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The impact of different glucocorticoid replacement schedules on bone turnover and insulin sensitivity in patients with adrenal insufficiency

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Summary

OBJECTIVE Optimization of physiological replacement of glucocorticoid in patients with adrenal insufficiency is controversial. The present study was undertaken to compare the relative impact of three different regimes of glucocorticoid replacement in patients with adrenal insufficiency on parameters of bone turnover and insulin sensitivity.

PATIENTS Six female and three male patients with adrenal insufficiency and 17 female and 14 male control subjects participated.

DESIGN This was an open study conducted in a university teaching hospital. Schedule 1 (S1) consisted of hydrocortisone 10 mg with breakfast and 5 mg with lunch. S2 was similar to S1 with the addition of 5 mg hydrocortisone with the evening meal. S3 utilized dexamethasone 0·1 mg/15 kg body weight given per day with breakfast only. Each schedule was given for at least 4 weeks in random sequence to nine patients with adrenal insufficiency.

METHODS Blood was obtained at 0900 h (fasting) and at 1300 h for measurement of the ionized calcium (Cai), PTH, 25-hydroxyvitamin D and the bone formation markers intact osteocalcin and amino-terminal propeptide of type 1 procollagen (PINP). Timed urine collections were made under standardized conditions, that is while fasting between 0700 and 0900 h (basal) and between 0900 and 1300 h for measurement of the bone resorption markers, free deoxypyridinoline (FDPD) and cross-linked *N*-telopeptide of type 1 collagen (NTX). Blood was drawn for measurement of fasting plasma glucose and serum insulin levels. Insulin (0·075 IU/kg) was administered i.v. while the patient was fasting prior to the first glucocorticoid replacement dose on each study day. Plasma glucose was measured before and 3, 6, 9, 12 and 15 min after insulin administration to calculate the glucose disappearance rate (Kitt). Insulin resistance (IR) and β-cell function were estimated using the homeostasis model assessment (HOMA). Glucocorticoid dosage was given according to the various schedules at approximately 0930 h.

RESULTS During all three treatment schedules the serum Cai level was significantly lower than that seen in control subjects. PTH levels in patients taking the three replacement schedules and in normal subjects were similar. Serum 25-hydroxyvitamin D levels were not suppressed in the patients during any of the three treatment schedules. The bone resorption marker urinary FDPD under basal conditions was significantly lower during S3 (dexamethasone) than during either hydrocortisone schedules, S1 or S2. Urinary NTX values were not significantly different in the three study groups. The bone formation markers intact osteocalcin and PINP were similar in the three replacement schedules. The indices of IR and β-cell function tended to be higher during treatment with dexamethasone than with S1 or S2 but did not achieve statistical significance.

CONCLUSIONS These data indicate that all three replacement schedules were associated with low serum ionized calcium levels without evidence of a compensatory increase in PTH levels. These findings are consistent with direct or indirect suppression of the bone remodelling cycle and suppression of PTH levels. Bone turnover in patients with adrenal insufficiency treated with schedule 3, dexamethasone, was associated with lower bone turnover than patients treated with hydrocortisone schedules 1 or 2. While indices of insulin sensitivity measured during schedules 1, 2 and 3 did not achieve statistical significance, there was an obvious trend for greater insulin resistance to occur with schedules 3 using dexamethasone.

