal cortisol contributing to the other

third.[21,22] Cortisol concentrations in the foetus are several folds lower than in the maternal circulation. 11-β-HSD-2 is highly expressed in the human placenta to term and in many foetal tissues till mid-gestation: it acts as a 'barrier' to the passage of maternal glucocorticoids, and limits foetal GR exposure to glucocorticoids of maternal or foetal origin.[23–25] In pregnant rats, administration of a synthetic glucocorticoid, which is incompletely metabolized by placental 11-β-HSD-2 (such as dexamethasone) or an 11-β-HSD inhibitor (such as carbenoxolone), results in low birth weight offspring, with permanently higher blood pressures, higher blood glucose levels and higher glucocorticoid levels throughout their lifespan.[23,24] In humans, a significant positive correlation has been observed between term placental 11-β-HSD-2 activity and term birth weight ($r = 0{\cdot}408$, $P = 0{\cdot}034$).[22] Glucocorticoid-mediated foetal programming has been implicated as the 'endocrine link' of Barker's hypothesis, which proposes that hormonal and metabolic changes involved in foetal adaptation to undernutrition may persist, so that small thin babies are more likely to develop the 'metabolic syndrome X' in adulthood:[26] this is the focus of much ongoing research.

Implications for our understanding of the normal physiology for glucocorticoid replacement therapy

For oral administration of glucocorticoids, hepatic first pass metabolism must be considered in determining the appropriate drug and dosage to use. Although it might seem logical to use a combination of cortisol and cortisone for optimal replacement, 11-β-HSD-1 in the liver has a high reductase capacity for reactivating cortisone to cortisol over a broad range of substrate concentrations: very little orally administered cortisone reaches the systemic circulation.[6,27,28] Most circulating cortisone is derived from 11-β-HSD-2 conversion of cortisol in the kidney.[6] Hydrocortisone probably remains the most physiological drug of choice. It is a natural substrate for 11-β-HSD-2 conversion to cortisone in the kidney and the placenta. Endogenous cortisol production rates of about 10 mg/day are lower than the standard replacement dose of 20 mg hydrocortisone daily, even allowing for factors such as variation in oral absorption. It is important to consider the metabolism of other synthetic glucocorticoids when considering their use as replacement therapy in adrenal insufficiency. Inactivation of prednisolone by 11-β-HSD-2 is more effective than that of cortisol, while 11-β-HSD-2 has a lower inactivating capacity for dexamethasone.[29–31] It is therefore logical to avoid dexamethasone in pregnancy if the treatment is predominantly 'for the mother' rather than 'for the foetus'.[29] Prednisone is the 'cortisone equivalent' of prednisolone, and relies on conversion by 11-β-HSD-1 in the liver for bioactivity.[5]

We must acknowledge our inability to mimic the normal circadian rhythm, and can only aim to provide a delayed diurnal rhythm that peaks later than the physiological norm. We can try to avoid unphysiologically high glucocorticoid levels in the diurnal trough, by recommending that patients take their last dose of hydrocortisone in the afternoon rather than the evening. Clearly we cannot mimic the ultradian pulsatility of cortisol secretion or the response to daily hassles, and can only provide relatively stable levels of glucocorticoid, acknowledging that they are likely to have different effects on steroid responsive enzymes than the normal physiological pulsatile exposure. If patients take most of their hydrocortisone in the morning and their last dose of hydrocortisone early, there will at least be a period of low receptor occupancy overnight.

Various methods have been used to try to work out the optimal dose and pattern of glucocorticoid replacement in hypoadrenal patients, including cortisol day curves (using serum samples, blood spots or saliva) and urinary-free cortisol (UFC) collections. Papers describing such techniques illustrate marked interindividual variation in the results obtained, irrespective of the method of assessment and dosage regimen.[32–35] Sources of variation may include heterogeneity in the groups of patients studied (primary and secondary hypoadrenalism, caused by different diseases, treated in different ways, with variable other hormone deficiencies and treatment), in addition to baseline characteristics of the patients. Day curves also re-emphasize our inability to mimic the natural rhythms of cortisol production, with twice daily doses resulting in supraphysiological cortisol concentrations postdose, later than the normal circadian peak, and subphysiological levels predose.[36] In patients with secondary hypoadrenalism and 'partial ACTH deficiency' (defined as a basal 9:00 h cortisol > 200 nmol/l and a peak stimulated cortisol < 500 nmol/l in response to an insulin tolerance test) day curves off treatment closely resembled the cortisol profile of healthy controls, suggesting that they may not need any glucocorticoid treatment under normal unstressed conditions.[37] However, without further evidence, this would be a high-risk strategy, with practical problems including patient education and maintaining a supply of hydrocortisone for emergency use: patients could potentially fall ill quickly and be at risk of a hypoadrenal crisis. It is probably safer to manage the glucocorticoid treatment of all hypoadrenal patients in a similar way, irrespective of the aetiology of their hypoadrenalism. It will also diminish the need to test adrenal activity on a regular basis to exclude further deterioration in endogenous hypothalamic-pituitary-adrenal function.

