Reversibility of exogenous corticosteroid-induced bone loss

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ABSTRACT: Osteoporosis is not usually considered to be reversible, as it is a consequence of the ageing process. However, an improvement of bone mineral density after successful surgery in Cushing’s syndrome has been shown in several reports. The question of reversibility of exogenous corticosteroid-induced osteoporosis is, as yet, unanswered, possibly because of the difficulty in discontinuing steroids after long-term use.

We describe six patients, all under 45 yrs of age, with chronic long-standing sarcoidosis, in whom long-term prednisone therapy resulted in 15±7% bone loss, as evaluated by quantitative computed tomography.

This side-effect appeared fully reversible after prednisone withdrawal. This report of the reversibility of exogenous corticosteroid-induced bone loss needs confirmation in elderly people, where the capacity for recovery of bone mass could be reduced. Such potential for recovery may have implications for the pattern of use of corticosteroids.


Osteoporosis is not usually considered to be reversible, as it is a consequence of ageing. However, the question of reversibility of exogenous corticosteroid-induced osteoporosis is as yet, unanswered since the effect of discontinuing steroid treatment on the course of osteoporosis has never been studied, possibly because of the difficulty in discontinuing steroids after long-term use.

A number of observations [1-4] have shown a quantitative improvement of bone mineral density after successful treatment of Cushing’s syndrome. However, patients receiving exogenous steroids differ from those with endogenous Cushing’s syndrome, because the diseases for which they are administered, either intermittently or for long-term use, may themselves predispose to osteoporosis [2, 5]. Hence, the reversibility of exogenous corticosteroid-induced osteoporosis still needs confirmation. We describe six patients with chronic long-standing sarcoidosis, in whom improvement of vertebral cancellous mineral content (VCMC) has been shown after discontinuation of corticosteroid therapy. To our knowledge this is the first report on the reversibility of bone changes induced by exogenous corticosteroids.

Patients

The aim of the study was to evaluate the reversibility of exogenous corticosteroid-induced mineral loss through periodic evaluation of VCMC. All sarcoid patients, with precisely defined characteristics seen in the last six years, were prospectively studied.

Criteria of inclusion

1) histologically proven sarcoidosis;
2) long-term prednisone therapy; we only treat patients with sarcoid activity plus functional impairment, evaluated according to a diagnostic work-up, including serum angiotensin-converting enzyme (ACE) and β2-microglobulin, calciuria (24 h), total body 67Ga-scan, bronchoalveolar lavage (BAL), pulmonary function, chest X-ray, and other tests when appropriate in relation to the individual case [6];
3) bone mineral loss at the end of prednisone therapy. Only patients with Z score (measurement of trabecular mass) arbitrarily chosen ≤-1.2 at the end of therapy were included. We have shown that bone mineral loss occurs only in 70% of sarcoid patients treated with steroids [7];
4) prednisone withdrawal as clinically unnecessary;
5) further control of VCMC at least six months after prednisone withdrawal.

Criteria of exclusion

1) conditions or diseases, different from sarcoidosis, able to induce bone mineral changes, evaluated by clinical and laboratory tests when appropriate;
2) patients treated with non-steroid drugs (calcium, oestrogens, calcitonin, etidronate etc.), able to induce bone mineral changes.

Over 400 patients with histologically proven sarcoidosis have been seen in our clinic in the last six years. One hundred and twenty (30%) needed long-term corticosteroid therapy; only six patients met our criteria of inclusion.

Methods

VCMC was measured as described previously [8-10], using a Siemens Somaton 2CT scanner through tomograms taken on lumbar vertebrae (L1, L2, L3, L4). The measurements had a precision of 1.7% and a mean accuracy of 3% (for K2HPO4 solutions of the phantom). Normal values for the patient's sex and decade of age (mean±SD) have been previously reported in 190 normal subjects [7].

For each patient the values for trabecular mass have been expressed as Z score [11].

The values of VCMC have also been expressed in terms of mineral loss (ML) in respect of the initial value, according to the formula:

$$ML\% = 100 \times \frac{(VCMC_{\text{final}} - VCMC_{\text{initial}})}{VCMC_{\text{initial}}}$$

Where ML% = mineral loss percent occurred in a given period, $VCMC_{\text{initial}} = VCMC$ at the beginning of the period, $VCMC_{\text{final}} = VCMC$ at the end of the period.

A similar formula was used for evaluating the mineral gain (MG%) after prednisone withdrawal.

Results

Six patients with histologically proven sarcoidosis were treated with prednisone as indicated in table 1.

All patients had a good response to prednisone, when it was required for the period and at the dosage indicated in table 1 and figure 1. No relapse was observed after prednisone withdrawal.

When starting corticosteroid therapy, disease had been known between 1 and 23 months; in patients nos. 2 and 3, disease had probably gone unrecognized for a long time because it was asymptomatic; long-standing untreated sarcoidosis, resulting in mineral loss [12], probably accounts for their low Z scores (-1.5 and -4.4, respectively) when starting corticosteroid therapy. Patient no. 3 also had high levels of 1,25-dihydroxy vitamin D (1,25(OH)2D3) and hypercalciuria due to sarcoidosis; when his VCMC dropped below 100 mg·cm-3 K2HPO4 eq, we prescribed calcitonin, but the patient discontinued the drug after one week due to side-effects (flushing).