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Introduction

Consensus on optimization of glucocorticoid replacement therapy in patients with adrenal insufficiency has not been achieved. Traditionally, the daily doses for hydrocortisone have ranged from 20 to 30 mg and for cortisone acetate, 25–37·5 mg (Besser & Jeffcoate, 1976; Sönksen, 1990; Cuneo, 1995). Recent measurements using isotope dilution/mass spectrometry methodologies have indicated that the normal daily cortisol production is lower than the original estimates (Esteban *et al*., 1991; Kerrigan *et al*., 1993). As a result lower doses of hydrocortisone replacement, 15–20 mg, have been recommended (Oelkers, 1996). Osteoporosis is a frequent complication associated with the use of pharmacological doses of glucocorticoids (Lukert & Raisz, 1990; Canalis & Giustina, 2001). Reduction in bone density has been reported also in patients with Addison's disease on replacement with glucocorticoid (Zelissen *et al*., 1994). Another concern when using glucocorticoid therapy is that excessive replacement may lead to insulin resistance and hyperglycaemia. Impaired glucose tolerance and diabetes mellitus occurred in adults with hypopituitarism on conventional traditional replacement therapy including glucocorticoids (Al-Shoumer *et al*., 1995). This study was designed to examine and compare the impact of three different glucocorticoid replacement schedules, each given for at least 4 weeks, on bone turnover and insulin sensitivity in patients with adrenal insufficiency using biochemical bone turnover markers, and indices of insulin sensitivity using the homeostasis model assessment, HOMA (Matthews *et al*., 1985), and the plasma glucose disappearance rate, Kitt (Bonora *et al*., 1989).

Subjects and methods

Patients and treatment schedules

Nine patients, three men and six women, aged 52 ± 8·4 years (mean ± SD), who were diagnosed with adrenal insufficiency and treated with glucocorticoid replacements for 16·7 ± 9·3 years, participated in this study. Eight patients had primary adrenal insufficiency and one woman had secondary adrenal insufficiency. Eight patients were treated with fludrocortisone. Two of the women also had premature ovarian failure. Three women were receiving oestrogen–progestogen replacement therapy and three patients were taking replacement L-thyroxine (Table 1). None of the patients were receiving a bisphosphonate, vitamin D

Table 1 Characteristics of patients with adrenal insufficiency

Patient no.	Sex	Age (years)	BMI (kg/m^2)	Diagnosis	Years since	Prestudy treatment diagnosis
1	Male	61	27·7	Addison's disease Hypothyroidism	20	Dexamethasone 0·5 mg Fludrocortisone 0·1 µg L-Thyroxine 0·1 mg
2	Male	47	24·0	Addison's disease	12	Hydrocortisone 25 mg a.m. Hydrocortisone 12·5 mg p.m. Fludrocortisone 0·1 µg
3	Male	46	23·1	Addison's disease	9	Hydrocortisone 15 mg a.m. Hydrocortisone 10 mg p.m. Fludrocortisone 0·1 µg
4	Female	51	24·4	Addison's disease Premature ovarian failure	20	Dexamethasone 0·5 mg Fludrocortisone 0·2 µg HRT
5	Female	49	35·1	Addison's disease Hypothyroidism	10	Hydrocortisone 10 mg a.m. Hydrocortisone 5 mg p.m. Fludrocortisone 0·1 µg L-Thyroxine 0·2 mg
6	Female	41	20·6	Addison's disease	9	Dexamethasone 0·5 mg Fludrocortisone 0·1 µg
7	Female	48	35·6	Addison's disease Premature ovarian failure	16	Dexamethasone 0·25 mg Fludrocortisone 0·1 µg HRT
8	Female	70	34·2	Hypopituitarism	16	Hydrocortisone 20 mg a.m. L-Thyroxine 0·1 mg
9	Female	55	29·6	Addison's disease Postmenopausal symptoms	39	Prednisolone 7·5 mg a.m. Fludrocortisone 0·1 µg HRT

BMI, body mass index.

or calcium supplements, or had a history of osteoporosis. Each patient received three different glucocorticoid replacement schedules given for at least 4 weeks, which were prescribed in random sequence. Schedule 1 (S1) consisted of hydrocortisone 10 mg with breakfast and 5 mg at approximately 1300 h with lunch; this achieved a hydrocortisone dose of 0·20 ± 0·04 mg/kg/day. Schedule 2 (S2) was similar to S1 with the addition of 5 mg hydrocortisone with the evening meal. This resulted in a hydrocortisone dose of 0·27 ± 0·06 mg/kg/day. Schedule 3 (S3) used dexamethasone 0·1 mg/15 kg body weight given with breakfast only. This dose of dexamethasone is based on the estimate that 20 mg of hydrocortisone is equivalent in potency to 0·5 mg of dexamethasone (Meikle & Tyler, 1977). Dexamethasone was prepared in suspension form using 1 mg/10 ml solution. On the study days patients were fasting overnight from midnight. There were no significant side-effects including evidence of under- or over-replacement with glucocorticoids. Each subject also underwent examination of indices of calcium metabolism and bone turnover biomarkers on a day on which glucocorticoid was withheld until 1300 h to examine for any spontaneous variation unrelated to glucocorticoid replacement. In addition, blood samples were also obtained from 31 normal subjects, 17 women and 14 men with a mean age 25·9 ± 4·5 years.