In one study, the peak cortisol concentration and area under the curve were greater if patients took their dose of cortisone acetate after breakfast, compared to taking it after an overnight fast,[32] although in another study of patients given 10 mg hydrocortisone, peak cortisol concentrations were higher in the fasted state.[35] Although these results are statistically significant, their clinical significance is uncertain. UFC excretion is influenced by the distribution of the dose, although again the two papers showing this report discrepant results with different glucocorticoids: one showed an increase in the UFC excretion of patients converted from twice daily to thrice daily cortisone acetate (with no change in their total daily dose),[38] while the other showed a decrease in the UFC excretion of patients converted from once daily, to twice daily, to five daily doses of hydrocortisone, as the total daily dose was split up.[39] Again, the clinical significance of these results is uncertain, other than casting doubt on the value of UFC measurements in this context.

Although most authors acknowledge the lack of a 'gold standard' method of assessing glucocorticoid replacement therapy, many endocrinologists still feel the need to adopt a 'rigorous approach'.[40] It is hard to avoid the conclusion that recommended reference ranges or targets are somewhat arbitrary. Although we may feel comfortable providing evidence that plasma levels remain within the physiological range for at least most of the day, our inability to mimic the

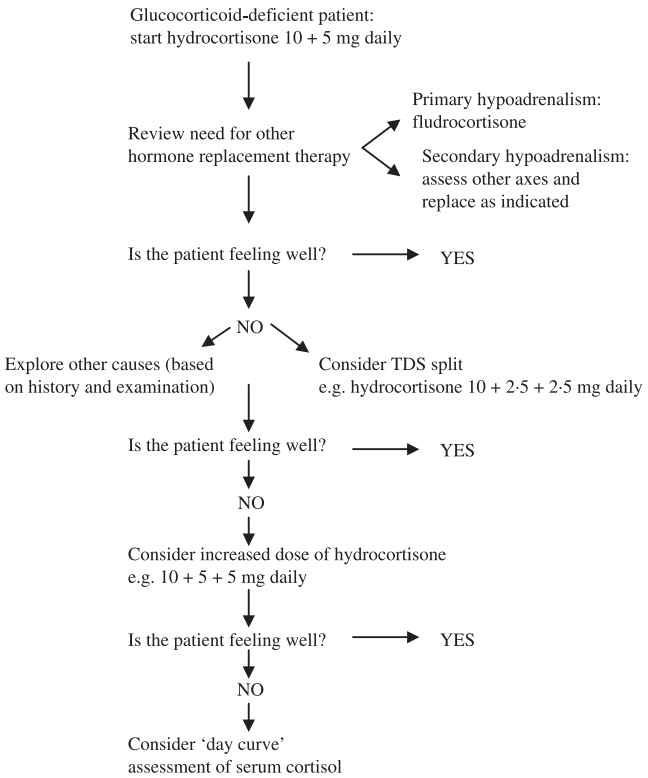

Fig. 1 Algorithm for treatment of the glucocorticoid-deficient patient. Patients should be reassessed at 6–8 week intervals while their treatment is optimized.

normal rhythms of cortisol secretion means that replacement will never be physiological for the tissues. There is a particular risk that we will ignore the fact that very low cortisol concentrations are seen in normal individuals, even during the diurnal peak, although they will be concealed by pooled data,[13] and thus the evidence of day curves may result in a tendency to overtreat our hypocortisolaemic patients.

