Evaluation of markers of bone and collagen turnover in patients with active and preclinical Cushing's syndrome and in patients with adrenal incidentaloma

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Abstract
Although steroid-induced negative effects on bone and collagen have been well described in corticosteroid-treated patients, few studies have extensively evaluated bone and collagen turnover in patients with endogenous Cushing's syndrome. In this work serum bone-Gla protein (BGP), C-terminal cross-linked telopeptide of type I collagen (ICTP) and N-terminal propeptide of type III procollagen (PIIINP) levels were determined in patients with active (n = 12) and preclinical (n = 6) Cushing's syndrome, adrenal incidentalomas (n = 35) and in healthy controls (n = 28). In patients with overt Cushing's syndrome, serum BGP (0.9 ± 0.2 ng/ml), ICTP (2.7 ± 0.2 ng/ml) and PIIINP (1.9 ± 0.2 ng/ml) levels were significantly lower (P < 0.0001) than in controls (5.5 ± 0.2, 3.9 ± 0.2 and 3.2 ± 0.2 ng/ml respectively). In preclinical Cushing's syndrome, serum BGP (2.5 ± 0.8 ng/ml), ICTP (2.2 ± 0.1 ng/ml) and PIIINP (2.2 ± 0.2 ng/ml) levels were significantly lower than in normal subjects (P < 0.0001, P < 0.0001 and P < 0.02 respectively), being similar to those recorded in overt Cushing's syndrome. In patients with adrenal incidentaloma, serum BGP (4.2 ± 0.5 ng/ml) and ICTP (2.9 ± 0.2 ng/ml) levels were significantly lower than those found in controls (P < 0.05 and P < 0.001 respectively), while serum PIIINP levels (3.6 ± 0.2 ng/ml) did not differ from those of normals. In particular, 9/35 patients with adrenal incidentaloma had markedly depressed BGP levels (<2.0 ng/ml; mean 0.8 ± 0.1 ng/ml); all patients of this subgroup showed an exaggerated 17-hydroxyprogesterone increase after ACTH administration. In the same patients, serum ICTP (3.0 ± 0.4 ng/ml) and PIIINP (3.6 ± 0.2 ng/ml) levels did not differ from those found in the incidentaloma group. In conclusion, our study indicates that bone and collagen turnover are markedly affected in patients with overt and preclinical Cushing's syndrome. Although patients with adrenal incidentaloma do not show any signs or symptoms of overt hypercortisolism, the presence of reduced BGP and ICTP levels might be considered a further index of an 'abnormal' pattern of steroid secretion in some of them. As a consequence, the presence of early alterations in markers of bone turnover might be useful for selecting those patients who need more accurate follow-up of the adrenal mass.

European Journal of Endocrinology 138 146–152

Introduction
Histological studies of bone in patients with steroid-induced osteopenia have demonstrated both decreased formation rates and increased numbers of osteoclasts and resorption sites (1–3). Until now, the precise evaluation of bone formation and resorption processes and of collagen synthesis in patients with Cushing’s syndrome has been hampered by the lack of specific markers capable of revealing the more subtle modifications occurring in bone and collagen turnover.

In recent years, specific and reliable biochemical markers of bone formation/resorption (i.e. bone Glα-protein (BGP); C-terminal cross-linked telopeptide of type I collagen (ICTP)) and collagen synthesis (N-terminal propeptide of type III procollagen (PIIINP)) have been introduced to monitor the course of several metabolic and endocrine disorders (4–10).

While previous papers have reported the existence of some alterations of these markers in patients with untreated Cushing’s syndrome (8, 11, 12), little is known about their evaluation in other adrenal disorders. Owing to the availability of sensitive imaging techniques, silent adrenal masses have been more frequently detected (13). This has led to the finding of some hormonal alterations in many patients (14, 15) and to the recognition of the so-called ‘preclinical’ Cushing’s syndrome (14, 16, 17). As a consequence, a
continuous spectrum of steroid abnormalities has been described from patients with silent incidentaloma to preclinical and active Cushing’s syndrome.

This prompted us to evaluate serum BGP, ICTP and PIIINP levels in such conditions, with the aim of investigating the potential role of these markers in the detection of precocious alterations in bone and collagen turnover.

