

## Steroid-induced osteoporosis – a cause for concern?

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### INTRODUCTION

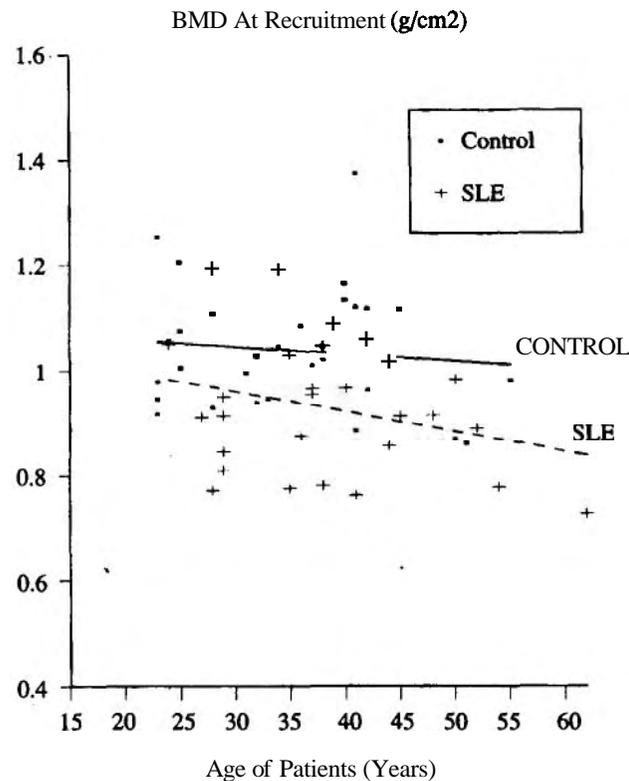
**Cushing**, in 1932, first reported the increased tendency to fracture in patients with hypercortisolism due to bilateral adrenal **hyperplasia** resulting from **ACTH-producing** pituitary adenomas.<sup>1</sup> Because of the relative rarity of the disease, the problem of glucocorticoid-induced osteoporosis (GIO) was not of significance until the next decade when cortisone was introduced as a therapeutic agent. This was followed by case reports of vertebral fractures indicating that exogenous hypercortisolism was also deleterious to the **skeleton**.<sup>2</sup> It soon became apparent that prolonged exposure to corticosteroids led to decreased bone **mass**.<sup>3,4</sup>

Today, with the widespread use of glucocorticoids in the management of numerous chronic medical conditions, it is increasingly

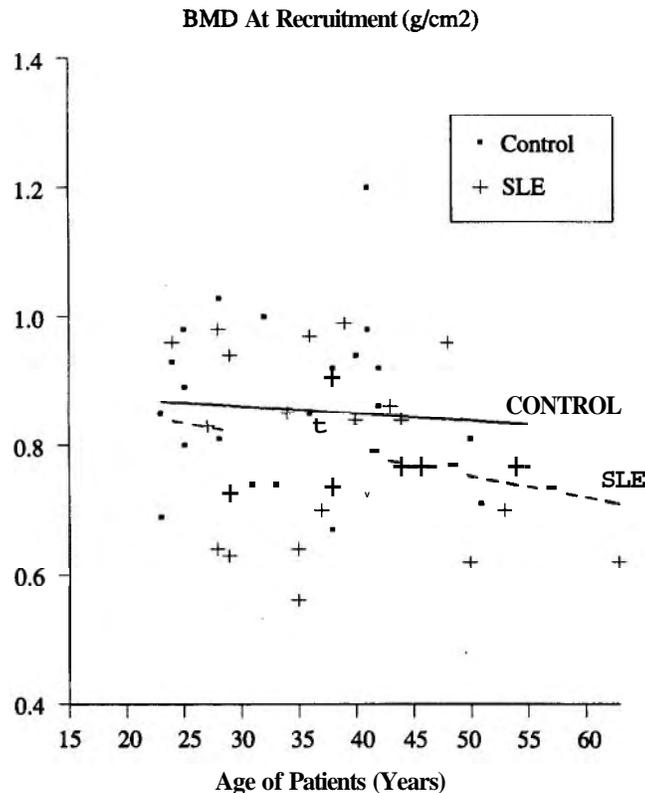
being recognised that osteoporosis is one of the more important side effects of long term glucocorticoid therapy. The true incidence of osteoporosis in patients on long term glucocorticoids is unknown. It is estimated that 50% of patients requiring prolonged glucocorticoids develop osteoporosis<sup>5</sup> and 30-50% of patients will suffer from fragility **fractures**.<sup>6,7</sup> Vertebral fractures are reported to be 4 to 5 fold more prevalent in patients with **GIO**,<sup>8,9</sup> whilst the incidence of appendicular fractures is **doubled**.<sup>10,11</sup>