Figure 1 shows a suggested algorithm for treatment of the glucocorticoid deficient patient. This is not intended to be dogmatic: we respect the fact that others will have different opinions, and acknowledge the very limited evidence base to support any recommendations. It will be seen that the algorithm relies on clinical assessments of the patient to optimize their therapy. It is important to accept that one can only make a definite clinical diagnosis of the extremes of over- or under-treatment (e.g. a patient who is becoming cushingoid with excessive weight gain, or a patient who shows skin pigmentation characteristic of untreated Addison's disease and has postural hypotension). However, a thorough clinical history is vital in the assessment of a patient's well being, and of any other factors that may be contributing to a feeling of ill health. Although some patients will experience a 'feel-good factor' when treated with pharmacological doses of steroids, it is inappropriate to continue to titrate the glucocorticoid replacement dose up beyond the equivalent of 20 mg hydrocortisone daily. The recommendation for a 'day curve' assessment of serum cortisol if the patient is still not feeling well at this point is as much to reassure the patient as the physician. Although some endocrinologists would advocate a greater dependency on 'day curve' assessments, in addition to their physiological limitations, which have already been discussed, one also has to take into consideration the inconvenience to the patient (in terms of time and discomfort) and the use of NHS resources. If day curves are undertaken, in this context the results of serum cortisol measures are easier to interpret than salivary cortisol concentrations. The use of capillary blood samples onto filter paper can be adopted from paediatric endocrine practice to allow the studies to be performed at home. Urinary free cortisol assessments are not useful in assessing the adequacy of glucocorticoid replacement therapy.

The regulation of hypothalamic-pituitary-adrenal activity is not simply a negative feedback relationship between circulating glucocorticoids and pituitary ACTH secretion. Adrenal activity is also regulated by N-terminal pro-opiomelanocortin (POMC) peptides and by afferent and crossed efferent neural pathways.[41] Trying to modify glucocorticoid replacement to the dose that suppresses ACTH into the normal range will result in supraphysiological plasma levels of glucocorticoids. In view of this, we very rarely measure plasma ACTH levels in hypoadrenal patients, except to confirm a clinical suspicion of noncompliance in a patient with primary hypoadrenalism.

The effect of different glucocorticoid replacement regimens on clinical outcomes

In the following sections, we will summarize studies examining the effect of various glucocorticoid replacement regimens on a range of relevant clinical outcomes (bone, glucose metabolism, cardiovascular function, quality of life and mortality). We will also consider interactions with other hormone replacement therapies and medication, and the evidence supporting 'sick day rules', 'well day recommendations' and the management of hypocortisolaemic patients in pregnancy. Details of the baseline characteristics of patients included in these studies are summarized in Table 1, to assist judgements regarding the quality and generalizability of the studies cited.

Bone

A number of observational and interventional studies have focused on bone turnover, bone mineral density and osteoporosis in patients on glucocorticoid replacement therapy.

Several groups of researchers have used dual energy X-ray absorptiometry (DEXA) scanning to measure the bone mineral density (BMD) of the lumbar spine and femoral neck in hypoadrenal patients, and compared the results to age-sex matched reference ranges in the normal local population using z scores. Valero *et al.* found that 3/8 (38%) of hypoadrenal men and 4/22 (18%) of hypoadrenal women had z scores of < -2 at the lumbar spine.[42] The BMD of the men and premenopausal women with Addison's disease was not significantly different to the controls, whilst the postmenopausal women with Addison's disease had a significantly lower BMD than the controls ($P < 0{\cdot}01$). There were no significant differences between the BMD of those treated with hydrocortisone and those on prednisolone, nor was there any correlation between the BMD and the length of glucocorticoid treatment. Zelissen *et al.* found that 10/31 hypoadrenal men (32%) and 4/60 hypoadrenal women

Table 1. Baseline characteristics of patients in studies looking at the effect of glucocorticoid replacement regimens on clinical outcomes

First author, year	Outcome				*n* (M : F)	Age/year mean ± SD or (range)	1°/2° adrenal failure	GC treatment/mg/day			
	Bone	CV	QOL	Other				HC	Pred	Dex	CA
Valero, 1994[42]	X				30 (8 : 22)	M 55·1 ± 13; F 53·3 ± 12	1°	30	7·5		
Florkowski, 1994[44]	X				14 (5 : 9)	M 56·6; F 56	1°	25–30			
Zelissen, 1994[43]	X				91 (31 : 60)	M 42·4 ± 14; F 46·9 ± 14	1°	M 29·2; F 28·5			
Peacey, 1997[45]	X				32 (13 : 19)	52 ± 15·7	1° (12) 2° (20)	20/30			
Wichers, 1999[46]	X		X		9 (5 : 4)	44 (23–60)	2°	15/20/30			
Suliman, 2003[47]	X	X			9 (3 : 6)	52 ± 8·4	1° (8) 2° (1)	15/20		~0·5	
Malerbi, 1988[49]		X			6 (3 : 3)	Range 38–53	1°		5/7·5		37·5
Al-Shoumer, 1995[50]		X			8 (3 : 5)	Range 46–76	2°	15/20/30			
Dunne, 1995[51]		X			13 (7 : 6)	Range 21–58	2°	15/30			
McConnell, 2002[52]		X			15 (9 : 6)	45 ± 2·4	2°	20			
Lovas, 2002[53]			X		79 (35 : 44)	M 40·2 ± 2; F 48·8 ± 2	1°				40
Groves, 1988[54]			X		7 (3 : 4)	Range 22–65	1°	30–50			
Riedel, 1993[55]			X		14 (6 : 8)	45 (32–68)	1°	30			37·5
Weaver, 1994[57]				X	19 (6 : 13)	47 (24–60)	2°	0–40			
Flemming, 1999[62]				X	84 (34 : 50)	59 (20–87)	1° & 2°				