Materials and methods

Patients

Active Cushing’s syndrome Twelve patients with Cushing’s syndrome were studied; seven suffered from Cushing’s disease (six females, 21–38 years; one male, aged 28 years); two female patients (aged 28 and 34 years) had an adrenal adenoma; one woman (aged 31 years) showed ectopic adrenocorticotropic hormone (ACTH) secretion from a bronchial carcinoid; two patients (one man, aged 42 years; one woman, aged 46 years) had bilateral hyperplasia with hormonal data equivocal for either ACTH-dependent or ACTH-independent Cushing’s syndrome.

The diagnosis of Cushing’s syndrome was made on the basis of standardized clinical, hormonal and radiological criteria.

Preclinical Cushing’s syndrome Six patients (four males and two females, age range 42–74 years) with preclinical Cushing’s syndrome were studied. The main clinical features and baseline hormonal data for these patients are shown in Table 1.

The ‘preclinical’ condition was defined as the presence of an ‘incidentally’ detected adrenal mass in patients with no signs or symptoms of hypercortisolism, who showed normal baseline serum cortisol, high urinary free cortisol excretion (UFC), depressed levels of plasma ACTH, cortisol levels not adequately suppressed by overnight dexamethasone and loperamide tests, and absent or impaired response to corticotrophin-releasing hormone (CRH) stimulation.

Incidentaloma Thirty-five patients (25 females and 10 males, age range 34–73 years) with adrenal incidentaloma were studied. The main clinical features and baseline hormonal data for these patients are shown in Table 2.

None of the patients showed specific signs or symptoms of endocrine abnormalities, except for three (cases no. 1, 14 and 20) who had a ‘silent’ phaeochromocytoma. The adrenal masses were discovered by imaging techniques, performed for the evaluation of non-endocrine diseases.

Control group Data obtained from patients were compared with those recorded in an age- and sex-matched
Table 2 Some clinical and laboratory data on patients with adrenal incidentaloma.

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I, increased; N, normal; R, reduced.
control group (n = 28, aged 25–69 years), recruited among friends and colleagues.

No clinical and biochemical evidence of intestinal malabsorption, hepatic or renal disease, or parathyroid disorders were present. None of the subjects were taking any drugs known to affect mineral, bone or collagen metabolism, including anticonvulsants, barbiturates, sex hormones, sodium fluoride, supplemental calcium and vitamin D.

**Laboratory investigations**

Baseline serum BGP, ICTP, PIIINP, cortisol, 17-hydroxyprogesterone (17-OHP), plasma ACTH and 24 h UFC were determined in all patients.

Exogenous ACTH(1–24) (0.25 mg i.v.; Synacthen Ciba Geigy, Origgio, Italy) was injected into all patients with incidentaloma and into those with preclinical Cushing’s syndrome; serum cortisol and 17-OHP levels were measured before and after ACTH injection. A 17-OHP response, evaluated as ‘rate increase’ (17-OHP_{30–0}/30 min) greater than 0.197 nmol/l per min was considered as indicative of 21-hydroxylase deficiency (18).

The ACTH and cortisol response to CRH stimulation (1 µg/kg i.v.; ovine CRH, Novabiochem, Laufelfingen, Switzerland) was evaluated in 15 of 35 patients with adrenal incidentaloma, and in all patients with preclinical and overt Cushing’s syndrome. Plasma ACTH and serum cortisol responses were considered normal when their net increases were respectively greater than 4.4 pmol/l and 200 nmol/l.

Pituitary–adrenal suppressibility was assessed in all patients by measuring cortisol levels after an overnight dexamethasone suppression test (1 mg at midnight) and loperamide administration (16 mg, orally), as previously reported (19); the suppression was considered normal when serum cortisol fell below 140 nmol/l.

**RIA methods**

Serum BGP, ICTP and PIIINP levels were determined using commercial RIA kits (CIS Diagnostics, Saluggia, Italy, Orion Diagnostica, Espoo, Finland).

The intra- and interassay coefficients of variation were 3.5 and 5.0% for BGP; 5.2 and 5.7% for ICTP; 4.3 and 5.3% for PIIINP; the sensitivity was 0.5 ng/ml for BGP, 0.5 ng/ml for ICTP and 0.2 ng/ml for PIIINP.

