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# The influence of hydrocortisone substitution on the quality of life and parameters of bone metabolism in patients with secondary hypocortisolism

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## Summary

**OBJECTIVE Hydrocortisone replacement regimes remain rather empirical and produce serum cortisol profiles very different from normal physiology. We have analysed the effects of different dosages of hydrocortisone (HC) replacement therapy on the health perception and general well-being of patients with secondary hypocortisolism. We also evaluated the effects of these regimens on bone metabolism.**

**DESIGN In a prospective randomized double-blind study, 3 groups of 3 patients were treated with 3 different dosages of HC (15, 20 and 30 mg/day), in different sequences, each sequence for two weeks.**

**PATIENTS Nine adult patients with complete secondary hypocortisolism.**

**MEASUREMENTS Serum cortisol, ACTH, aldosterone, renin, alkaline phosphatase, bone specific alkaline phosphatase, osteocalcin, PTH, C-telopeptides of type-I collagen, sodium, potassium, phosphate; urinary free cortisol, pyridinium cross-links, urine sodium, potassium and phosphate were measured at the beginning and after each week of the study.**

**For quality of life assessment the patients completed three different questionnaires, the Basler Befindlichkeits-Skala (BBS), the Befindlichkeits-Skala (Bf-S), the Beschwerde-Liste (BL) each week.**

**RESULTS With increasing doses of 15, 20 and 30 mg hydrocortisone a significant increase of free urinary cortisol was achieved (298 ± 26 nmol/day, 454 ± 43, 819 ± 59, respectively; $P < 0{\cdot}01$). The mean scores of the psychological questionnaires did not change significantly during the whole study (BBS 81·8 ± 3·9; 82·8 ± 3·9, 83·6 ± 3·9; Bf-S 15·9 ± 3·4, 11·3 ± 2·6, 12·5 ± 2·8; BL 15·7 ± 2·3, 14·4 ± 2·5, 14·8 ± 2·6, respectively). Osteocalcin decreased significantly (2·3 ± 0·49, 2·1 ± 0·42, 1·8 ± 0·38, $P < 0{\cdot}01$) with increasing HC doses but remained within the normal range. The other investigated parameters were within or nearly within the normal range in all patients at the beginning and did not change during the study.**

**CONCLUSION Dosages of 15, 20 or 30 mg hydrocortisone/day have equivalent effects on quality of life in patients with secondary hypocortisolism. With 15 or 20 mg hydrocortisone/day the patients feel nearly as well and content as normal healthy individuals. Since long-term treatment with a high replacement dose of glucocorticoids (hydrocortisone 30 mg/day) induces bone loss, this risk can be avoided with a substitution dosage of 20 mg or even 15 mg hydrocortisone/day, without influencing the well-being of the patient.**

Glucocorticoid (GC) substitution in patients with hypocortisolism is generally implemented according to a uniform, conventional treatment schedule; usually the daily dose is 25–30 mg of hydrocortisone (15/20 mg in the morning, 10 mg in the afternoon) or 37·5 mg cortisone acetat (25 mg in the morning, 12·5 mg in the afternoon) (Besser & Jeffcoate, 1976; Sönksen, 1990; Cuneo, 1995). These recommendations are based on the daily circadian rhythm of cortisol production rates in healthy subjects. Daily secretion rates of 12–15 mg/m$^2$ (Kenny *et al*., 1970; Peterson & Wyngaarden, 1956) and 16·2 ± 5·7 mg (Cope & Pearson, 1965; Zumoff *et al*., 1974) were measured with radioisotope analysis. However, new dilution/mass spectrometry examinations have shown that cortisol production is considerably lower (5·7 mg/m$^2$ equivalent to 9·9 ± 2·7 mg/day) (Esteban *et al*., 1991; Kerrigan *et al*., 1993). The optimal substitution dosage has therefore not yet been determined.

Generally sufficient substitution is monitored by the following variables: the hydrocortisone excretion in urine collected for 24 h and the concentration of sodium and potassium in serum (Loriaux, 1995). If the patient's condition and vitality is not impaired, the hydrocortisone dosage can be decreased to 20 or 15 mg per day (Oelkers, 1996).

