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Editorial

Corticosteroids and osteoporosis

The undoubted benefits of therapeutic corticosteroids carry a high price in side effects. Prominent among these is extensive loss of trabecular bone with widespread structural collapse. As in practice the good and the bad effects cannot be separated, the prevention and treatment of iatrogenic corticosteroid osteoporosis has been a largely ineffectual compromise (for reviews see refs 1–6). Recent investigations of the microstructure and histomorphometry of this form of osteoporosis and advances in new forms of treatment now provide a more logical basis for its management.[7–9]

Cushing's disease and corticosteroid osteoporosis

The osteoporosis of endogenous Cushing's disease closely resembles that due to exogenous corticosteroids and, although there are differences in the clinical and endocrine environment,[10] the study of one provides lessons for the other. There are many indications for corticosteroid treatment; for instance, to subdue the short term illness of sensitivity reactions; to avert catastrophe, as in the potential blindness of temporal arteritis; and to provide long term control of chronic diseases where alternative treatments prove to be ineffective (as in asthma and rheumatoid arthritis). Although bone loss may rapidly develop in patients given large doses of corticosteroids for a short time, prolonged treatment is the most frequent cause of bone problems. Patients who develop corticosteroid osteoporosis may have an underlying condition which itself predisposes to bone loss, such as rheumatoid arthritis or Crohn's disease; or the skeleton may be unharmed before corticosteroids are given, as in chronic respiratory disease. The skeletal effects of corticosteroids will be influenced by the patient's age, which determines pretreatment bone mass and potential reversibility. The growing skeleton may be severely affected by corticosteroid excess but this is reversible, whereas in the elderly the effects of corticosteroids are imposed on pre-existing involutional osteoporosis and this is not in practice reversible.

Against this clinical background the clinician will want to know how corticosteroids act on the skeleton, the clinical consequences of these effects, whether there is a threshold dose below which the bone is unaffected, and the measures that can be taken to try to prevent or treat bone loss.

Effects of corticosteroids on the skeleton

PHYSIOLOGY

Much of the experimental work on the skeletal effects of corticosteroids is contradictory.[6] Single and mixed populations of cells in culture and in tissues respond differently, as do different animal species, the result being a very opaque view of the effects in man (reviewed in ref 11). In physiological amounts cortisol exerts a permissive effect on many cellular and hormonal functions via the ubiquitous glucocorticoid receptor. At higher, non-physiological concentrations corticosteroids directly and profoundly suppress the activities of the osteoblast and the differentiation of its progenitor cells (figure). The effects of corticosteroids on osteoclasts are controversial, but are probably mediated through osteoblasts to increase bone resorption. Corticosteroids also directly block calcium transport through the enterocytes, independently of any effect on the metabolism or actions of vitamin D, and they have a minor suppressive effect on the renal reabsorption of calcium, causing hypercalcuria. In addition to these direct effects, corticosteroids have indirect effects on the skeleton through their influence on the actions of other hormones. When given initially corticosteroids increase the activity of parathyroid hormone, probably as a result of reduced intestinal transport and increased renal loss of calcium; and there is also evidence that they potentiate the activity of parathyroid hormone on osteoblasts (and through them the osteoclasts). Corticosteroids are also likely to have important effects on local cellular messengers within bone, such as the cytokines, and on growth factors. Finally, corticosteroids have a complex effect on sex hormone secretion; in addition to suppression of pituitary gonadotrophins there is evidence of direct suppressive effects on the ovary and testes, and of reduced production of adrenal androstenedione. The important reduction in sex hormones contributes to further loss of bone from the skeleton. Although the effects of corticosteroids are complex and in some areas the evidence is confused (see refs 4–6), suppression of new bone formation appears to be a major reason for corticosteroid osteoporosis. Biochemically the degree of this suppression is well indicated by reduced plasma concentrations of osteocalcin, a major osteoblast product,[12] and anatomically by widespread thinning of the bony trabeculae.