Abbreviations: cardiovascular (CV), quality of life (QOL), number in study (*n*), male (M), female (F), standard deviation (SD), primary (1°), secondary (2°), glucocorticoid (GC), hydrocortisone (HC), prednisolone (Pred), dexamethasone (Dex), cortisone acetate (CA).

(7%) had z scores of < –2 in at least one region.[43] In men, the hydrocortisone dose was higher in the group with a low BMD (31 *vs.* 28·4 mg/day, $P = 0{\cdot}032$), and there was a significant linear correlation between the hydrocortisone dose (mg/kg body weight) and the BMD at the lumbar spine ($r = -0{\cdot}86$, $P = 0{\cdot}029$), but not at the femoral neck. In women, there was no significant difference in hydrocortisone dose between the groups, and no significant correlation between the hydrocortisone dose and the BMD at either site. Florkowski *et al.* report mean z scores of –1·21 at the lumbar spine and –0·57 at the femoral neck in hypoadrenal women, and z scores of 1·32 at the lumbar spine and 0·62 at the femoral neck in hypoadrenal men.[44] There was no significant correlation between the z scores and either the duration of the Addison's disease or the 'mean plasma cortisol'.

Other groups have studied the effects of changing the glucocorticoid used, and/or the dosage. Peacey *et al.* studied a group of 32 hypoadrenal patients, and a group of 30 age and sex-matched controls.[45] Within the patient group, 24/32 had their dose of hydrocortisone reduced from a mean of about 30 mg/day to a mean of about 20 mg/day: of these patients, 19/24 were studied both before and a mean of 3·5 months after the dosage reduction. There was no significant difference in the serum osteocalcin concentrations (a marker of osteoblast activity) of the patient group compared to the controls. A significant correlation was observed between the reduction in hydrocortisone dose and an increase in osteocalcin concentration (mean increase of 19%, $r = 0{\cdot}47$, $P = 0{\cdot}04$). The BMD at the lumbar spine measured by DEXA scanning was significantly lower in the patient group compared to the controls ($P < 0{\cdot}02$), and there was a significant negative correlation between the BMD and the dose of hydrocortisone prior to adjustment ($r = -0{\cdot}43$, $P < 0{\cdot}03$). Wichers *et al.* studied a group of 9 patients with secondary hypoadrenalism.[46] In a 6-week, randomized double-blind study, with the patients divided into three groups of three, they received 2 weeks each of the three different doses of hydrocortisone (15, 20 and 30 mg daily). On 30 mg/day, both the UFC and serum cortisol concentrations were greater than the upper limit of their normal reference range. Osteocalcin levels (a marker of osteoblast activity) fell with increasing doses of hydrocortisone. No significant differences were seen in levels of alkaline phosphate or its bony isoenzyme (also a marker of osteoblast activity), or in the levels of a variety of markers of bone resorption. Suliman *et al.* studied a group of nine hypoadrenal patients and a control group of 31 subjects.[47] Three dosage schedules were given in a random order for 4 weeks each: S1 (hydrocortisone 10 + 5 mg), S2 (hydrocortisone 10 + 5 + 5 mg) and S3 (dexamethasone 0·1 mg/15 kg body weight). Ionized calcium concentrations were lower in all three patient groups compared to the controls ($P < 0{\cdot}001$), but there were no significant differences in the parathyroid hormone concentrations. 25-hydroxy-vitamin D concentrations tended to be higher in patients than in controls, a result which only reached statistical significance in the dexamethasone-treated group (S3) ($P < 0{\cdot}01$). The urinary free deoxypyridinoline (a marker of bone resorption) was lower in S3 than S1 or S2, but there were no significant differences in a range of other markers of bone formation and resorption between the three treatment groups.

