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Clinical Investigations

Effective Therapy of Glucocorticoid-Induced Osteoporosis with Medroxyprogesterone Acetate

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Summary. The effect of long-acting medroxyprogesterone acetate (MPA) on the trabecular bone density in patients with glucocorticoid-induced osteoporosis (GCO) was evaluated. Thirteen steroid-dependent asthmatic male patients with GCO were administered 200 mg MPA intramuscularly at 6-week intervals and 1 g of elemental calcium daily for a period of 1 year. Ten additional matched steroid-dependent asthmatic male patients received 1 g of elemental calcium daily (controls). All 23 patients involved in the study had vertebral trabecular bone densitometry (TBD) by quantitative computed tomography (QCT) at baseline and at 6 and 12 months into the study. A 17% increase in TBD was found in the MPA-treated patients at 1 year (from 68.5 ± 5 to 80.2 ± 4 mg K_2HPO_4/cc) in contrast to the control group who experienced a 21% decrease in TBD during the same period of time (from 80.5 ± 7 to 63.7 ± 8 mg K_2HPO_4/cc) ($T = 6.90$, $P = 0.0001$ df = 21). There were no significant changes in other parameters followed during the study in the MPA-treated group (serum calcium, phosphorus, magnesium, PTH, alkaline phosphatase, triglycerides, total and HDL cholesterol, urinary excretion of calcium, phosphate, creatinine) except for a decrease in the serum luteinizing hormone (LH) and testosterone ($P < 0.01$) as well as of the hydroxyproline-creatinine ratio ($P < 0.01$). The results lend support to the hypothesis of a progesterone-glucocorticoid competitive antagonism at the bone level, though other possibilities can be entertained, and suggest MPA as an effective therapy for glucocorticoid-induced osteoporosis in men.

Key words: Glucocorticoid-induced osteoporosis — Progestins — Trabecular bone density.

Among the osteoporoses secondary to various drugs, the variety induced by chronic pharmacologic doses of glucocorticoids is the most frequent, severe, and disabling. Glucocorticoid (GC) drugs are widely prescribed for the treatment of conditions such as bronchial asthma and connective-tissue diseases. It has long been recognized that chronic GC therapy can result in significant loss of bone mass [1–4] in both men and women [5]. Current data indicate that the average risk of fracture, as measured by loss of bone mass, increases with the duration [5] and cumulative doses of GC therapy [6, 7]. The majority of patients on chronic GC therapy will develop osteoporosis, and over 50% will experience a fracture [8]. In spite of numerous attempts to overcome this undesirable side effect of chronic GC therapy [5, 9–15], the prevention and/or correction of GC-induced osteoporosis (GCO) remains a severe therapeutic problem [16].

The well-established inverse relationship between bone mass and the fracture risk suggests that increasing an individual's bone mass is likely to reduce the risk of developing pathologic fractures [5].

Bone cells contain specific cytoplasmic receptors

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for GC [17] and probably for progesterone [18]. A suggestión of a common receptor for GC and progesterone was also made [19]. There is evidence indicating the following factors: First, progesterone competes effectively with cortisol and dexamethasone for GC receptors in bone cells [19, 20], and it is possible that progesterone may function as a GC antagonist, as it has been shown in other systems [21, 22]. The decline in progesterone secretion at the menopause by approximately 60% [23] may allow GC to act fully on bone [24]. The observation that rapid bone losers, as compared to slow losers, have significantly lower levels of serum progesterone but not serum estrogens [25], suggests the importance of cortisol/progesterone interaction.

Second, progesterone stimulates calcitonin secretion from the C-cells of the thyroid gland [26]. Calcitonin promotes intestinal calcium absorption, stimulates the osteoblasts, and is a potent inhibitor of the osteoclasts [27].

These considerations led us to examine the possibility that medroxyprogesterone acetate (MPA), a 17 alpha-hydroxyprogesterone derivative progestin, by antagonizing the GC effect on bone, and by inhibiting the osteoclasts through its effect on calcitonin secretion, could produce an increase in bone density in GCO patients on chronic GC therapy.

Materials and Methods

Patients

Twenty-three Caucasian male patients with steroid-dependent bronchial asthma, of similar age (average: 66 ± 4 years) and glucocorticoid dosage (10–20 mg prednisone/day for over 1 year; mean duration of therapy = 22 months; mean glucocorticoid dosage = 16 mg/day) were enrolled in the study, following signing an informed consent. Of these, 10 randomly selected subjects formed the control group, and were administered 1 g elemental calcium daily for 1 year. The other 13 patients enrolled in the study received 1 g elemental calcium daily plus 200 mg MPA intramuscularly every 6 weeks. All study patients had initial trabecular bone densitometry (TBD) of the lumbar vertebrae by single energy quantitative computed tomography (QCT) which was repeated at 6-month intervals during the study. A phantom was used for calibration. Precision error for repeated QCT measurements was 4–5%. The measurements were made in the first four lumbar vertebrae, unless a compression fracture was present in one of the vertebrae, in which case the vertebra was excluded. One of the treated group patients (No. 1) had a vertebral compression fracture before the initiation of the study. None of the treated patients experienced compression fractures during the study period. Two control patients had each a vertebral compression fracture before (Nos. 16 and 23) and one experienced a vertebral compression fracture during the study period (No. 17).