Estimation of bone turnover

Blood was obtained at 0900 h (fasting) to provide assessment of the long-term effect of each schedule, and at 1300 h to gain insight into the acute effect of glucocorticoid replacement. Measurements performed were of ionized calcium, PTH, 25-hydroxyvitamin D, and the bone formation markers intact osteocalcin and amino-terminal propeptide type 1 procollagen (PINP). Timed urine collections were made under standardized conditions (i.e. while fasting between 0700 and 0900 h), that is under basal conditions to provide an index of the long-term effect, and between 0900 and 1300 h to provide an index of the acute effect as glucocorticoid was taken at 0900 h. The bone resorption markers, free deoxypyridinoline (FDPD) and cross-linked *N*-telopeptide of type 1 collagen (NTX) were assayed and the results were expressed as a ratio of the simultaneous creatinine (Cr) concentration.

Estimation of insulin sensitivity

We used the homeostasis model assessment, HOMA, which has been demonstrated to provide sensitive validated assessments of insulin sensitivity and β-cell function (insulin secretion) and has been used to predict the development of type 2 diabetes mellitus (Matthews *et al*., 1985). Insulin resistance (IR) was calculated from the formula: fasting insulin (mU/l) × fasting glucose (mmol/l) ÷ 22·5. β-Cell function (insulin secretion) was derived from the formula: 20 × fasting insulin (mU/l) ÷ fasting glucose (mmol/l) – 3·5 (Matthews *et al*., 1985).

We have also assessed insulin sensitivity using the plasma glucose disappearance rate, Kitt (Bonora *et al*., 1989). Blood was drawn for measurement of fasting plasma glucose and serum insulin levels. Insulin (0·075 IU/kg) was administered i.v. while the patient was fasting and prior to the first glucocorticoid replacement dose on each study day. Plasma glucose was measured before and 3, 6, 9, 12 and 15 min after insulin administration for estimation of Kitt.

Analytical methods

Serum Cai (reference range 1·19–1·35 mmol/l) was measured by an ion-selective electrode (Radiometer, Copenhagen, Denmark). Plasma glucose levels were measured on a Beckman CX7 (Brea, CA, USA). The following analytes were measured by immunoassay: insulin, using an Abbott IMX (IL, USA), with an intra-assay coefficient of variance (CV) of 6·3%, with a normal range of 2–15 mU/L; 25-hydroxyvitamin D (Diasorin, Stillwater, USA), which involves pre-extraction of 25-hydroxyvitamin D, with an assay sensitivity of 3·2 nmol/l and intra- and interassay CVs of 10·8% and 12·8%, respectively, with recommended serum levels > 70 nmol/l for the months June–September and > 50 nmol/l for the months October–May. Intact serum PTH was assayed by two-site immunoradiometric analysis (Allegro-Nichols, San Juan Capistrano, CA, USA). The assay sensitivity was 1·1 ng/l and intra- and interassay CVs were 6·7% and 8·1%, respectively, while the normal reference range was 2–52 ng/l. PINP was measured by radioimmunoassay (Orion Diagnostica, Espoo, Finland). The assay sensitivity was 2 μg/l and intra- and interassay CVs were 4·1% and 5·7%, respectively, while the normal reference range was 27·2–72·0 μg/l (combined male and female). Osteocalcin was measured by an immunoradiometric assay ELSA-OST-NAT (CIS BIO International). The assay sensitivity was 0·05 μg/l and intra- and interassay CVs were 1·3% and 4·8%, respectively, with a normal reference range of 9·5–22·2 μg/l. FDPD was measured by a competitive enzyme immunoassay (Metra Biosystems, Mountain View, CA, USA). The assay sensitivity was 2 nmol/l and intra- and interassay CVs were 6·4% and 9·7%, respectively, with normal reference ranges of 4·1–8·1 nmol/mmol Cr (women) and 2·9–6·0 nmol/mmol Cr (men). NTX was measured using an enzyme-linked immunosorbent assay (ELISA; Osteomark, Ostex) with a sensitivity of 15·3 nmol bone collagen equivalence, BCE/mmol Cr, and intra- and interassay CVs were 6·1% and 9·8%, respectively, with a normal reference range of 25·5–72·4 nmol BCE/mmol Cr.