### PATHOPHYSIOLOGY

A review of the literature on **GIO** showed a bone loss of 5-15% during the **first** year of treatment.<sup>12</sup> It mainly affects the trabecular **bone**<sup>15-16</sup> and maximal bone loss seems to occur within the first 6 to 12 months of **treatment**.<sup>17-18</sup> Fig. 1a



**FIG. 1a:** Age-related changes of bone mineral density (BMD) in SLE patients and controls for lumbar spine at recruitment.



**FIG. 1b: Age-related changes of bone mineral density (BMD) in controls and SLE patients for femoral neck at recruitment.**

shows the bone mineral density (BMD) at the L2-4 vertebrae of 29 of our female SLE subjects who had had at least 6 months of treatment with glucocorticoid and 29 age and sex matched controls. The BMDs were measured using the technique of dual energy X-ray absorptiometry (Norland XR-26). The BMD of SLE patients were significantly lower than that of the normal subjects at all ages. Similar changes were also seen at the femoral neck though the reduction was not as profound as in the lumbar vertebrae (Fig. 1b). At recruitment, the mean BMD of SLE subjects who had had at least 6 months of glucocorticoid treatment was significantly lower than normal controls at the lumbar vertebrae and femoral neck. There was, however, no significant difference at the distal and proximal radius (Fig. 2). Thus, our data were consistent with the observation that GIO mainly effects the cancellous bone.<sup>15-16</sup>

We also examined the BMD of SLE subjects at recruitment and after 6 to 12 months of first measurement (Fig. 3). Although there was a small decrease in BMD at L2-4 and the femoral neck on follow-up, they were, however, not

statistically significant. This could perhaps be explained in part by the fact that glucocorticoid-induced bone loss is most marked during the first 6 to 12 months of treatment.<sup>17-18</sup> Larger amounts of corticosteroids is usually required initially to control disease activity. Further, the adverse effect of SLE on bone mass, if any, would be expected to be most pronounced during this stage of the disease.

The rate of bone loss differs among individuals exposed to long term glucocorticoid.<sup>12-14</sup> This variation in susceptibility may be genetically and hormonally determined. Postmenopausal women are more susceptible to GIO than premenopausal women,<sup>19</sup> whilst the rate of bone loss seems to be more rapid in young adult men receiving glucocorticoids than older men.<sup>7</sup> It is also unclear whether a threshold dose for the development of GIO exists although it is quite clear that the majority of those who are on more than 10 mg of prednisolone a day over a long period of time develops GIO. Controversies remain as to whether the degree of bone loss correlated with the cumulative dose of glucocorticoid