Fasting serum samples were collected initially (baseline), and at 6-week intervals thereafter, for the measurement of calcium, phosphate, magnesium, immunoreactive parathyroid hormone (PTH), alkaline phosphatase (AP), luteinizing hormone (LH), testosterone, triglycerides, high density lipoprotein (HDL)-cholesterol and total cholesterol. Twenty-four-hour urines were collected before (baseline) and at 6-week intervals during the study for the measurements of calcium, phosphate, hydroxyproline, and creatinine. Only baseline serum and urinary measurements were performed in the control group.

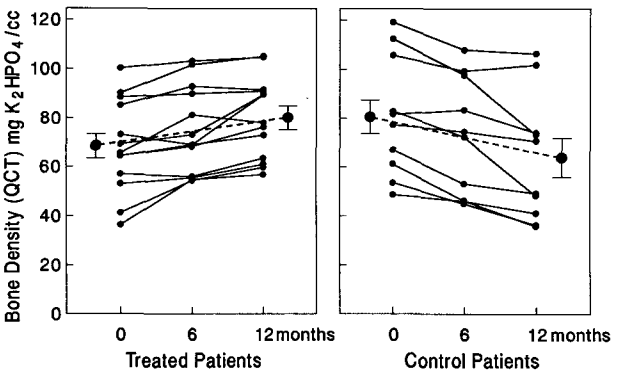


Fig. 1. Change in trabecular bone density of glucocorticoid-induced osteoporosis patients following medroxyprogesterone acetate therapy, as compared to the control group (T = 6.90; P = 0.0001; df = 21).

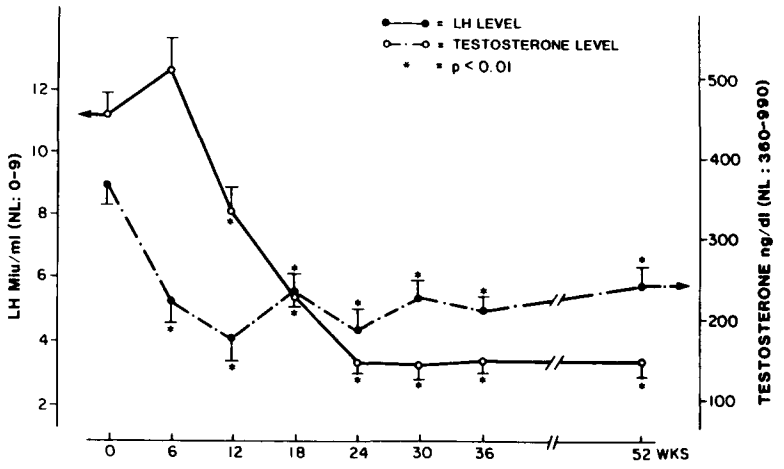
Serum calcium, phosphate, magnesium, and alkaline phosphatase activity, as well as urinary calcium, were measured by automated colorimetric methods using a SMAC Technicon Autoanalyser (Techicon, USA). Urinary phosphate was measured on Technicon RA-1000 using a colorimetric method in a commercial laboratory (International Clinical Laboratory—Western). Urinary hydroxyproline was measured using column extraction and spectrophotometry (Smith Kline Laboratory). Testosterone and LH measurements were performed by radioimmunoassay in a commercial laboratory (International Clinic Laboratory—Western). PTH was measured by a midregion PTH radioimmunoassay [28] in the Calcitropic Hormone Reference Laboratory, U. C. San Francisco. Cholesterol, HDL cholesterol, and triglycerides were measured by enzymatic methods using a SMAC Technicon Autoanalyser (International Clinical Laboratory—Western).

Statistical analyses were performed using the Student's t test. Results are expressed as means ± SEM.

Results

At the end of 1 year, the MPA-treated patients have shown an average of 17% increase in their TBD (from 68.5 ± 5 to 80.2 ± 4 mg K_2HPO_4/cc), whereas the control group experienced on average of 21% decrease in their TBD during the same period (from 80.5 ± 7 to 63.7 ± 8 mg K_2HPO_4/cc) (Fig. 1). These findings were statistically highly significant (T = 6.90; P = 0.0001; df = 21). Three of the MPA-treated patients followed on this treatment for 2 years have continued to gain in TBD.