Statistical analysis

The Student *t*-test was used to compare values obtained in patients during each treatment schedule with those found in

control subjects. A P-value of $< 0{\cdot}05$ was accepted to indicate a significant difference. One-way analysis of variance (ANOVA) was used to identify statistical differences in indices of bone turnover biomarkers and insulin sensitivity obtained in the same patients during the three glucocorticoid replacement schedules using the statistical package 'Analyse it' from Microsoft Excel. The paired Student t-test was used to detect the difference between the groups when the ANOVA detected a significant difference, $P < 0{\cdot}05$, between treatments. This study was approved by The Research and Ethics Committee of St Vincent's University Hospital, and all patients gave informed written consent.

Results

Bone turnover

The long-term effect of the replacement schedules given for the last 4 weeks and indicated by measurements performed on early morning fasting blood and urine samples are outlined in Tables 2 and 3.

During all three treatment schedules of adrenal insufficient patients the serum Cai levels were significantly lower than in the control subjects. However, PTH levels were similar in patients and control subjects. 25-Hydroxyvitamin D levels tended to be higher in the patients than in the control subjects and achieved statistical significance during treatment schedules 2 and 3 (Table 2). Urinary FDPD, a marker of mature bone resorption, was significantly lower in adrenal insufficient patients on S3, that is dexamethasone replacement, compared to FDPD values for the patients on hydrocortisone replacement schedules S1 or S2 (Table 3). Mean values for NTX, also a bone marker for resorption, were not significantly different during the three replacement schedules (Table 3). Bone formation, as indicated by osteocalcin and PINP values, was not significantly different during the three replacement schedules although values obtained on dexamethasone tended to be the lowest.

The acute effects of glucocorticoid replacement as indicated by comparison of measurements in blood and urine under early morning fasting conditions with those obtained 3 h after glucocorticoid administration are outlined in Table 4.

Table 2 Effects of different glucocorticoid replacement schedules on basal ionized calcium and bone turnover biomarkers in patients with adrenal insufficiency (mean ± SD)

	Hydrocortisone		Dexamethasone	
	Schedule 1 10 and 5 mg	Schedule 2 10, 5 and 5 mg	Schedule 3 0·1 mg/15 kg	Control subjects
Ionized calcium (mmol/l)	1·19 ± 0·02‡ $n = 9$	1·18 ± 0·03‡ $n = 9$	1·20 ± 0·04‡ $n = 9$	1·26 ± 0·03 $n = 31$
PTH (ng/l)	21·7 ± 7·2 $n = 8$	24·3 ± 10·5 $n = 8$	21·9 ± 10·2 $n = 8$	26·2 ± 9·3 $n = 31$
25-Hydroxyvitamin D (nmol/l)	70·4 ± 38·4 $n = 9$	70·8 ± 35·1* $n = 9$	87·1 ± 44·3† $n = 9$	50·9 ± 21·9 $n = 31$

*$P < 0{\cdot}05$, †$P < 0{\cdot}01$, ‡$P < 0{\cdot}001$, significantly different from control subjects. To convert PTH ng/l to pmol/l, multiply by 0·106.