MICROSTRUCTURE AND HISTOMORPHOMETRY

Normal bone is constantly being removed by osteoclasts and replaced by osteoblasts. These closely linked functions occur in coordinated cellular groups or remodelling units (basic multicellular units). The timing of the different activities within bone remodelling cycles is known approximately.[13] Activation of a remodelling unit leads to bone resorption (which is initially osteoclastic and continues for two to three weeks). This resorption is followed by a phase of reversal (about nine days) followed by osteoblastic new bone formation (about two weeks) and subsequently mineralisation (130 days). The total period of a remodelling cycle in a normal adult is about 200 days. This is followed by a very variable period of quiescence, which may last from weeks to years. Against this background, bone loss occurs because of an imbalance between resorption and formation that favours resorption. Such imbalance can clearly result from reduced formation, increased resorption, or both, and has its first major but not exclusive effect on trabecular bone. Trabecular bone has a

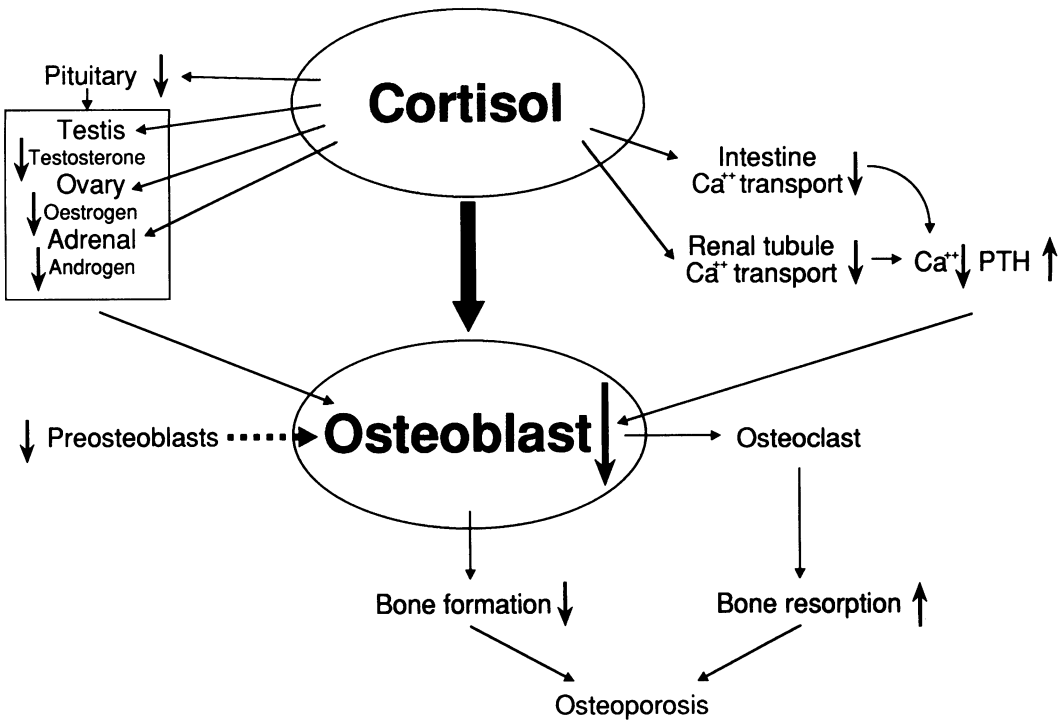

Diagram showing the main effects of excess corticosteroids (cortisol) on bone cells. This emphasises the central importance of the osteoblast. Minor pathways are excluded.

larger metabolically active surface than cortical bone; it is found particularly in vertebral bodies and the ribs and is the type of bone that is affected most severely by cortisol excess.

In the simplest analysis, bony trabeculae may be either universally thinned or perforated and removed piecemeal, and these processes may occur separately or together.[14] Removal or perforation of trabeculae, which effectively removes the struts, weakens the bone more than generalised thinning; in addition to this disproportionate fragility, trabeculae that have been broken or removed cannot, in theory, be replaced by any current treatment. In contrast, trabeculae that have been thinned but remain are able to provide a template for new bone formation after therapeutic interventions.

