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Editorials

Steroid Osteoporosis

An association between glucocorticoid excess and osteopenia has been suggested from the time of Cushing's first description of the syndrome which now bears his name [1]. Subsequently, Fuller Albright [2] postulated that the anti-anabolic action of glucocorticoids contributed to the development of osteoporosis, and when these hormones became available for therapeutic use in the 40s and 50s, case reports of clinical osteoporosis soon followed [3]. Since that time, numerous investigations have shown that bone mass is subnormal in steroid-treated patients [4–6] though the contribution of the underlying disease to this bone loss is still debated. Adinoff and Hollister [7] addressed this issue by studying fracture prevalence in steroid-treated and nonsteroid-treated asthmatic patients. They found no evidence of vertebral fracture in their control group, in contrast to a fracture prevalence of 11% in asthmatics who had received steroids for at least 1 year. We also have data indicating that distal forearm bone mineral content is reduced by almost 20% in asthmatic subjects who have received steroid therapy for a mean period of 7 years, compared with nonsteroid-treated asthmatics (Reid et al., in preparation). Because glucocorticoid-induced bone loss is more marked in trabecular than in cortical bone, it is probable that the degree of spinal osteopenia is even more marked than that demonstrated in the forearm.

Clearly, not all patients on steroid treatment develop fractures. Fracture is dependent on a reduction in bone mass to a level below the fracture threshold. Whether this occurs will depend on the patient's premorbid bone mass (which in turn is determined by, among other things, sex, age, race, and menopausal status) and the duration of time the patient is exposed to glucocorticoids. The average glucocorticoid dose and the nature of the underlying disease may be additional contributing factors [6, 8].

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Pathogenesis

Glucocorticoids have a number of effects on calcium metabolism and bone cell function. The relative contribution of each of these to the development of osteopenia is unknown and its elucidation is complicated by the existence of significant interspecies differences in the response to glucocorticoids. Feldman et al. [9] have demonstrated the presence of glucocorticoid receptors in bone, making a direct action of steroid hormones on bone a possibility. A number of workers have demonstrated direct glucocorticoid effects in cultured rodent bone cells. Protein and collagen synthesis, cell growth, and RNA synthesis are all inhibited by glucocorticoids [10, 11]. Similar changes are seen in human osteoblasts cultured long term with supraphysiological steroid concentrations, though low glucocorticoid concentrations and short incubation periods appear to stimulate growth and collagen synthesis [12]. Rodent bones in organ culture show a similar pattern of response; protein synthesis is stimulated during the first 48 hours of exposure to cortisol but is subsequently inhibited [13]. Both these effects appear to require the presence of the periosteum [14] and it has been postulated that glucocorticoids inhibit the proliferation of the osteoblast precursor cells in the periosteum [15].

Histmophometric studies of bone from both steroid-treated animals and humans confirm the *in vitro* evidence of impaired bone formation. In humans, mean wall thickness and the active formation period of trabecular bone packets are decreased by steroid treatment [4]. These changes are reflected in the rapid and dose-related reduction in bone glaprotein levels produced by glucocorticoid treatment [16].

The effects of glucocorticoids on bone resorption appear to vary markedly from one experimental system to another. Several groups using bone organ cultures have found that basal- or parathyroid hormone-stimulated resorption is inhibited by steroids. More recently, however, two groups have documented a stimulation of bone resorption in organ culture by hydrocortisone [17, 18]. In contrast, most animal studies have found a reduction in bone resorption following steroid therapy, though the usual finding in steroid-treated patients is of increased osteolysis. These results have been explained by the presence of hyperparathyroidism in steroid-treated humans [19] but the use of much higher prednisone doses in the animal studies may also be relevant, as Jee et al. [20] have demonstrated that modestly supraphysiological doses of steroids increase bone resorption in rats.