Overall, there is some evidence of a lower bone mineral density in hypoadrenal patients on glucocorticoid replacement therapy, perhaps particularly in postmenopausal women, although less evidence of

a negative correlation between glucocorticoid dose and bone mineral density. Serum osteocalcin (a marker of osteoblast activity) does seem to correlate inversely with the glucocorticoid dose, although no trends are seen in other markers of bone formation or resorption: this may reflect a pharmacological effect of glucocorticoids on osteocalcin secretion *per se*, which is recognized to be very sensitive to glucocorticoid excess.[23,48]

Glucose metabolism and cardiovascular function

A number of observational and interventional studies have focused on glucose metabolism and cardiovascular function in patients on glucocorticoid replacement therapy.

Malerbi *et al.* studied six patients with primary adrenal failure and eight controls.[49] The hypoadrenal patients were assessed while taking their glucocorticoid replacement therapy, and again having omitted their medication for 72 h. After an overnight fast, a constant infusion of tritiated glucose was started, with measurements of plasma insulin, glucose and tritiated glucose over 2 h. There were no significant differences in the steady state plasma glucose concentrations of the untreated hypoadrenal group, the replaced hypoadrenal group and the controls. The steady state plasma insulin concentrations of the controls were higher than the untreated patients ($P < 0{\cdot}01$), but there were no significant differences between the untreated and replaced groups, or the replaced group and the controls. The steady state glucose turnover rate (equivalent to hepatic glucose production after an overnight fast) was not significantly different between the three groups.

Al-Shoumer *et al.* studied eight patients with secondary hypoadrenalism who were all also growth hormone-deficient.[50] They attended a metabolic ward after an overnight fast on two occasions for a 75-g oral glucose tolerance test (OGTT). On one occasion (the 'glucocorticoid day' [GD]), they took their hydrocortisone 60 min prior to the OGTT, on another occasion (the 'nonglucocorticoid day' [NGD]) they omitted their hydrocortisone until after the OGTT. Fasting glucose and insulin concentrations were similar on both days. The area under the curve (AUC) for both glucose and insulin was higher on the GD than the NGD ($P < 0{\cdot}05$ and $P < 0{\cdot}02$ respectively). On the GD, three patients had impaired glucose tolerance (IGT) by WHO criteria, one of who also had IGT on the NGD. There was a significant correlation between the difference in the AUC for glucose on the GD compared to the NGD and the maximum plasma cortisol concentration on the GD (Spearman correlation coefficient 0·83, $P < 0{\cdot}01$). No significant correlation was observed between the difference in AUC for insulin and the maximum cortisol concentration.

Dunne *et al.* studied 13 hypopituitary patients and 20 controls.[51] The patients were assessed twice: once while taking hydrocortisone 30 mg/day, then again after their dose of hydrocortisone had been reduced by 5 mg per week, from 30 mg/day to 15 mg/day, and they had been taking 15 mg/day hydrocortisone for 3 months. There were no significant differences in plasma glucose, HbA_1c or body weight between the three groups (controls, patients on 30 mg/day and patients on 15 mg/day). The mean 24-h systolic and diastolic blood pressures were lower in patients than controls, independent of the hydrocortisone dose. There were no differences in various echocardiogram parameters between the three groups. There was no evidence of postural hypotension following the dosage reduction. Appropriate and similar blood pressure responses were observed to tests of cardiovascular reflexes.

McConnell *et al.* studied 15 patients with secondary hypocortisolism.[52] In a random crossover design, patients were studied twice at an interval of 3–4 weeks: they were either given a hydrocortisone infusion to mimic normal physiological cortisol concentrations, or 15 mg hydrocortisone orally at 8 a.m. Insulin sensitivity and endogenous glucose production were measured using a euglycaemic hyperinsulinaemic clamp and a tritiated glucose infusion: there were no significant differences in either parameter between the oral treatment regimen and the intravenous infusion.

In the study by Suliman *et al.* described previously (see 'Bone'), the homeostasis model assessment (HOMA) was used to estimate insulin resistance and beta cell function, and insulin sensitivity was assessed using an intravenous insulin infusion (0·075 IU/kg) followed by plasma glucose measurements for 15 min.[47] There were no significant differences in fasting insulin, insulin resistance, beta-cell function or insulin sensitivity between the three groups (S1 [hydrocortisone 10 + 5 mg], S2 [hydrocortisone 10 + 5 + 5 mg] and S3 [dexamethasone 0·1 mg/15 kg body weight]).