Since we are aware of the danger of glucocorticoids inducing

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bone loss in men, we determined parameters of the bone metabolism (Lukert & Raisz, 1990; Canalis, 1996). We regarded alkaline phosphatase (AP), its bone specific isoenzyme (BAP) and serum osteocalcin as enzymatic markers of osteoblast activity, and urinary hydroxypyridinium crosslinks, pyridinoline (Pyr), and deoxypyridinoline (D-Pyr) and degradation products of C-terminal telopeptides of type-I collagen in serum (Crosslaps) as markers of bone resorption.

To our knowledge there has been no study to date which has analysed the effect of different dosages of hydrocortisone on patient's well-being and bone metabolism. Therefore, in a double-blind study, we gave patients with secondary hypocortisolism various doses of hydrocortisone and by monitoring subjective (patients' well-being) and objective criteria (urinary free cortisol, cortisol, electrolytes, aldosterone, active renin in plasma, blood pressure and parameters of bone metabolism) we aimed to identify the optimum substitution dosage and to detect possible metabolic influences of different dosages within the physiological range.

## Materials and methods

### *Patients*

We prospectively studied nine adults, mean age 44 years, range 23–60 years, 4 females (f, body weight 55–75 kg) and 5 males (m, body weight 61–124 kg) with complete secondary adrenocortical insufficiency after surgery of a nonsecretory (3 m), prolactin-secreting (2 f) and ACTH-secreting pituitary adenoma (1 f, 1 m), a craniopharygioma (1 m) and after hypophysitis (1 f). Morning serum cortisol concentrations were below 83 nmol/l (normal range 221–690 nmol/l) and after stimulation with corticotrophin releasing hormone or insulin tolerance test below 157 nmol/l (normal > 552 nmol/l) (Harsoulis *et al*., 1973; Schlaghecke *et al*., 1992). All patients had been on a constant replacement therapy for more than six months either with 15 mg (2 f), 20 mg (2 f, 2 m) or 25 mg (3 m) hydrocortisone per day in divided doses (2/3 in the morning, 1/3 in the afternoon) plus, if necessary, thyroid and/or gonadal hormone replacement therapy and/or desmopressin (AVP).

### *Study design*

In a 6-weeks randomized double-blind study (9 patients) 3 groups of 3 patients each were treated with hydrocortisone according to the following schedule: one group received 15 mg for the first two weeks, 20 mg the next two weeks and 30 mg the last two weeks; the second group received 30, 20, 15 mg, respectively, and the third group 20, 30, 15 mg, respectively. All additional medical treatment was not changed during the study. Before the study and on the last day of each week, the patients completed three different questionnaires (Basler Befindlichkeits-Skala, Befindlichkeits-Skala, Beschwerde-Liste); urine was collected for 24 h, blood pressure and weight were measured and blood was taken.

### *Quality of life investigation*

Emotional well-being and general health perception was assessed by 2 questionnaires, the Basler Befindlichkeits-Skala (Hobi, 1981) and the Befindlichkeits-Skala (Zerssen, 1976). They were initially developed for serial assessments of mood in longitudinal psychopharmacological studies and have become a standard measure for mood alterations in different clinical settings (Hürny *et al*., 1992; Kuhs *et al*., 1996). The subjective impairment due to physical symptoms was assessed by the Beschwerde-Liste (Zerssen & Koeller, 1976).

The Basler Befindlichkeits-Skala (BBS) is a self-rating polarity profile used for the examination of mood and psychological activity. It contains 16 items with a total sum score of 112 (range 16–112). Normal healthy subjects have high scores ($77{\cdot}6 \pm 1{\cdot}2$; Hobi, 1981), which are reduced in certain patient groups and increased with mood improvement.

The Befindlichkeits-Skala (Bf-S) is a one dimensional descriptive check-list for emotional well-being and mood. It contains 28 items with a total sum score of 56 (range 0–56). The scores have been found to be low in normal individuals ($12{\cdot}2 \pm 0{\cdot}2$; Zerssen, 1976).

The Beschwerde-Liste (BL) is a self-estimation scale which covers subjective impairment due to physical symptoms. It contains 48 items with a total sum score of 72 (range 0–72). Normal subjects have low scores ($14{\cdot}2 \pm 0{\cdot}3$; Zerssen & Koeller, 1976) and different patient groups increased scores.