There were no significant changes during the treatment period in the serum levels of calcium, phosphate, magnesium, PTH, alkaline phosphatase, total and HDL cholesterol, and triglycer-



LH and Testosterone Blood Levels During Medroxyprogesterone and Calcium Therapy

Fig. 2. LH and testosterone levels during medroxyprogesterone and calcium therapy.

ides. In contrast, both LH and testosterone levels fell significantly ($P < 0.01$) during the treatment period and remained low for the duration of the study (Fig. 2).

The 24-hour urinary excretion of calcium and phosphate did not change significantly during the study (Table 1). The urinary total hydroxyproline/creatinine ratio, though, showed a gradual decline that reached statistical significance after the first 6 months of MPA treatment ($P < 0.01$) (Fig. 3).

No significant differences were found between the baseline values of the serum or urinary parameters measured in controls vs. MPA-treated patients.

Discussion

The significant increase in the TBD of the GCO patients on chronic GC during one year of MPA therapy, as shown in our study, lends support to the hypothesis of a progesterone-glucocorticoid competitive antagonism at the bone level [19, 20]. It is thus possible that progesterone (MPA) may antagonize and effectively block the known inhibitory effect of glucocorticoids on the osteoblast function [29–30] leading probably indirectly to an increase in bone formation (progesterone itself, though, has been shown, in vitro, to inhibit the osteoblast [31]).

The lack of an increase in serum alkaline phosphatase during MPA administration in our patients does not invalidate the above hypothesis, considering its nonspecificity to the osteoblast function [32]. The bone isoenzyme of alkaline phosphatase, a specific osteoblast product [33] was not measured. Interestingly, there was no evidence of progesterone-glucocorticoid antagonism at the bronchial level in these steroid-dependent asthmatic patients: their prednisone requirements and pulmonary status remained essentially unchanged during the MPA therapy.

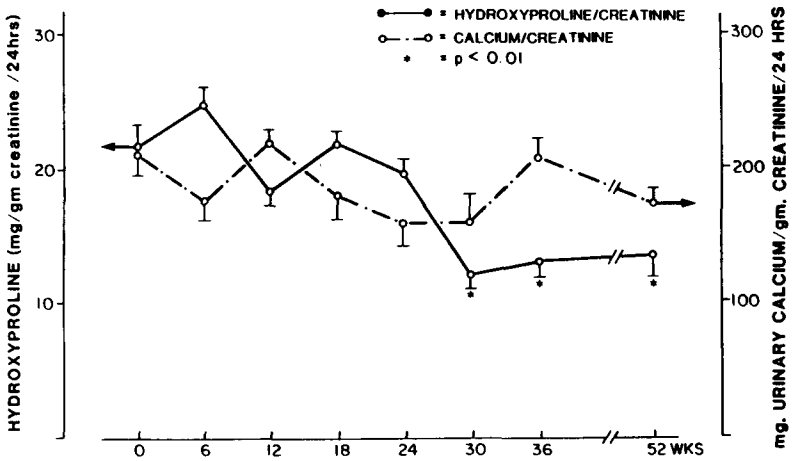
The gradual decline in the hydroxyproline/creatinine ratio during the study suggests a decrease in bone resorption, possibly following progesterone-stimulated calcitonin production [26] with consequent osteoclast inhibition [27]. Another possible explanation for this finding could be the PTH inhibition by the daily calcium administration, with the correction of the postulated secondary hyperparathyroidism in the pathogenesis of GCO [10, 34–36]. We did notice a slight decrease in the serum PTH levels in our patients during the study, but it did not reach statistical significance.

The decrease in serum LH and testosterone levels in our subjects during MPA therapy was expected, considering previous data in the literature [37]. Directly [38] or indirectly, by modulating the secretion rate of, or the target cell sensitivity to calcitonin [39, 40], testosterone seems to have a role in bone metabolism: hypogonadal males may develop secondary osteoporosis [41, 42]. Our study patients had a baseline testosterone in the low normal range (367 ± 25 ng/dl) and an elevated LH level (10.13 Miu/ml) suggesting a primary hypogonadism, likely induced by the known serum testosterone lowering effect of pharmacologic doses of glucocorticoids [43–45]. The patients were also sexually dysfunctional. The further lowering of the serum testosterone levels to the clear hypogonald range (215 ± 25 ng/dl) under MPA therapy did not significantly worsen their sexual dysfunction and, obviously, did not prevent the increase in TBD. It is possible,

Table 1. Individual data of patients with GCO, treated (1–13) and controls (14–23)