Table 3 Effects of different glucocorticoid replacement schedules on basal indices of bone turnover biomarkers in patients with adrenal insufficiency

	Hydrocortisone		Dexamethasone
	Schedule 1 10 and 5 mg	Schedule 2 10, 5 and 5 mg	Schedule 3 0·1 mg/15 kg
Osteocalcin (intact) (μg/l)	12·1 ± 4·7 $n = 8$	11·3 ± 5·3 $n = 8$	9·3 ± 3·2 $n = 8$
PINP (μg/l)	44·4 ± 15·6 $n = 9$	42·3 ± 15·8 $n = 9$	32·6 ± 13·0 $n = 9$
Urinary FDPD (nmol/mmol Cr)	7·5 ± 2·3 $n = 9$	6·8 ± 2·5 $n = 9$	4·3 ± 1·0* $n = 9$
Urinary NTX (nmol BCE/mmol Cr)	26·8 ± 6·8 $n = 9$	25·4 ± 7·2 $n = 9$	25·4 ± 5·9 $n = 9$

*$P < 0{\cdot}05$ significantly different from Schedules 1 and 2. To convert PINP μg/l to nmol/l, multiply by 0·029.

Table 4 Acute effects of glucocorticoid replacement therapy on bone biomarkers in patients with adrenal insufficiency

	Schedule 1			Schedule 2			Schedule 3		
Bone biomarkers	Basal	+3 h post HC 10 mg	*P*	Basal	+3 h post HC 10 mg	*P*	Basal	+3 h post Dex 0·1 mg/15 kg	*P*
Urinary FDPD (nmol/mmol Cr) *n* = 9	7·5 ± 2·3	7·5 ± 2·7	NS	6·8 ± 2·5	7·2 ± 2·6	NS	4·3 ± 1·0	4·7 ± 1·2	NS
Urinary NTX (nmol BCE/mmol Cr) *n* = 9	26·8 ± 6·8	28·8 ± 9·3	NS	25·4 ± 7·2	27·7 ± 7·5	0·04	25·4 ± 5·9	25·7 ± 7·8	NS
PINP (μg/l) *n* = 8	43·2 ± 16·2	33·9 ± 11·5	0·003	40·3 ± 15·5	32·8 ± 11·3	0·04	30·9 ± 12·9	26·8 ± 10·5	0·04
Osteocalcin (intact) (μg/l) *n* = 8	12·1 ± 4·7	11·6 ± 5·0	NS	11·3 ± 5·3	11·4 ± 4·6	NS	9·3 ± 3·2	8·8 ± 2·9	NS

HC, hydrocortisone; Dex, dexamethasone.

Table 5 Effects of different glucocorticoid replacement schedules on fasting insulin, β-cell function and plasma glucose disappearance rate (Kitt) in patients with adrenal insufficiency (mean ± SD)

	Hydrocortisone		Dexamethasone	
Insulin parameters	S1: 10 and 5 mg	S2: 10, 5 and 5 mg	S3: 0·1 mg/15 kg	*P*
Fasting insulin (mU/l) *n* = 8	7·8 ± 6·5	7·0 ± 3·0	11·6 ± 5·7	NS
Insulin resistance (HOMA) *n* = 8	1·6 ± 0·9	1·4 ± 0·7	2·3 ± 1·2	NS
β-Cell function (HOMA) *n* = 8	124 ± 69	125 ± 58	182 ± 111	NS
Kitt (mmol/l/min) *n* = 9	0·03 ± 0·01	0·03 ± 0·01	0·04 ± 0·01	NS

While NTX levels were higher after glucocorticoid administration using all three schedules, a statistically significant elevation was observed only with S2 (Table 4). Serum PINP showed a significant fall between the basal value and the values obtained 3 h after the first glucocorticoid dose in all the three schedules examined. However, this change was also seen on a control day when glucocorticoid was withheld and measurement made on samples obtained at the usual study times, basally 35·9 ± 17·6 and 3 h later 32·6 ± 15·2 μg/l, $P < 0·05$. No other acute effects of glucocorticoid administration were observed in the bone-related parameters examined.