### *Analytical methods*

Serum was assayed for cortisol by fluorescence polarization immunoassay (TDx, Abbott, Wiesbaden). The assay sensitivity was 18 nmol/l, the intra-and interassay coefficients of variation (CV) were 2·6% and 4·0%, respectively (at mean serum cortisol 428 nmol/l, $n = 10$). ACTH, PTH and renin (active molecule) were measured by immunoradiometric assays (Nichols, San Juan Capistrano, USA). The ACTH assay sensitivity was 1·1 pmol/l, the intra- and inter-assay CV were 2·3% (mean 30 pmol/l, $n = 10$) and 7·7% (mean 3·2 pmol/l, $n = 10$). The PTH assay sensitivity was 0·34 pmol/l, the intra- and inter-assay CV were 2·8% (mean 7 pmol/l, $n = 10$) and 6·9% (mean 23 pmol/l, $n = 20$). The renin assay sensitivity was 0·13 nmol/l, the intra-and interassay CV were 3·6% (mean 0·3 nmol/l, $n = 10$) and 4·8% (mean 0·3 nmol/l, $n = 10$). Serum was assayed for aldosterone and alkaline phosphatase, its bone-specific subunit (BAP, alkalase-B) by radioimmunoassay (RIA) (DPC, Biermann, Bad Nauheim,

Germany). The aldosterone assay sensitivity was 69·4 pmol/l, the intra- and inter-assay CV were 5·5% (mean 500 pmol/l, $n = 10$) and 6·2% (mean 441 pmol/l, $n = 10$). The alkalase-B™ assay sensitivity was 0·01 μkat/l, the intra- and inter-assay CV were 4·5% (mean 0·3 μkat/l, $n = 10$) and 7·6% (mean 0·59 μkat/l, $n = 12$). Osteocalcin was measured by RIA (Sorin Biomedica, France) with a sensitivity of 0·5 μg/l. The intra- and inter-assay CV were 2·4% (mean 5 μg/l, $n = 10$) and 7·8% (mean 5 μg/l, $n = 10$). Crosslaps were measured by an enzyme-linked immunosorbent assay (CrossLaps™, Osteometer Biotech, Denmark) with a sensitivity of 92·0 pmol/l. The intra- and inter-assay CV were 6·0% (mean 3500 pmol/l, $n = 10$) and 6·5% (mean 3501 pmol/l, $n = 12$).

Urine was tested for pyridinium cross-links by enzyme-immunoassay (DPC, Biermann, Bad Nauheim, Germany). The Pyr assay (Pyrilinks-II™) sensitivity was 7·5 nmol/l, the intra- and interassay CV were 4·1% (mean 66 nmol/l, $n = 20$) and 4·5% (mean 66 nmol/l, $n = 20$). The D-Pyr assay (Pyrilinks-D™) sensitivity was 1·1 nmol/l, the intra-and interassay CV were 6·0% (mean 46·0 nmol/l, $n = 10$) and 4·6% (mean 11 nmol/l, $n = 9$). The results were expressed as the ratio of pyridinium cross-links to creatinine (nmol Pyr or D-Pyr/mmol creatinine) to adjust for urine concentrations.

### *Statistics*

The results are expressed as the mean ± SEM. Undetectable hormone concentrations were expressed as the detection limit for statistical purposes. Due to the small group of patients a multivariant factor analysis could not be performed. To detect changes in the different variables of a single patient nonparametric statistics (Wilcoxen and Friedman test) were applied. A $P < 0·05$ was accepted as significant.

## Results

### *Baseline characteristics*

Before the study the urinary free cortisol (UFC) was in normal limits (147–535 nmol/day) in all patients. Also serum values of sodium, potassium and the blood pressure were in the normal range. The results of the three questionnaires were variable. They are summarized in Table 1.

### *Effects of different HC dosages on gluco- and mineralocorticoids*

UFC increased significantly ($P < 0·01$) with increasing dosages of hydrocortisone. The amounts were in the normal range (147–535 nmol/day) at 15 and 20 mg and elevated at 30 mg hydrocortisone/day (Fig. 1).

Morning serum cortisol concentrations were slightly above the normal range (221–690 nmol/l) at 15 and 20 mg and only increased significantly ($P < 0·01$) at 30 mg hydrocortisone/day. As a sign of secondary hypocortisolism ACTH was below the normal range during the whole study.