Microstructural study of corticosteroid treated bone (and the bone in endogenous Cushing's syndrome) shows that the predominant change is thinning of the trabeculae.[8] In the vertebrae both horizontal and vertical trabeculae are affected, and the result is an "empty bone" appearance. This contrasts with involutional osteoporosis, where trabeculae are often perforated or lost completely, the minor, non weight-bearing, horizontal elements of the vertebrae being preferentially removed. Static and dynamic histomorphometry of bone affected by corticosteroid osteoporosis has shown, among other features, a reduction in mean wall thickness, suggesting that corticosteroid induced bone loss is due to widespread reduction in both the rate and the amount of bone formed. Osteoblasts appear to synthesise bone matrix less effectively and to spend less time than normal in this activity, behaving as if they are sleepy.

Corticosteroid treated bone contains an excess of resorption (Howship's) lacunae. This may be because resorption is increased early in corticosteroid treatment, for which there is evidence, but it could be because the lacunae have not been adequately refilled owing to defective formation. Aaron *et al*[9] found that only a quarter of the resorption sites in corticosteroid treated bone were occupied by one or more osteoclasts. Finally, as Dempster has pointed out,[8] the deleterious effect of suppressed bone formation on bone mass is enhanced by an increase in the rate of activation of new remodelling units (probably owing to hypersecretion of parathyroid hormone), and this will accelerate the rate of bone loss.

Thus anatomical studies on corticosteroid treated bone confirm the experimental and biochemical evidence that most bone loss occurs soon after corticosteroids are given, and that it results primarily, though not exclusively, from osteoblastic suppression.

CLINICAL FEATURES

Because trabecular bones bear the brunt of the cortisol attack both in endogenous osteoporosis and in iatrogenic Cushing's syndrome, the vertebrae are rapidly and severely affected and the ribs and pubic rami also show striking changes.[15] Apparently spontaneous fractures (which may be painless) occur at all these sites, and are well demonstrated by isotopic bone scan; radiographs confirm severe osteoporosis, including patchy loss of bone from the skull. There is often striking hypertrophic callus at the site of fractures, including the end plates of wedged vertebrae. Osteonecrosis may contribute to vertebral fracture and to the collapse of femoral heads.

Iatrogenic corticosteroid osteoporosis may occur at any age in either sex; but it is more likely where bone has already been lost and where large amounts of corticosteroids are given (either as a big daily dose or in a prolonged course, or both).

The incidence of osteoporosis in patients taking glucorticosteroids is unknown. A recent review suggested that it is 30–50%, similar to the estimate of 50% in Cushing's disease.[6]

Predicting the skeletal outcome of corticosteroid treatment in individual patients is difficult and clinicians are only too well aware of the inexplicable individual variations in susceptibility of the skeleton (and other tissues) to corticosteroids. Within the general guidelines that corticosteroid osteoporosis is dose dependent and that major effects may occur early, there are few clues. Osteoblast suppression is reflected by a rapid decline in circulating osteocalcin, an effect proportional to the dose of corticosteroids.

There is also little information on the reversibility of corticosteroid induced osteoporosis. After the surgical correction of Cushing's disease in children the vertebrae

reform and growth resumes, and in young adults there is an increase in bone mass and biochemical and histological evidence of increased bone formation.[16] By analogy, we might reasonably expect some reversibility of osteoporosis, if corticosteroids are discontinued, in the young but not necessarily the old skeleton.

Preventing and treating corticosteroid osteoporosis

The most logical and effective way to prevent bone loss due to corticosteroids is to stop giving them and to use a less harmful alternative; but many patients take corticosteroids for good reason and there may be only limited latitude in the dose that can be given. Other strategies include a variation in timing and methods of administration, the use of alternative steroids, and the use of specific osteotropic agents to increase bone formation, reduce bone resorption, or both.