Insulin sensitivity

Estimation of indices of insulin sensitivity observed in this study are summarized in Table 5. The mean fasting serum insulin levels were higher during the treatment with S3 than with S1 or S2, but a statistically significant difference was not observed. The index of insulin resistance (IR) as derived by HOMA tended to be higher during treatment with dexamethasone than with either of the hydrocortisone schedules but did not achieve statistical significance. A similar trend was apparent for β-cell function (estimated insulin secretion). The plasma glucose disappearance rate was similar during the three replacement schedules.

Discussion

Both children and adults with Cushing's disease who have low bone mineral density have evidence of suppressed bone formation and enhanced bone resorption (Di Somma *et al*., 2002). Inhibition of bone formation by supraphysiological doses of glucocorticoids is the major cause of glucocorticoid-induced osteoporosis (Canalis & Giustina, 2001). It has previously been reported that prednisolone in an equivalent or lower dose to that chosen for the present study, 2·5 mg per day, was associated with an increased fracture rate compared to that seen in untreated

subjects (Van Staa *et al*., 2000). In addition, in healthy elderly men after adjustment for all other known risk factors bone density may be affected by serum cortisol concentrations in the normal range (Dennison *et al*., 1999). Zelissen *et al*. (1994) reported that bone mineral density was 2 SD below the mean value for age-matched control subjects in 32% of men and 7% of women with Addison's disease. In that study male patients received hydrocortisone in a dose of 31·0 ± 6·3 mg/day or 0·43 ± 0·08 mg/kg per day and female patients received hydrocortisone 26·8 ± 5·4 mg/day or 0·37 ± 0·11 mg/kg per day for a mean duration of 10·6 years. In our study we used lower doses of hydrocortisone for replacement.

Serum Cai values were significantly lower in patients on all glucocorticoid replacement schedules than in normal subjects. The lower calcium values are consistent with the reported depression of calcium absorption associated with glucocorticoid administration (Lukert & Raisz, 1990). There was no evidence of vitamin D depletion as judged by serum 25-hydroxyvitamin D levels. However, although serum Cai was lower in the patients, PTH levels were not increased in patients on glucocorticoid replacement compared to control values. Although the control population used in this study tended to be younger than the patients, this is unlikely to explain the findings in our study as serum calcium levels are reported to be similar in young women, 34 ± 5 years, and older women, 80 ± 3 years (Chapuy *et al*., 1996), or to be slightly higher in the older group (Endres *et al*., 1987). Similarly, differences in 25-hydroxyvitamin D levels probably do not explain the failure of PTH levels to rise in the patients in response to lower Cai levels than in control subjects. The relationship between vitamin D metabolites and calcium in feeding back on PTH secretion is complex (Dawson-Hughes *et al*., 1997). Increased vitamin D in blood may have an indirect effect if serum calcium levels are raised, but this does not apply to our study patients. It is likely that calcium exerts the dominant control on PTH secretion. PTH levels tend to rise significantly with age (Endres *et al*., 1987; Landin-Wilhelmsen *et al*., 1995). The absence of higher PTH levels in our older patients is therefore particularly remarkable as the patients demonstrated lower Cai levels than the control subjects. The absence of a compensatory PTH response to the lower calcium levels in the glucocorticoid-treated patients may have some role in the bone loss associated with glucocorticoid therapy, as PTH is reported to exert a potent anabolic effect on trabecular bone (Dempster *et al*., 1993). Hauache *et al*. (1999) reported a trend for a decrease in PTH in patients with moderate asthma treated with inhaled glucocorticoid for 10 weeks. Manelli *et al*. (2001) reported a decreased PTH basal secretion rate in patients chronically treated with glucocorticoids although the fractional pulsatile PTH secretion was increased. Indeed, Lane *et al*. (1998) reported that intermittent administration of PTH intravenously to patients receiving glucocorticoid reversed the trend to osteoporosis. Hodsman and Steer (1993) found histomorphometric evidence of *de novo* bone formation on quiescent cancellous bone surfaces in response to PTH therapy in osteoporosis. The adrenal insufficiency patients in this study received mineralocorticoid replacement as clinically appropriate. Adrenal androgen replacement was not prescribed. It is highly unlikely that calcium and PTH differences between patients and control subjects could be explained by omission of androgens as similar levels of calcium and PTH are observed in normal men and women (Endres *et al*., 1987).