Renin was subnormal during the whole study. It was constant at 15 and 20 mg hydrocortisone/day (0·30 ± 0·06 nmol/l) and decreased distinctly, but not significantly to 0·21 ± 0·05 nmol/l at the 30 mg dose. Aldosterone was in the normal range at 15 mg HC/day (152 ± 30·9 pmol/l) and decreased at 20 mg and 30 mg hydrocortisone/day (87·3 ± 14·1 pmol/l and 86·2 ± 19·3 pmol/l).

### *Effects of different HC dosages on well-being and physical complaints*

The mean scores of the psychological questionnaires did not change significantly during the study (Table 2, Fig. 2).

**Table 1** Baseline characteristics of personal data, replacement therapy and scores of questionnaires

| Patient | Age (years) | Sex | Weight (kg) | HC therapy (mg/day) | UFC (nmol/day) | BBS score | Bf-S score | BL score |
|---|---|---|---|---|---|---|---|---|
| 1 | 42 | f | 56 | 20 | 199 | 58 | 46 | 31 |
| 2 | 57 | f | 75 | 15 | 276 | 107 | 2 | 4 |
| 3 | 49 | m | 62 | 25 | 488 | 78 | 10 | 28 |
| 4 | 60 | m | 75 | 20 | 317 | 94 | 7 | 8 |
| 5 | 48 | m | 95 | 20 | 226 | 90 | 5 | 36 |
| 6 | 58 | m | 124 | 25 | 386 | 92 | 3 | 11 |
| 7 | 24 | m | 82 | 25 | 361 | 98 | 5 | 1 |
| 8 | 41 | f | 71 | 15 | 3393 | 52 | 34 | 42 |
| 9 | 23 | f | 69 | 20 | 425 | 93 | 6 | 8 |
| Normal | | | | | 147–535 | > 77·6 | < 12·2 | < 13·3 |

HC, hydrocortisone; UFC, urinary free cortisol; BBS, Basler-Befindlichkeits-Skala; Bf-S, Befindlichkeits-Skala; BL, Beschwerde-liste; f, female; m, male.

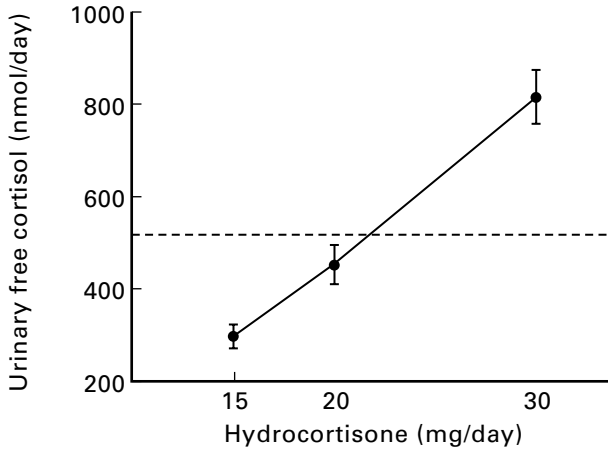


**Fig. 1** Urinary free cortisol over a period of 24-h at 15 mg, 20 mg and 30 mg HC/day in 9 patients. Data are shown as mean ± SEM; ----- Upper normal limit.

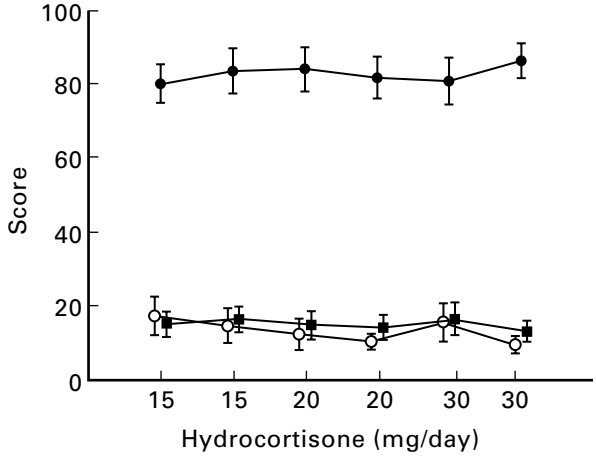


**Fig. 2** Sum scores of the questionnaires, Basler-Befindlichkeits-Skala (●), Befindlichkeits-Skala (○) and Beschwerdeliste (■) investigated the well-being and subjective impairment due to physical symptoms at 15 mg, 20 mg and 30 mg HC/day in 9 patients. (Scores of normal individuals: BBS 77·6 ± 1·2; Bf-S 12·2 ± 0·2; BL 14·2 ± 0·3). Datas are shown as mean ± SEM.