Plasma ACTH (1 pmol/l = 4.5 ng/l) and serum cortisol (1 nmol/l = 0.362 µg/l) levels were measured on unextracted samples by IRMA and RIA methods (Nichols Institute, San Juan Capistrano, CA, USA and Diagnostic Products, Los Angeles, CA, USA respectively). The intra- and interassay coefficients of variation were 3.1–7.3% and 4.6–5.4% respectively. UFC excretion was measured after dichloromethane extraction by RIA (Diagnostic Products). RIA methods were used for measuring serum 17-OHP (Medgenix, Fleurus, Belgium). The intra- and interassay coefficients of variation were <10%.

**Statistical analysis**

All data are expressed as means ± standard error (s.e.). Student’s unpaired t-tests were calculated as appropriate; P values less than 0.05 were considered significant.

**Results**

***Active Cushing’s syndrome***

Mean BGP (0.9 ± 0.2 ng/ml), ICTP (2.7 ± 0.2 ng/ml) and PIIINP (1.9 ± 0.2 ng/ml) levels were significantly lower (P < 0.0001) in patients with active Cushing’s syndrome than in controls (5.5 ± 0.2, 3.9 ± 0.2 and 3.2 ± 0.2 ng/ml respectively), as shown in Figs 1 and 2; no significant differences in BGP, ICTP and PIIINP levels were found in relation to the different aetiologies.

***Preclinical Cushing’s syndrome***

Mean BGP (2.5 ± 0.8 ng/ml), ICTP (2.2 ± 0.1 ng/ml) and PIIINP (2.2 ± 0.2 ng/ml) levels of patients with

![Figure 1](https://example.com/figure1.png)

**Figure 1 (A)** Serum BGP levels in healthy controls (C) and in patients with adrenal incidentaloma (AI), preclinical Cushing’s syndrome (PCC) and active Cushing’s syndrome (CS). C vs AI: P < 0.05; C vs PCC: P < 0.0001; C vs CS: P < 0.0001; AI vs CS: P < 0.0001. (B) Serum ICTP levels. C vs AI: P < 0.001; C vs PCC: P < 0.0001; C vs CS: P < 0.0001; AI vs CS: not significant.
preclinical Cushing’s syndrome were significantly lower (P < 0.0001, P < 0.0001 and P < 0.02 respectively) than those recorded in controls, as shown in Figs. 1 and 2.

No differences in BGP, ICTP and PIIINP levels were found in patients with exaggerated (i.e. 17-OHP rate of increase greater than 0.197 nmol/l per min, as previously defined (14)) or normal 17-OHP response to ACTH.

Adrenal incidentaloma

Patients with adrenal incidentaloma showed significantly (P < 0.05 and P < 0.001 respectively) lower BGP (4.2 ± 0.5 ng/ml) and ICTP (2.9 ± 0.2 ng/ml) levels than controls, as shown in Fig. 1; on the other hand, serum PIIINP levels (3.6 ± 0.2 ng/ml) did not differ from those found in normals, as reported in Fig. 2.

Mean BGP and PIIINP values were significantly (P < 0.0001 and P < 0.05 respectively) higher in patients with adrenal incidentaloma than in patients with active Cushing’s syndrome, as shown in Figs 1 and 2.

It is worth noting that nine patients (cases no. 13, 17–19, 28–31, 35) showed markedly depressed BGP levels (<2.0 ng/ml; mean 0.8 ± 0.1 ng/ml), which were similar to those recorded in patients with overt Cushing’s syndrome. All these patients showed an exaggerated 17-OHP increase (0.57 ± 0.2 nmol/l per min) after ACTH administration; however, this mean value did not differ from that recorded in the remaining 16 patients who also had an augmented 17-OHP response (0.41 ± 0.08 nmol/l per min). In this subgroup of nine patients, serum ICTP (3.0 ± 0.4 ng/ml) and PIIINP (3.6 ± 0.2 ng/ml) levels did not differ from those of the whole group.

In patients with adrenal incidentaloma, baseline serum cortisol levels and UFC excretion did not differ significantly from those in normal subjects. Moreover, no significant correlations were found between basal cortisol or 17-OHP and BGP, ICTP and PIIINP levels.