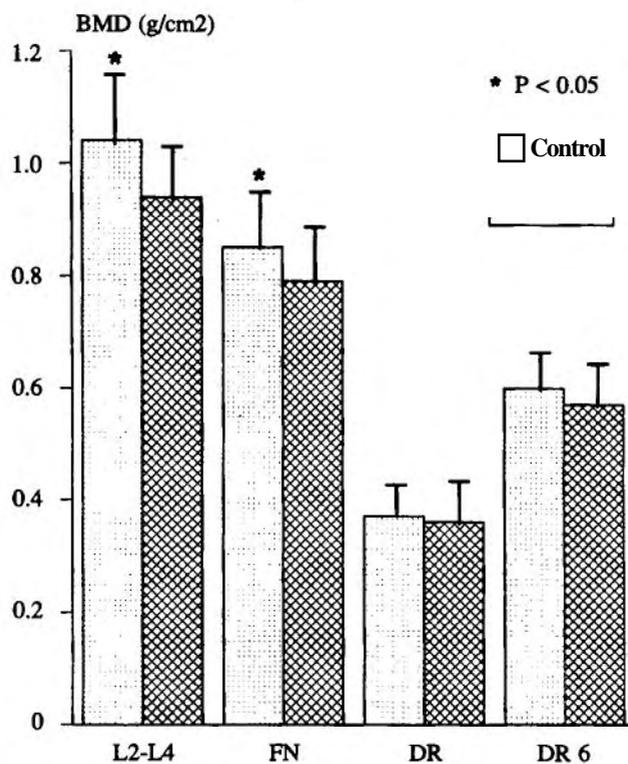


FIG. 2: Mean BMD of controls and SLE patients at recruitment.

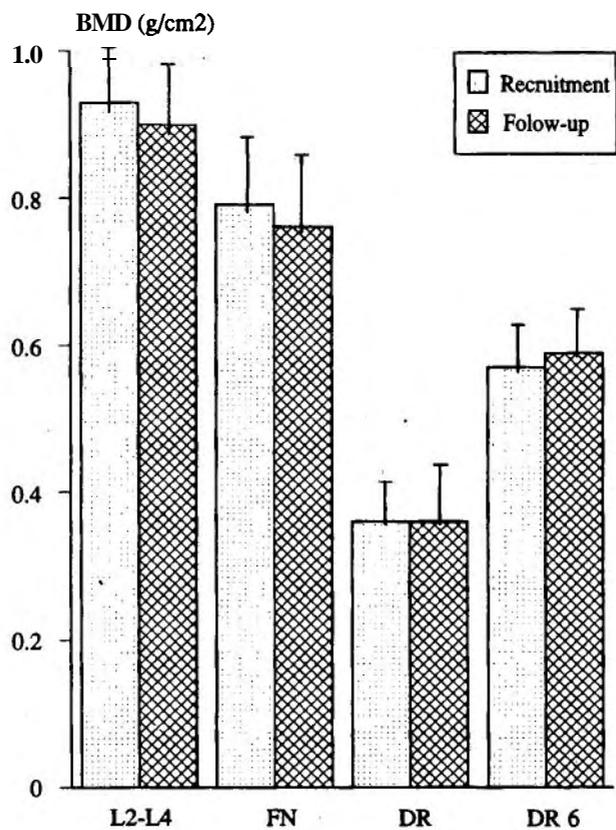


FIG. 3: Mean BMD of SLE patients at recruitment and on follow-up.

received.<sup>13,17</sup> Our data showed that neither the total amount of glucocorticoids ingested nor the duration of therapy had significant correlations with BMD (Figs. 4 & 5). This observation is consistent with the hypothesis that the adverse effect of glucocorticoid on bone mass is maximally exerted during the first 6 months of exposure.<sup>17,20</sup>