Thus there is some evidence that untreated hypoadrenal patients may start with relatively favourable cardiovascular risk profiles, such as lower insulin concentrations and lower blood pressures than controls. There is evidence that glucocorticoid replacement therapy increases postprandial glucose and insulin concentrations in hypoadrenal patients. The studies do not suggest that there is much to choose between different glucocorticoid treatment regimens or doses in relation to glucose metabolism and cardiovascular function.

Quality of life

In a postal survey of patients with primary adrenal failure from Norway, the short form 36 was used to assess subjective health status.[53] Seventy-nine out of 97 patients (81%) responded. Comparison was made with normative data from the general population. General health and vitality perception were most consistently impaired in the patients with Addison's disease. Scores for fatigue (both physical and mental) were also higher than normal (i.e. more fatigue) and correlated with vitality scores. 24% of patients in the 18–67 years age range and 41% of patients in the 40–67 years age range were out of work and receiving disability benefit, compared to 10% and 17%, respectively, in the general population (both $P < 0{\cdot}001$).

Groves *et al.* studied a group of seven patients: four had Addison's disease and three had had a bilateral adrenalectomy for Cushing's disease.[54] They were admitted on two occasions for an open-label unblinded study: on day 1, their hydrocortisone dose was given in three equal doses, at 09 : 00, 14 : 00 and 20 : 00 h. On day 2, their hydrocortisone dose was given in two doses, two-thirds at 09 : 00 and one-third at 20 : 00 h. Subjects scored their well-being on a visual analogue scale. On the thrice daily regimen, plasma cortisol concentrations were lower at 12 : 00 h ($P < 0{\cdot}05$), while on the twice daily regimen, plasma cortisol concentrations were lower from 16 : 00 to 20 : 00 h ($P < 0{\cdot}001$–$P < 0{\cdot}02$). The mean well-being score showed a diurnal variation: it was lowest prior to the first morning dose. There was a nonsignificant trend towards reduced well-being at all time

points on the twice daily dosage. There was a significant correlation between simultaneous cortisol concentrations and well-being scores ($r = 0{\cdot}268$, $P < 0{\cdot}05$). The results of this study should be treated with some circumspection, as it was unblinded, based on only one day of treatment with each regimen, and used only one visual analogue scale to assess quality of life.

Riedel *et al.* studied a group of 14 patients with primary adrenal insufficiency.[55] In a double-blind study, all patients were given three different modes of glucocorticoid replacement therapy: each mode of treatment was given for 1 week in a randomized order, and subsequently repeated in a different random order. The treatments were hydrocortisone 20 mg at 07 : 00 h and 10 mg at 19 : 00 h (mode 1), hydrocortisone 30 mg at 07 : 00 h and placebo at 19 : 00 h (mode 2), and placebo at 07 : 00 h and hydrocortisone 30 mg at 19 : 00 h (mode 3). Quality of life was assessed using two questionnaires, one to assess physical symptoms and the other to assess emotional health and general health perception. 'General contentment' was achieved in 9/14 patients in mode 1 (64%), 4/14 patients in mode 2 (29%) and 2/14 patients in mode 3 (14%).

In the randomized double-blind study by Wichers *et al.* described previously (see 'Bone' section), questionnaires designed for serial assessment of mood were used to assess emotional well-being, general health perception and subjective impairment caused by physical symptoms.[46] There was no significant change in the mean scores of the questionnaires as the dose of hydrocortisone was switched between 15, 20 and 30 mg daily.

Thus, the available evidence suggests that patients may complain of an impaired quality of life even on relatively high doses of steroids. Although one study showed a correlation between plasma cortisol concentrations and well-being, a more rigorous study showed no correlation between hydrocortisone dose (and urinary free cortisol excretion) and quality of life. There is some evidence that the quality of life of hypoadrenal patients is better on a twice daily replacement regimen than a once daily regimen, and may be better on a thrice daily regimen (although as discussed this data is not strong).

Mortality

In a large prospective study of 1014 patients with hypopituitarism, 769 had biochemically confirmed corticotrophin deficiency, all of whom were treated with glucocorticoid replacement therapy.[56] There was no significant difference in all-cause mortality between the patients with treated hypoadrenalism (standardized mortality ratio [SMR] of 1·82 compared with national controls) and the rest of the group (SMR 1·87 for the whole group, SMR 2·41 for those who were not corticotrophin-deficient, $P = 0{\cdot}3$ [deficient *vs.* not deficient]). It is generally stated that mortality in patients treated for autoimmune Addison's disease is now normal, but we are not aware of data to support this assertion.