REDUCTION IN CORTICOSTEROID DOSE

Progressive bone loss is said to be prevented by reduction of the dose of prednisone or prednisolone to below 7·5 mg a day, the amount regarded as physiological (as judged by its equivalent in serum cortisol concentration); but there is little evidence to support this. Observations suggest that bone loss may occur with lower doses, especially in men and postmenopausal women,[6] and plasma osteocalcin may be reduced in patients given prednisone in doses as low as 2·5 mg daily.[17]

ALTERNATE DAY ADMINISTRATION

In children corticosteroids given on alternate days may inhibit growth less than a daily regimen, though the limited evidence suggests that bone loss still occurs. In a comparison of patients with various rheumatic diseases given either an alternate day or a daily schedule for at least six months forearm bone loss occurred in both groups.[18]

HIGH DOSE INTRAVENOUS METHYLPREDNISOLONE

Megadose methylprednisolone given intravenously (1 g daily) for short periods is part of the rheumatologist's armamentarium. Although we might expect that the apparent beneficial effects of such large doses would be accompanied by severe osteoporosis, some limited data suggest that this is not so. Egsmose *et al*[19] measured forearm bone mineral density in 15 patients who had three days of intravenous methylprednisolone (1 g daily) followed by a course of gold and found no difference in the change in bone mineral density in this group over the next eight months when they were compared with 15 patients who had saline instead of corticosteroids before gold treatment.

INHALED CORTICOSTEROIDS

Despite the widespread use of inhaled corticosteroids for respiratory disease, little is known about their effect on the skeleton. Side effects are widely accepted to be much less than with the systemic administration of corticosteroids because the drugs have a high first pass metabolism. The maximum doses for high dose corticosteroid inhalers are in fact associated with very little adrenal suppression. Patients taking high doses of inhaled corticosteroids should be given a steroid card, and may require corticosteroid cover during an operation.[20]

ALTERNATIVE STEROIDS

Several synthetic corticosteroids have been developed in an attempt to reduce some of the detrimental effects seen with cortisol, particularly salt retention. In addition to prednisone and prednisolone they include methylprednisolone, betamethazone, dexamethazone, and triamcinolone. Although many of these compounds cause less sodium retention the severity of other side effects appears to be proportional to their anti-inflammatory action. Intramuscular triamcinolone has been used as an alternative treatment for patients with chronic severe asthma having high oral doses of prednisolone but the side effects are troublesome. There is no information about what happens to the skeleton during such treatment.

Deflazocort (an oxazoline derivative of prednisone, not available for general use) is said to have less severe side effects on calcium metabolism and on the skeleton than cortisol when given in equivalent anti-inflammatory doses. Assessment of the anti-inflammatory dose is difficult, however. In one study 26 men with rheumatoid arthritis given 6 mg deflazocort or 5 mg prednisone daily for 15 months lost bone at a mean annual rate of 1·2% and 3·4% respectively from the lumbar vertebrae. The anti-inflammatory equivalence of these daily doses was based only on equivalent changes in the erythrocyte sedimentation rate.[21] In juvenile chronic arthritis deflazocort appeared to have an advantage over prednisone for lumbar growth in relation to somatic growth with doses of the

Therapeutic options in corticosteroid osteoporosis

Options	*Agent*	*Approximate doses used*	*Comments*
1 Increase bone formation	Exercise	—	Limited by pain and fractures
	Sodium fluoride	50–75 mg sodium fluoride (with 1500 mg calcium) daily	Prohibitive side effects Use low dose
	Anabolic steroids	Intramuscular nandrolone 50 mg every 3 weeks	Virilisation in women Use testosterone in men
		Stanozolol 5 mg daily	
2 Decrease bone resorption	Calcium	1 to 1·5 g daily	No significant side effects
	Vitamin D and metabolites	1·25 mg thrice weekly (vitamin D) 40 μg 25-OHD daily	Need to check plasma calcium regularly
	Calcitonin	100 MRC units thrice weekly	Nasal preparation may be useful
	Pamidronate	150 mg daily (with 1000 mg Ca)	Effective orally
	Hormone replacement therapy	Oestradiol 75 mg	Subcutaneous implant; as required in postmenopausal women
		Testosterone 100 mg every 6 months	
	Bendrofluazide	5–10 mg 1–2 times weekly	Reduces urinary calcium
3 Combine 1 and 2	MCHC and nandrolone	1·6 Ca daily and intramuscular nandrolone 50 mg every 3 weeks	
4 Modify remodelling cycles (ADFR regimens)	Cyclical etidronate with phosphate	Variable; in postmenopausal osteoporosis etidronate alone (400 mg daily for 2 weeks repeated every 13 weeks)[35]	