The scores of the BBS showed normal values all the time. While the Bf-S showed slightly impaired mode only at the lowest dosage of 15 mg hydrocortisone/day, the scores of the BL were slightly increased at 15 and 30 mg HC/day. This signifies that our patients had slightly more physical complaints than normal healthy subjects.

### *Effects of different HC dosages on parameters of bone metabolism*

Before and during the whole study AP was within the normal range and its subunit BAP at the lower level of the normal range (Table 3). Neither changed significantly. Osteocalcin was also within normal limits during the study, but decreased with rising amounts of HC. The change was significant between 15 mg and 30 mg HC/day ($P < 0{\cdot}01$), less significant between 20 mg and 30 mg HC/day ($P < 0{\cdot}05$).

**Table 2** Sum-scores of the three questionaires. Given as mean ±SEM

| Hydrocortisone (mg/day) | BBS | Bf-S | BL |
|---|---|---|---|
| 15 | 81·8 ± 3·9 | 15·9 ± 3·4 | 15·7 ± 2·3 |
| 20 | 82·8 ± 3·9 | 11·3 ± 2·6 | 14·4 ± 2·5 |
| 30 | 83·6 ± 3·9 | 12·5 ± 2·8 | 14·8 ± 2·6 |
| Normal individuals | 77·6 ± 1·2 | 12·2 ± 0·2 | 13·3 ± 0·3 |

BBS, Basler-Befindlichkeits-Skala; Bf-S, Befindlichkeits-Skala; BL, Beschwerdeliste.

The parameter for bone resorption, Pyr, was at the upper limit of the normal range and D-Pyr within the normal range. They did not change significantly during the whole study.

The Crosslaps were in the normal range. They changed slightly during the whole study, but independent of the hydrocortisone dosages.

Serum calcium and the urinary excretion of calcium were also in the normal range during the study.

### *Clinical and chemical data*

Clinical parameters (blood pressure, pulse and weight) and chemical variables (serum sodium, potassium and phosphate and the urinary excretion of sodium, potassium and phosphate) did not change significantly during the whole study.

## Discussion

An important consideration when determining the HC substitution dose in patients with secondary hypocortisolism is the patient's well-being and quality of life (Loriaux, 1995; Oelkers, 1996). The conventional dose is 25–30 mg hydrocortisone/day. Symptoms of GC deficiency are lethargy, gastrointestinal symptoms, weight loss, hypotension and hyponatraemia. Overdosage can lead to weight gain, muscle weakness, cardiovascular symptoms and osteoporosis (Cuneo, 1995).

The measurement of well-being and quality of life in a clinical setting is a difficult task depending on a variety of

**Table 3** Parameters of bone metabolism. Given as mean ±SEM

| HC (mg/day) | AP (U/l) | BAP ($\mu$kat/l) | Osteocalcin ($\mu$g/l) | Crosslaps (pmol/l) | S-Calcium (mmol/l) | Pyr (nmol/mmol creatinine) | D-Pyr (nmol/mmol creatinine) | U-Calcium (mmol/24 h) |
|---|---|---|---|---|---|---|---|---|
| 15 | 87·9 ± 6·9 | 0·21 ± 0·03 | 2·3 ± 0·49 | 1520 ± 331 | 2·3 ± 0·02 | 39·6 ± 5·5 | 5·4 ± 0·68 | 3·6 ± 0·72 |
| 20 | 87·3 ± 6·8 | 0·21 ± 0·03 | 2·1 ± 0·42 | 1680 ± 372 | 2·3 ± 0·02 | 36·5 ± 5·5 | 5·3 ± 0·85 | 3·3 ± 0·54 |
| 30 | 86·0 ± 5·8 | 0·21 ± 0·03 | 1·8 ± 0·38 | 1483 ± 263 | 2·3 ± 0·02 | 35·8 ± 3·9 | 5·1 ± 0·50 | 3·4 ± 0·46 |
| Normal | 55·0–170 | 0·19–0·73 | 1·8–6·6 | 302–7579 | 2·1–2·6 | 12·8–37·0 | 2·3–9·5 | < 6·2 |

HC, hydrocortisone; AP, alkaline phosphatase; BAP bone specific alkaline phosphatase; Pyr, urinary pyridinoline; D-Pyr, urinary deoxypyridinoline; S-Calcium, serum calcium; U-Calcium, urinary calcium.

medical, psychological and sociocultural factors (Häyry, 1991). To date there are no studies concerning well-being and physical strength during therapy with different amounts of hydrocortisone. Therefore we analysed general health perception in a randomized double-blind study using three questionnaires for self-rating which have been validated in normal individuals and different patient groups and are applicable for longitudinal studies (Hürny *et al*., 1992; Kuhs *et al*., 1996).