Interactions with other hormone replacement therapy and medication

Weaver *et al.* studied a group of 19 hypopituitary patients with growth hormone (GH) deficiency.[57] Three subjects had a peak cortisol of > 550 nmol/l in response to an insulin tolerance test; the other 16 subjects were treated with hydrocortisone. They participated in a 6-month double-blind placebo controlled trial of GH treatment, with a 6-week washout phase. After 6 months of GH therapy, in the patients treated with hydrocortisone, their 24-h urinary free cortisol metabolite (CoM) excretion fell by a mean decrement of 21% ($P < 0{\cdot}01$), with a nonsignificant trend towards a reduced urinary free cortisol excretion rate. This suggests a reduction in availability of administered hydrocortisone (as assessed by the urinary excretion rates). There was no change in the urinary CoM excretion of the patients not on hydrocortisone treatment. In the patients treated with hydrocortisone, there was a reduction in the ratio of 11-hydoxy ('F') to 11-oxo ('E') urinary cortisol metabolites from 1·27 to 1 ($P = 0{\cdot}04$, reference range 0·33–1·29). There was also a 25% fall in the F/E ratio for the patients not on hydrocortisone therapy. This suggests either reduced 11-β-HSD-1 activity and/or increased 11-β-HSD-2 activity. Subsequent *in vitro* studies showed inhibition of 11-β-HSD-1 activity by insulin-like growth factor-I, but no effect on 11-β-HSD-2 activity.[58] The clinical significance of these interesting observations is uncertain: it has been suggested that initiation of GH treatment could precipitate secondary adrenal failure or necessitate an increased dose of glucocorticoid replacement therapy,[58] but there are no reports of such eventualities actually occurring. Some authors have speculated that a fall in 11-β-HSD-1 activity with GH therapy could contribute to the reduction in intra-abdominal adipose tissue and other beneficial effects of GH treatment in growth hormone-deficient adults.[6,58]

Hyperthyroidism increases the metabolism and clearance of cortisol.[5,7] Rifampicin and phenytoin also increase cortisol clearance[5]: adrenal crises have been reported in patients receiving corticosteroid replacement therapy for primary adrenal failure who were treated with rifampicin.[59]

'Sick day rules', 'well day recommendations' and pregnancy

Patients on glucocorticoid replacement therapy are usually advised to double their dose if they are febrile, with higher doses to cover more severe illnesses or surgical procedures. A number of papers include recommendations regarding 'sick day rules',[60,61] and while these are generally accepted as beneficial and not harmful in the short term, there is no evidence available to give accurate guidance. In a survey of hypoadrenal patients under follow-up in an endocrine clinic, 84/97 (87%) returned an eight-item questionnaire about 'sick day rules'.[62] Forty-five out of 84 (54%) were assessed as being 'capable of appropriate action' (i.e. they answered 5/8 questions correctly). This included 31/46 (67%) of the 20–60 years age group, and 14/38 (37%) of the > 60 years age group. Patients' self-rating of being well-informed or not did not correlate with their ability to answer the questions correctly.

Hypoadrenal patients may also seek advice about what adjustments they should make to their glucocorticoid replacement therapy when they run a marathon or take an examination. Again, although some papers include 'well-day recommendations' (e.g. to increase the dose of hydrocortisone by 5–10 mg before a strenuous activity[63]), there is no evidence base to support them. In a study of nine adolescents with CAH using a randomized, double-blind, crossover-design,

an additional morning dose of hydrocortisone before short-term high-intensity exercise did not affect blood levels of glucose, lactate or free fatty acids, exercise capacity, perceived exertion or the peak blood pressure response.[64] The peak heart rate was marginally (but statistically significantly) higher following the extra dose of hydrocortisone (mean 193 *vs.* 191 beats/min). Of the nine patients, one correctly identified the session at which he had received the extra dose of hydrocortisone, three identified the wrong session, and five said they did not notice a difference. Patients should be advised not to take extra doses of hydrocortisone regularly to 'cover' day-to-day physical or psychological stressors, as this puts them at risk of the long-term effects of chronic glucocorticoid over-dosage.