In patients nos. 5 and 6 computed tomography (CT) was not performed before corticosteroid therapy. Patient no. 5 had been studied in our clinic in the years 1981-1985, when CT was not yet available. Patient no. 6 reached our clinic when therapy had already been given elsewhere for 19 months without bone controls. For these two patients, demonstration that corticosteroid therapy resulted in a clear mineral loss is lacking. However, at the end of corticosteroid therapy their Z score (-1.7 in both) also indicated mineral loss: the exclusion of other causes of bone loss, and the mineral gain observed after therapy withdrawal, suggest that prednisone has most probably been the very likely cause of their mineral loss.

After a period varying between 16-49 months, prednisone therapy could be discontinued without relapse in all six patients, and we could follow them for another period.

Prednisone was given for a mean period of 25±11 months, at the mean daily dosage of 15±7 mg. The above mean values are for 6 patients, while initial Z score was known for 4 patients only; their Z score averaged -1.8±1.6 before corticosteroid therapy and

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Disease duration</th>
<th>Initial Z score</th>
<th>During therapy*</th>
<th>After prednisone withdrawal Z score</th>
<th>Period without therapy ML%</th>
<th>After prednisone withdrawal MG%</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>24</td>
<td>7 yrs</td>
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<td>14 yrs -1.4</td>
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<tr>
<td>2</td>
<td>M</td>
<td>35</td>
<td>&gt;12 yrs</td>
<td>-1.5</td>
<td>-2.1</td>
<td>25 yrs -1.5</td>
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<td></td>
</tr>
<tr>
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<td>M</td>
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<td>&gt;7 yrs</td>
<td>-4.4</td>
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<td>12 yrs -4.8</td>
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<td>M</td>
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<td>-1.7</td>
<td>-1.7</td>
<td>16 yrs -0.5</td>
<td>25 yrs</td>
<td></td>
</tr>
</tbody>
</table>

*: Results in brackets are at the time of prednisone withdrawal. ML: mineral loss; MG: mineral gain, in respect to therapy withdrawal vertebral cancellous mineral content; m: months; >: indicates the disease had gone unrecognized for many months or years before; -: data not available.
Discussion

For evaluation of the reversibility of corticosteroid-induced bone loss, our model of sarcoïdosis could be subject to criticism. When this disease has been present for at least 20 months, it may result in a mild trabecular bone loss [12], so that it may be difficult to distinguish (as in patient no. 5) bone loss due to corticosteroids from that caused by sarcoïdosis. However, corticosteroid-induced bone loss may be rapid and severe [13], and thus far more important with respect to a possible concomitant mild sarcoïdosis-induced bone loss. The reason why sarcoïdosis may result in osteoporosis is not known; we recently presented three hypotheses [12].

The significant corticosteroid-induced decrease in serum osteocalcin [14-16] suggests that steroids may reduce the activity of bone-forming osteoblasts. Thus, osteocalcin could be regarded as a marker of separate sarcoïdosis-induced and steroid-induced bone loss in future prospective studies.

Bone loss due to the action of sarcoïdosis itself was probably larger when patients needed therapy than after withdrawal. Although this may be regarded as a bias of our study, the sarcoïd-induced bone changes are probably much smaller than corticosteroid-induced bone changes.

Other disease (or models) needing long-term corticosteroid therapy, such as rheumatoid arthritis, lupus erythematosus or chronic obstructive lung disease, probably predispose to more severe bone loss and, moreover, steroids may be more difficult to discontinue. Ideally, a normal population should be studied. For obvious ethical reasons, long-term corticosteroid drugs cannot be given to normal volunteers, but have been given for a brief period of one month [17].

We also admit that only a small number of patients have been studied. However, the difficulty of selecting a population with the described inclusion criteria is probably the main reason why this type of study, has not been reported previously.

An overestimation of the increase in VCMC following steroid withdrawal, could arise due to regression towards the mean; nor can an underestimation be excluded. Since, however, the increase in VCMC has always been greater than the stated accuracy (3%), the described effect appears indeed to be a real one. Moreover, the observed rise of VCMC is of the same magnitude (20%) reported in the studies [2-4] on Cushing’s patients.

Glucocorticoids may induce osteopenia, mainly through the following mechanisms [13, 18-20]: a) direct inhibition of osteoblastic replication and differentiation; and b) indirect stimulation of bone resorption: corticosteroid-reduced absorption of dietary calcium and increased calcium loss in urine, due to reduced tubular reabsorption, have both been invoked to explain the mild degree of hyperparathyroidism of many patients chronically treated with glucocorticoids.

High levels of 1,25-dihydroxyvitamin D and of 24h urine calcium are markers of sarcoïd activity, and may return into the normal range with appropriate corticosteroid therapy, in spite of the corticosteroid-induced hypercalciuria [20]. Five of our six patients had hypercalciuria, which disappeared when therapy was given.

Trabecular bone loss may be due to trabecular perforations or to a negative bone balance at the level of cells participating in the remodelling process. In type I (postmenopausal) and in type II (age-related) osteoporosis, a negative balance at the remodelling site results in perforations and loss of trabeculae [21-23]. Corticosteroid-induced osteoporosis is more likely to be reversible because only a thinning, with less destruction of trabeculae and without major perforations, occurs [24, 25]. Moreover, corticosteroid withdrawal could normalize the corticosteroid-induced hyperparathyroidism, thereby reducing the activation frequency, which is the main regulator of the remodelling space [26].

Conclusion

Our results suggest that when the cause of mineral loss is removed, the bone is able to return to its previous mineral content. This reversibility has been seen in our patients, all under 45 yrs of age, but needs confirmation in elderly people, where the capacity for recovery of bone mass could be reduced. Such potential for recovery could have implications for the pattern of use of exogenous corticosteroids, at least in younger persons.
CORTICOSTEROID-INDUCED BONE LOSS REVERSIBILITY

References