In our patients the sum scores of these three questionnaires did not change significantly over the entire period of the study and with different dosages of hydrocortisone. The patients' quality of life was hardly influenced by the different dosages of hydrocortisone. At the lower dose of 15 or 20 mg HC/day the patients' well-being was not impaired and the patients had no more complaints than with the conventional substitution dose of 30 mg HC/day.

It should be noted, however, that for statistical reasons of test power, the absence of significant differences should be interpreted with caution, due to the small number of observations in this study. It would be desirable to replicate the study with larger samples of patients for the above-mentioned statistical reasons.

Another important variable is the UFC (Warner, 1982; Trainer *et al*., 1991). Despite the short period of only 2 weeks for each dosage, we noted a significant increase of UFC under increasing amounts of hydrocortisone. The cortisol excretion at 15 and 20 mg/day were found within, and at 30 mg HC/day above the normal range. This suggests that a long-term dosage of 30 mg HC/day leads to elevated UFC.

It has been proven that GC influence bone metabolism (Canalis, 1996). As an enzymatic marker of the osteoblastic activity we measured AP and its bone specific isoenzyme BAP, neither showed any significant change during the time of our study. Processes associated with matrix formation are reflected by serum concentrations of osteocalcin; it is completely synthesized from the osteoblasts and is considered a highly specific marker of bone formation (Calvo *et al*., 1996). A decrease in serum levels of osteocalcin reflects depression of the osteoblastic function; this can be induced by an excess of GC (Peretz *et al*., 1989; Seibel & Raue, 1996; Pearce *et al*., 1998). One study showed that a dose reduction of hydrocortisone from 29·9 ± 1·2 to 20·8 ± 1·0 mg/day causes a significant increase of mean osteocalcin from 16·7 $\mu$g/l to 19·9 $\mu$g/l after a few weeks of treatment (Peacey *et al*., 1997). Studies on bone mineral density measurement have shown that long-term treatment with standard replacement dosages of GC (HC 30 mg/day) induces bone loss in men with Addison's disease (Zelissen *et al*., 1994). Adult patients with congenital adrenal hyperplasia (21-hydroxylase deficiency) showed a loss of bone mineral density during a substitution of more than 10–15 mg/m$^2$ HC/day (Jääskeläinen & Voutilainen, 1996).

Our study confirmed these findings, osteocalcin showed a slight but significant fall with increasing HC doses indicating the possibility of bone loss in our patients.

Markers for bone resorption are certain degradation products of the organic matrix: urinary hydroxypyridinium crosslinks. Pyr are present in bones, body and ligaments, whereas D-Pyr are mainly present in bones. Both components are specific parameters for the estimation of skeletal tissue state (Garnero *et al*., 1994). A further important parameter are the degradation products of C-terminal telopeptides of type-I collagen, crosslaps in serum (Bonde *et al*., 1997). Of the three markers, only the crosslaps showed a slight significant fluctuation, but independent of the increased amounts of HC.

In conclusion, our study shows that dosages of 15, 20 or 30 mg hydrocortisone/day have equivalent effects on quality of life in patients with secondary hypocortisolism. With 15 or 20 mg hydrocortisone/day patients feel nearly as well and content as normal healthy individuals. We would like to point out that the daily substitution dosage must be several times higher under increased physical or psychological stress. The

patient must be able to self-adjust the dosage under these circumstances. The measurement of urinary free cortisol is a meaningful marker for substitution adjustment and monitoring. Even though the study was carried out for only 6 weeks, we found decreasing osteocalcin values with increased amounts of hydrocortisone and this is a sign of osteoblastic function depression. Long-term treatment with a high replacement dose of GC (HC 30 mg/day) induces bone loss (Zelissen *et al*., 1994). Our study shows that this risk may be avoided with a substitution dosage of 20 mg or even 15 mg hydrocortisone/day, without influencing patient well-being.

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