TBD				Serum										Urine			
				Testosterone		LH		Calcium		PTH		A. phosph.		Calcium		H.Pr.	
Case	0	6	12 mo.	0	1 yr	0	1 yr	0	1 yr	0	1 yr	0	1 yr	0	1 yr	0	1 yr
1	41.3	54.4	59.8	320	170	9.6	1.0	9.4	8.8	38	34	64	63	363	255	19.1	10.7
2	65.7	81.3	78.1	230	88	9.9	3.8	9.0	8.9	52	43	72	46	148	230	18.9	11.0
3	100.5	103.4	105.0	530	350	6.3	3.1	9.5	8.9	35	35	78	60	257	245	28.6	19.0
4	90.4	102.0	105.4	680	410	11.1	2.6	9.1	9.0	50	32	66	59	125	95	30.1	15.6
5	36.3	54.8	56.39	360	300	13.3	2.7	9.5	9.6	69	61	54	45	317	229	17.0	17.0
6	57.1	56.1	63.6	210	65	14.3	1.3	9.9	10.1	86	63	88	63	261	201	15.0	11.1
7	53.1	55.7	61.2	525	216	9.2	2.9	8.9	9.3	36	29	105	110	210	301	17.5	15.9
8	85.4	93.1	91.8	471	350	7.0	2.8	9.9	9.1	37	54	67	70	315	300	15.6	10.1
9	73.2	69.1	89.97	450	214	8.1	5.9	9.8	10.2	52	62	119	90	370	205	15.0	18.0
10	64.5	68.44	76.33	342	185	11.5	4.5	9.3	8.6	58	40	60	58	121	160	31.0	15.0
11	64.5	69.0	73.1	420	340	10.2	3.6	9.6	9.2	62	56	39	42	430	378	18.0	16.0
12	88.75	90.1	91.21	340	234	10.6	0.9	9.6	9.5	32	30	56	39	176	248	17.0	13.0
13	69.3	73.2	89.97	280	160	12.6	4.2	9.4	9.0	65	35	54	52	472	285	35.0	12.6
Average:	68.5 ± 5	74.7 ± 5	80.2 ± 4	396	237	10.3	3.0	9.4	9.2	52	44	71	61	274	241	21.0	14.2
14	53.6	45.0	36.21	402		9.1		9.2		45		55		405		35.0	
15	83.0	72.3	48.3	281		11.2		9.0		38		50		275		62.5	
16	67.1	53.1	49.2	388		10.9		8.6		48		61		252		27.0	
17	81.7	83.5	73.9	366		9.8		9.1		44		70		310		31.5	
18	105.8	99.4	101.8	424		9.2		9.1		41		41		320		38.0	
19	112.5	97.8	73.2	375		8.1		9.3		40		29		282		27.3	
20	119.3	108.0	106.48	512		5.0		8.9		44		72		310		19.0	
21	61.39	46.4	35.8	265		7.9		9.0		36		55		205		31.9	
22	77.3	74.5	70.69	372		11.6		9.0		52		48		425		43.0	
23	48.76	46.0	41.18	210		10.4		8.8		56		63		291		15.6	
Average:	80.5 ± 7	72.6 ± 7	63.7 ± 8	359		9.3		9.0		44		54		307		31.9	

Normal ranges: TBD >140 mg K_2HPO_4/cc; Serum testost.: 270–1070 ng/ml; LH: 1.5–9.2 Miu/ml; Serum Ca^{2+}: 8.9–9.5 mg%; S. alk. phosph.: 30–105 U/liter; PTH <40 μleq/ml; Urinary Ca^{2+}: <250 mg/24 hr; Urinary hydroxyproline (total): 15–45 mg/24 hr



Urinary Total Hydroxyproline/Cr. and Calcium/Cr./24hrs During Medroxyprogesterone and Calcium Therapy

Fig. 3. Urinary total hydroxyproline/creatinine and calcium/creatinine/24 hours during medroxyprogesterone and calcium therapy.

though, that the rate of the observed increase in TBD would have been higher in the presence of normal serum testosterone levels. In order to clarify this possibility, we intend to administer replacement doses of long-acting testosterone preparation to our subjects in a second phase of the study, and compare the rates of TBD gains with those obtained in the first phase, presented in this paper.

There is evidence in the literature suggesting a lack of risk for dyslipidemia in patients treated with MPA [46, 47]. Similarly, in our study patients we found no significant changes in the serum levels of HDL and total cholesterol, nor in the triglyceride levels.

In conclusion, administration of injectable long-acting MPA seems to reverse the progression of the glucocorticoid-induced osteoporosis in steroid-dependent asthmatic male patients, while on prednisone therapy of 10–20 mg/day, as reflected by a gradual increase in their TBD. Though the mechanism of this MPA action is not clear, the possibility of a competitive progesterone-glucocorticoid antagonism at the bone cell receptor level, as well as a progesterone-stimulated calcitonin production, are factors to be considered. Finally, further work concerning MPA effects on intestinal calcium absorption, osteoblast function, and calcitonin production in patients on GC therapy is required.

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