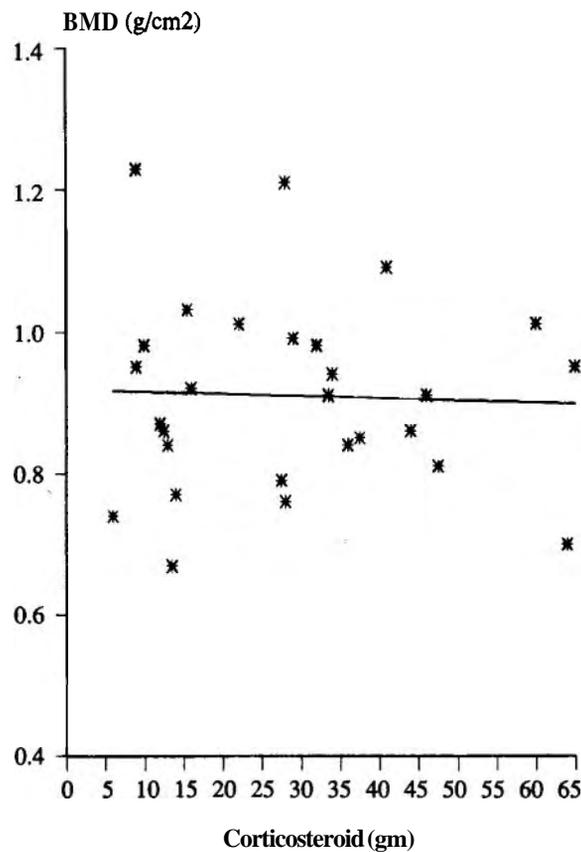
It is hypothesized that glucocorticoid induces bone loss by uncoupling bone formation and resorption. The former is suppressed while the latter is enhanced.<sup>17,20</sup> Biochemical markers of bone formation such as serum levels of osteocalcin<sup>23,24</sup> and carboxyterminal of propeptide of type I procollagen are suppressed in patients on glucocorticoids.<sup>25</sup> In vitro studies have demonstrated the presence of a direct negative effect of supraphysiological doses of glucocorticoids on osteoblasts recruitment and differentiation.<sup>26</sup> In addition, glucocorticoid-induced myopathy could curtail physical activities and this in turn would affect bone formation. However, markers of bone resorption, such as urinary hydroxyproline have been shown to be elevated in some studies only<sup>27,28</sup> and a

study using urinary deoxypyridinoline which is a more specific marker of bone resorption did not show an increase in excretion of this breakdown product of type I procollagen.<sup>29</sup> The increase in bone resorption in GIO is attributed to a reduction in serum sex steroids levels<sup>30,31</sup> as a result of corticosteroid-induced suppression of pituitary gonadotrophin secretion and inhibition of testosterone secretion by the testes,<sup>32,33</sup> and secondary hyperparathyroidism.<sup>34,35</sup> The latter is in turn due to decreased intestinal calcium absorption and increased urinary calcium excretion.<sup>35,36</sup>

**MANAGEMENT**

*Prevention*

In those who are at greatest risk of developing GIO, preventive measures should be instituted at the outset as bone loss in GIO is most rapid during the first 6 months of treatment. Patients with additional risk factors for osteoporosis such as immobilisation, connective tissue disorders, menopausal states, low calcium intake and family history of osteoporosis should have their bone



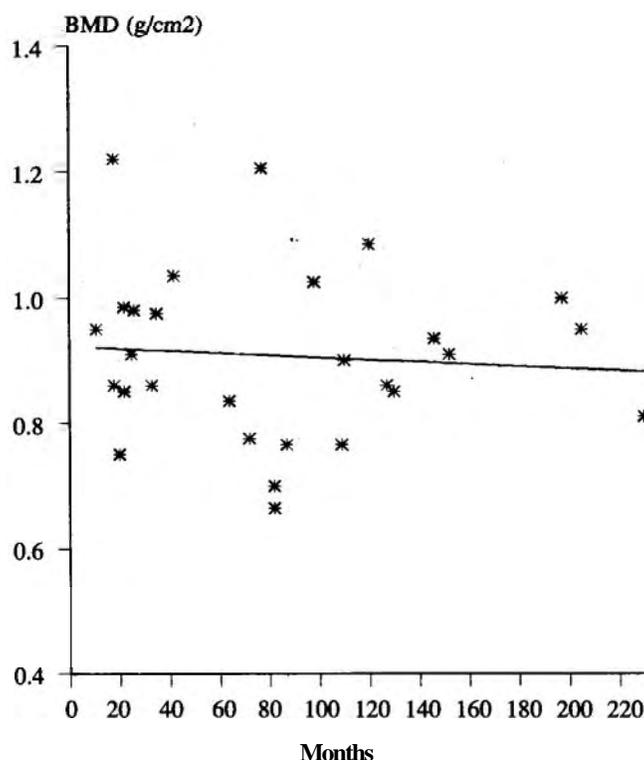


FIG. 5: No correlation between BMD of patients at L2-L4 and duration of treatment.