Some authors recommend that patients on glucocorticoid replacement therapy should increase their dose of hydrocortisone by 50% in the last trimester of pregnancy[63] or by 5–10 mg/day.[5] This judgement may vary depending on the woman's usual treatment dose: it has been noted that a dose increase is rarely necessary (on empirical grounds) in women treated with 20–30 mg hydrocortisone daily.[21] As discussed, hydrocortisone or prednisolone, which are both substrates for 11-β-HSD-2, may be preferred to dexamethasone in pregnant hypoadrenal patients.[21,23,24,29] High doses of hydrocortisone (e.g. 50 mg intramuscularly every 6 h) are recommended from the start of labour to 48 h postpartum, analogous to the management of a major surgical procedure.[21,63]

Discussion

There is good physiological evidence that normal endogenous cortisol production is only about 10 mg/day and shows both circadian and pulsatile ultradian rhythms. The diurnal peak anticipates wakening. Tissue specificity is achieved by a prereceptor mechanism involving the 11-β-HSD enzymes, and by the distribution of low and high affinity receptors (GR and MR). 'Pharmacological' continuous prolonged steroid exposure has different effects to 'physiological' intermittent pulses. These factors make it difficult to recommend any method of assessment of glucocorticoid replacement therapy: urinary free cortisol estimates do not seem useful in this context, nor is there an evidence base to support specific targets or standards for the interpretation of cortisol day curves in patients on treatment. Whatever regimen we prescribe, we cannot mimic the physiological rhythms of cortisol secretion.

What we can do is assess the potential adverse effects of 'too much' glucocorticoid replacement therapy, in terms of risk factors for osteoporosis and cardiovascular disease. There is no evidence that patients experience adverse effects on low dose replacement therapy (15 mg hydrocortisone daily).[46,51] There is some evidence in relation to general well-being to support a 'two-thirds, one-third' split in the total glucocorticoid dose, and avoid taking large doses of glucocorticoids in the evening.[55] There is no outcome data to favour one glucocorticoid rather than another.

It is difficult to justify complex monitoring protocols if our patients will fare equally well taking the lowest dose of hydrocortisone we dare to prescribe, on which they feel physically and mentally fit. Some of our patients will complain of lack of vitality and fatigue, even on relatively high doses of steroids:[53] given the limitations of our current glucocorticoid replacement regimens, this is perhaps unsurprising, and there is no evidence of improved quality of life on higher doses of steroids.[46] There is some evidence that quality of life may be improved in women with adrenal insufficiency treated with dehydroepiandrosterone,[65] but this is beyond the scope of this review. Advice about 'sick day rules' is based on expert consensus and experience rather than evidence: it may be that hypoadrenal patients are often over-treated in this context, with excessively high doses that are not tapered fast enough. A caveat regarding patient empowerment comes from the study suggesting that older hypoadrenal patients in particular may not have the knowledge needed to support self-management in the context of intercurrent illnesses.[62] The available evidence does not support additional doses of hydrocortisone to cover short-term high-intensity exercise.[64]

Part of the reason why the management of corticosteroid deficiency is still controversial may be the paucity of evidence to support or refute our current practices and prejudices. Many of the studies described in this review have small subject numbers including heterogeneous groups of patients, and short durations of different treatment regimens. Some have other methodological weaknesses, such as the lack of appropriate control groups, blinding and randomization. They generally rely on surrogate markers of risk rather than hard end points. Individual variation is inherent in hypoadrenal patients: both in patients with secondary hypoadrenalism and in those with primary hypoadrenalism associated with other autoimmune endocrine diseases, a variety of other hormonal factors may need to be considered in relation to their bones, cardiovascular risk factors and quality of life. These include an initial diagnosis of Cushing's syndrome, over- or under-replacement with thyroxine, periods of untreated hypogonadism, and growth hormone deficiency/treatment.[40,48]

Thus based on our current knowledge, our ability to manage physiological replacement therapy for corticosteroid-deficient patients has a number of limitations. Perhaps in the future, manipulation of the 11-β-HSD enzyme system may enable us to fine tune glucocorticoid treatment and protect patients from adverse effects on the cardiovascular system, central nervous system and bone. Manufacturers may be able to design 'modified release' glucocorticoid preparations to provide an anticipatory diurnal peak before patients wake up. Might it be feasible to mimic the ultradian rhythmicity and physiological responses to daily hassles? At present, the best we can do is to attempt to imitate a normal circadian rhythm using two or three daily doses of hydrocortisone, and try to avoid chronically over-dosing our patients.

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