In addition to these direct effects on bone cells, glucocorticoids influence the movement of calcium into and out of the body. In both animals and humans there is general agreement that intestinal calcium absorption is inhibited by steroids. This effect has been documented after as little as 2 weeks treatment, and is dose related [21]. Phosphate absorption seems to be similarly reduced [21]. It was originally thought that these changes were due to glucocorticoid effects on vitamin D metabolism. This now appears to be unlikely since, in the short-term studies referred to above, levels of 1,25-dihydroxyvitamin D were actually elevated and levels of 25-hydroxyvitamin D were unchanged at the time that intestinal calcium absorption was reduced. These findings imply a direct glucocorticoid effect on the gut with a secondary effect on vitamin D metabolism which is probably mediated by parathyroid hormone (PTH) [21]. The mechanism of steroid action on the gut is not known but may be related to the observation that cortisol reduces levels of the soluble calcium-binding protein in chick intestinal mucosal cells [22].

In spite of reduced intestinal calcium absorption, 24-hour urine calcium excretion is actually increased during the first month of glucocorticoid therapy and fasting calcium excretion is elevated in those receiving chronic steroid treatment [19]. This appears to be related to reduced tubular reabsorption of calcium in steroid-treated subjects [23]. Such effects have not been seen, however, following acute cortisol infusion in normal volunteers [24]. The mechanism of the glucocorticoid effect on renal calcium handling is unknown, but the kidney contains a calcium-binding protein which appears to be identical to that found in the duodenum [25], so the mechanism of steroid action may be the same at both sites.

Reduced absorption of dietary calcium and increased calcium loss in the urine have both been invoked to explain the mild degree of hyperparathyroidism that has been documented in many patients chronically treated with glucocorticoids [19]. Steroids may also act directly on the parathyroid gland, as cortisol infusions in normal volunteers raise the serum PTH level in the absence of changes in serum calcium [26]. Cortisol has also been found to be a secretagogue for rat parathyroid glands *in vitro* [27].

In addition to influencing serum levels of calcitropic hormones, glucocorticoids may affect tissue sensitivity to these factors. Osteoblast production of cyclic AMP in response to PTH is increased following steroid treatment [10] though the mechanism of this effect is uncertain. Glucocorticoids also modulate the number of receptors to 1,25-dihydroxyvitamin D [28]. There are interspecies differences in this effect, however, and whether such changes occur in human cells is unknown.

There are a large number of local and systemic factors which influence bone metabolism and which in turn have their actions modified by glucocorticoids. Interleukin-1 (alpha and beta) and the tumor necrosis factors (alpha and beta) are potent stimulators of both bone resorption and prostaglandin production. They also inhibit collagen synthesis. In contrast, interferon-α inhibits bone resorption as well as the synthesis of collagen and DNA. Glucocorticoids inhibit the synthesis of these lymphokines and interfere with their actions on target tissues [29]. Epidermal growth factor, fibroblast growth factor, and platelet-derived growth factor also promote bone resorption via prostaglandin-dependent mechanisms. Prostaglandins are synthesized in bone and markedly influence both bone formation and resorption in bone organ culture. Because corticoids block prostaglandin synthesis, the actions of endogenous prostaglandins will also be blocked.

Growth hormone has anabolic actions on bone, and some data suggest that growth hormone levels are suppressed by steroid therapy, though this is by no means a universal finding. It is more certain that circulating insulin-like growth factor 1 (IGF-1) bioactivity is reduced by steroid therapy, probably as a result of increased IGF-1 inhibitor levels [30]. In males, testosterone is critical to the maintenance of skeletal mass, and circulating levels of this hormone are reduced by 40% in steroid-treated subjects [31]. Unlike most of the other pathogenic mechanisms cited above, the effect of glucocorticoids on testosterone levels is readily reversible with currently available pharmaceuticals.

Prevention and Treatment

The literature contains fewer investigations of the

treatment of steroid-induced osteoporosis than those addressing its etiology. This is reflected in clinical practice by the lack of scientifically proven and freely available prophylactic regimens. It is not even clearly established what effect discontinuation of steroid therapy has on bone mass, though two groups have reported significant increases in bone mass following cure of Cushing's syndrome [32, 33]. Withdrawal of glucocorticoids is not usually a realistic option in clinical medicine, but a number of groups have studied the administration of steroids on alternate days as a more viable alternative. Unfortunately, available evidence suggests that this apparoach does not lessen the degree of bone loss [8].