When comparing the adrenal replacement schedules, osteocalcin, PINP and FDPD levels tended to be lower during S3, dexamethasone treatment, than during S1 or S2. This trend achieved statistical significance for FDPD. Sugimoto *et al*. (1989) reported a direct effect of dexamethasone on the oestocalcin gene and suppression of osteocalcin. No differences were identified in indices of bone turnover when comparing the two hydrocortisone schedules. Schedule 2 represented a 33% dosage increase on S1. The indices of bone turnover examined in the morning fasting state are interpreted as providing insight into the cumulative impact of the different glucocorticoid replacement doses over 24 h. It is possible that examination of the indices 2–3 h following the administration of the glucocorticoids might have identified a difference. However, when bone turnover indices were compared before and 2–3 h after administration in the morning of hydrocortisone 10 mg to patients following either S1 or S2, or dexamethasone, 0·1 mg/15 kg, S3, a significant difference was seen only in PINP values (Table 4). However, when this study was repeated but glucocorticoid was not given, a similar decline in PINP levels was also observed. In addition, 3 h after administration of hydrocortisone 10 mg in the morning in S2, the NTX levels rose significantly although the difference was small and within the lower part of the reference range. A similar trend was seen during S1, but this did not achieve statistical significance although it also involved use of hydrocortisone 10 mg given to the same subjects. Nielsen *et al*. (1991) reported a significant fall in circulating osteocalcin levels a few hours after glucocorticoid administration. In general, these findings therefore suggest that hydrocortisone or dexamethasone in the doses given has little immediate impact on bone turnover biomarkers. The significant reduction in fasting urinary FDPD levels during the dexamethasone replacement schedule is most consistent with an accumulative effect of dexamethasone to reduce bone turnover.

Glucocorticoids increase hepatic glucose production (Tyake & Katz, 1997) and inhibit glucose uptake and glucose utilization by peripheral tissues (Munck, 1962; Fain, 1979). These actions are due in part to a direct effect on glucose transport into the cells (Olefsky, 1975). In our study although fasting insulin levels, insulin resistance and β-cell function as estimated by HOMA tended to be higher during the replacement with dexamethasone therapy than with the hydrocortisone schedules (Table 4), a statistical significance difference was not observed. Increased insulin resistance secondary to glucocorticoid treatment was

observed in previous studies (Olefsky, 1975; Al-Shoumer *et al*., 1995; Sakoda *et al*., 2000). Perley and Kipnis (1966) suggested that glucocorticoid therapy leads to excessive pancreatic insulin release. Hyperplasia of islets of Langerhans has been observed in animals following chronic glucocorticoid administration (Kinash & Haist, 1954; Volk & Lazarus, 1959; Varnic, 1965). In the present study the glucose disappearance rate was not significantly different in the treatment schedules studied. However, McConnell *et al*. (2002) reported similar indices of peripheral and hepatic insulin action in hypopituitary patients with adrenal insufficiency when treated with hydrocortisone 20 mg and when physiological levels are achieved by intravenous cortisol infusion.

Glucocorticoid replacement with dexamethasone was associated with greater suppression of bone remodelling than with hydrocortisone. A tendency towards insulin resistance induced by glucocorticoid treatment was also apparent. These observations provide a rationale for careful monitoring of skeletal status and carbohydrate metabolism for patients on glucocorticoid therapy. Treatment with dexamethasone was associated with the least favourable results. This may be dose related. However, the present findings support the use of hydrocortisone in low dose as replacement treatment for adrenal insufficiency.

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