density measured at the start of glucocorticoid therapy and subsequently at 6 monthly intervals. Those with **BMD** of more than 1 **SD** below that of a young adult (T score = -1 or less) should receive specific treatment for osteoporosis.

General preventive measures which apply to all patients on corticosteroids include the use of lowest effective dose and the use of topical steroids whenever possible. The addition of steroid-sparing drugs like azathioprine and cyclophosphamide for those on long term and high dose **therapy** should be considered. **Do not** prolong treatment unnecessarily. Avoid immobility, excessive alcohol, cigarettes and caffeine.

**Treatment**

Treatment is indicated in **those** whose **BMD** is more than 1 **SD** below that of the young adult. Currently the approved treatment for **GIO** is aimed at decreasing the rate of resorption by using **antiresorptive** agents and or vitamin **D** and calcium supplementation to counter secondary hyperparathyroidism. As in postmenopausal osteoporosis, hormone replacement therapy (HRT) is the mainstay of treatment in those with **GIO** who are oestrogen deficient

(postmenopausal, premature ovarian failure and oophorectomy) and where HRT is not **contraindicated**.<sup>37,38</sup> Testosterone is indicated in males with low testosterone **levels**.<sup>39</sup> Calcium supplementation is relatively safe and inexpensive. It slows the rate of bone loss but by itself is inadequate.<sup>40</sup> The addition of vitamin **D** has been shown to be effective in reducing bone loss of the axial **skeleton**.<sup>18</sup> This regime may be most effective in elderly subjects where calcium absorption and the synthesis of active vitamin **D** metabolites as well as its action are often **impaired**.<sup>41</sup> However, the combination of calcium and vitamin **D** increases the risk of hypercalcemia and nephrocalcinosis and therefore requires regular monitoring of serum calcium and renal **function**.<sup>18</sup> The use of nasal calcitonin plus calcium supplementation has also been demonstrated to maintain bone mass at the lumbar spine in those on long term **corticosteroids**.<sup>18</sup> The results with bisphosphonates are similar to that of **calcitonin**.<sup>4,42</sup> Recently, the use of low dose fluoride has been shown to increase the **BMD** of the axial skeleton and this was associated with a reduction in vertebral fracture rate without adversely affecting appendicular **BMD** in patients with postmenopausal **osteoporosis**.<sup>43</sup>

Slow release low dose fluorides may have a future in the treatment of established GIO.

## CONCLUSION

The widespread use of glucocorticoids in many chronic medical disorders has led to the increasing prevalence of GIO. The adverse effects of glucocorticoids on the skeleton are purportedly due to its inhibition of bone formation without a parallel reduction in bone resorption. It predominantly affects the cancellous bone during the initial 6 to 12 months of therapy. Strategies to prevent GIO include minimisation of systemic exposure to glucocorticoids, avoidance of risk factors of osteoporosis, adequate calcium intake and regular monitoring of BMD. Patients with BMD of more than 1 SD below that of the young adult should be treated without delay. Treatment is aimed at reducing the rate of bone resorption by employing single or a combination of **antiresorptive** agents. HRT is still the most cost-effective treatment in those who are oestrogen deficient. Where HRT is **contraindicated** or not tolerated, nasal calcitonin or bisphosphonate plus calcium is a reasonable alternative. Vitamin D and calcium supplementation are perhaps most useful in the elderly where calcium absorption and synthesis of active vitamin D **metabolites** and its action are compromised. Cyclical slow release low dose fluorides may have a future role in the management of established GIO.

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