A small number of studies on the effect of pharmacological doses of vitamin D or its metabolites have been carried out. Hahn's group [34–36] have found benefit from calciferol and from 25-hydroxyvitamin D but not from 1,25-dihydroxyvitamin D. Two other groups have found a beneficial effect from 1α-hydroxyvitamin D, although these studies were very short term [37, 38]. Vitamin D and its metabolites are not widely used for prophylaxis of steroid osteoporosis because of this uncertainty as to their efficacy and the significant risk of hypercalcemia associated with their use.

In contrast, calcium supplementation is regarded as safe and is commonly employed in the prophylaxis and treatment of steroid osteoporosis. Despite this, it has received little formal assessment. Nilsen et al. [39] carried out a prospective randomized trial of microcrystalline hydroxyapatite versus control in patients with rheumatoid arthritis and found a slight reduction in the rate of radial (but not ulnar) bone loss in the treated subjects. We have demonstrated a significant reduction in bone resorption (as measured by hydroxyproline excretion) in steroid-treated subjects given calcium (1 g/day) [40]. However, we have recently shown that calcium supplementation alone does not completely arrest steroid-induced bone loss at either axial or peripheral sites [41].

These measures aimed at improving intestinal calcium absorption can be combined with the use of a thiazide diuretic to limit the fasting hypercalciuria of the steroid-treated patient [19]. Though no formal assessment of the effects of thiazides on the bone mass of steroid-treated subjects has been carried out, it has been shown that thiazides have a beneficial effect on the bone mass of postmenopausal women [42] and patients with hypertension [43]. Like the use of calcium supplements, thiazides are inexpensive and safe.

The dramatic inhibition of osteoblast function by steroid treatment has led to the use of both fluoride and anabolic steroids as stimulators of bone formation. Fluoride has been shown to be ineffective in preventing steroid-induced bone loss in the forearm [44], but this is not particularly surprising because its most significant effects in postmenopausal osteoporosis are observed in the spine. Meunier et al. [45] have recently reported significant increases in the trabecular bone volume of steroid-treated patients given fluoride. Similarly, short-term studies have demonstrated a beneficial effect of the anabolic steroid nandrolone in postmenopausal women taking steroids [46]. In glucocorticoid-treated males in whom reduced serum testosterone levels are frequently found, it is more appropriate to provide testosterone replacement itself rather than use a synthetic anabolic agent. Similarly, in postmenopausal women, estrogen deficiency is a further contributor to the development of osteoporosis and should be countered by hormone replacement therapy [47].

The increased osteolysis caused by steroid treatment has led to the use of agents that inhibit bone resorption as a way of stabilizing bone mass. Ringe et al. [48] have recently demonstrated a beneficial effect of calcitonin on bone mass in a 6-month prospective study in steroid-treated subjects. Using the second generation bisphosphonate, APD, we have found an initial increase followed by subsequent stabilization of bone mass over a 12-month period [41]. Both these approaches show promise, but the low patient acceptability of parental calcitonin and the limited availability of potent bisphosphonates limit the routine use of either therapy at the present time.

A novel approach to the prevention of steroid osteoporosis has recently been suggested by the development of deflazocort, a synthetic glucocorticoid with significantly reduced effects on bone and calcium metabolism [49]. It has been suggested that differences in the antiinflammatory potency of deflazocort and prednisone may account for its apparent calcium-sparing effect but recent studies do not support this view. As with the potent bisphosphonates, lack of general availability limits its use at present.

In conclusion, it can be stated that there is no completely effective, safe, and freely available regimen for preventing or treating steroid osteoporosis. On the basis of theoretical considerations rather than conclusive clinical trials, calcium supplements, thiazide diuretics, and, where appropriate, sex hormone replacement can be advocated. These agents are well tolerated by patients and are inexpensive. Vitamin D and some of its metabolites are probably effective also, but should only be used where long-term monitoring for hypercalciuria and hypercalcemia is possible. Because of their side-effects, calcitonin, anabolic steroids, and fluoride should be regarded as second-line agents for pro-

phylaxis and will more frequently find a role in the treatment of established steroid osteoporosis. With increased availability in the future, second-generation bisphosphonates may be widely used for both purposes.

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