Discussion

Steroid-induced effects on bone are well described in patients treated with high amounts of corticosteroids for long periods (20–24) and, although to a lesser extent, also during short-term treatment (25). Inhibition of osteoblasts, resulting in decreased work rate and active osteoblast lifespan, has proved to be the major alteration in patients treated with high doses of glucocorticoid (20, 26, 27).

However, bone and collagen turnover has not been extensively evaluated in patients with endogenous Cushing’s syndrome, probably because of the low prevalence of this condition.

Preliminary studies on endogenous Cushing’s syndrome reported a reduced BGP concentration, indicating low osteoblastic activity, which significantly increased after surgery in cured patients (8, 11). Recently, these results have been confirmed by Piovesan et al. (12), who demonstrated inhibitory effects on both osteoblastic activity and soft tissue collagen synthesis, as documented by the presence of reduced levels of PIIINP.

As far as bone resorption is concerned, few data are available on the steroid-induced effects on osteoclast activity in patients with endogenous Cushing’s syndrome. This is also true in patients with ‘preclinical’ Cushing’s syndrome (14, 16, 17), a condition that is increasingly recognized because of the wider availability of sensitive imaging techniques for detecting adrenal masses (13).

Similarly, in the present series, a marked reduction in BGP levels was found in patients with active Cushing’s syndrome, confirming the notion that osteoblastic activity is negatively affected by prolonged steroid excess. This finding is in line with observations that exogenous glucocorticoids depress BGP levels (23).

Although with an adequate overlap with the normal range, it is interesting to note that serum ICTP concentration was also significantly reduced. This result is in line with observations that exogenous steroids exert different effects on bone resorption depending on the duration of treatment (i.e. early stimulation after short-term therapy, decline with more prolonged administration) (28).

In endogenous Cushing’s syndrome, the existence of reduced resorption activity associated with an extremely low rate of bone formation might contribute to develop osteopenia deserving a specific treatment.

As far as collagen synthesis is concerned, the finding of reduced PIIINP concentration confirms the existence of reduced soft tissue collagen synthesis (12).

In patients with preclinical Cushing’s syndrome, BGP, ICTP and PIIINP levels are reliable indicators of early involvement of bone and collagen turnover before the onset of active Cushing’s syndrome.

Many patients with adrenal incidentaloma showed abnormal bone turnover, as indicated by the reduction in BGP and ICTP levels. Notably, markedly depressed
BGP concentrations were found in a subset of the above patients. In all these patients a heterozygous 21-hydroxylase deficiency was present, as indicated by an exaggerated 17-OHP response to ACTH, which is reported to be the most sensitive indicator of a minor enzyme deficiency (29). Since an untreated 21-hydroxylase deficiency is frequently associated with androgen excess, our finding of reduced BGP levels may be considered surprising, since the effects of these hormones favour bone formation. However, no excess androgen secretion was evident in our patients with heterozygous 21-hydroxylase deficiency. Four patients with adrenal incidentaloma, who had elevated BGP levels, were carefully considered; however, no clear differences were found in the clinical and hormonal data between these patients and those with normal or reduced BGP levels. Moreover, decreased bone turnover (i.e. reduced BGP, bone alkaline phosphatase, urinary cross-linked N-telopeptides of type I collagen levels) has been recently described in adult patients with congenital adrenal hyperplasia on long-term treatment with glucocorticoids (30).

The finding of decreased bone resorption in patients with adrenal incidentaloma and in those with congenital adrenal hyperplasia is in variance with a preliminary report by Osella et al. (31), who found increased ICTP levels in patients with adrenal incidentaloma.

In conclusion, the presence of early alterations in markers of bone turnover might be considered as a precocious sign of an ‘abnormal’ pattern of steroid secretion and therefore may be useful for selecting patients who need more accurate follow-up. Hence, their evaluation might be a complementary criterion for opting for a surgical approach in patients with preclinical Cushing’s syndrome.

Finally, the finding of reduced bone turnover in patients with incidentaloma, with or without small alterations in steroidogenesis, confirms that a ‘continuum’ of abnormalities exists from ‘silent’ adrenal masses to active adrenal Cushing’s syndrome.

Acknowledgements

This work was partially supported by Progetti di Ricerca Corrente, Istituto Auxologico Italiano, IRCCS, Milan, Italy.

References


Received 3 March 1997
Accepted 6 October 1997