ADFR—cycles consisting of activation, depression and freedom from treatment, with repetition of cycle; MCHC—microcrystalline hydroxyapatite.

drugs that just controlled the disease and hence were judged to be equivalent.[22]

SPECIFIC OSTEOTROPIC AGENTS

Many agents are potentially capable of altering bone turnover and bone mass through a final common pathway of action on bone cells. As the main effect of corticosteroids is to suppress bone formation, it would seem most logical to use anabolic agents to prevent this. In practice, however, to suppress bone resorption is easier. Because the activities of the osteoblast and osteoclast are closely linked it is difficult to influence them separately in the long term, though temporary dissociation may be achieved. Thus suppression of bone resorption is always followed, after an interval of several months, by reduced formation. In practice any active antiresorptive agent that temporarily dissociates formation from resorption will give encouraging results within the first year so far as bone mass is concerned.[23] Such results account for early enthusiastic reports,[24] which are rarely confirmed.

Osteotropic agents that stimulate new bone formation and suppress resorption may be used separately or together, or in alternating regimens intended to modify bone remodelling cycles.[13] Therapeutic alternatives are listed in the table. These should be considered in conjunction with the specific recommendations outlined by Lukert and Raisz.[6]

STIMULATION OF BONE FORMATION

Bone formation may be increased by using the skeleton, by taking sodium fluoride, or by the use of anabolic steroids, including testosterone.

There is increasing evidence that appropriate exercise can prevent bone loss and in some instances increase bone mass by increasing new bone formation and preventing its resorption. Appropriate advice may be difficult to follow, especially where there is painful vertebral collapse or severe underlying illness. The usefulness of exercise in corticosteroid osteoporosis is not formally established.

In contrast, there is no doubt that oral sodium fluoride stimulates the formation of new bone matrix, which can be mineralised provided that adequate calcium and (according to some) vitamin D are given. Radiological vertebral bone density increases, and early studies suggested a decrease in the rate of vertebral fracture. Recent double blind placebo controlled trials have not confirmed this, however, and there are now serious reservations about the use of fluoride.[25] These reservations arise not only from the apparent ineffectiveness of fluoride in preventing vertebral fractures but also from the high incidence of side effects. These affect the gastrointestinal tract and the skeleton, causing a painful lower extremity syndrome with increased isotope uptake in the affected areas (particularly the lower tibial metaphyses), which may indicate stress fractures; there is also some evidence that femoral neck fractures may be increased in patients treated with fluoride. Consequently, although limited histological studies suggest that the effects of corticosteroids on bone remodelling can be reversed by using fluoride, and have shown a substantial increase in trabecular bone volume,[26] the side effects must be regarded as prohibitive.

Limited short term studies have investigated the effects of anabolic steroids in postmenopausal women with corticosteroid osteoporosis. Nandrolone has been shown to be beneficial but the use of such agents in women is limited by their virilising side effects. Serum testosterone concentrations are reduced in men treated with glucocorticoids and hormone replacement therapy should be beneficial. In women testosterone is given with oestrogen in the form of subcutaneous implants (see below). Whether the testosterone in these implants contributes to the recorded increase in bone density that occurs is not clear.

SUPPRESSION OF BONE RESORPTION

The ways in which bone resorption may be inhibited include relatively simple measures such as giving oral calcium and vitamin D to increase intestinal calcium absorption (and hence, by increasing plasma calcium, reduce parathormone mediated resorption); direct suppression of the osteoclast by the use of either calcitonin or bisphosphonate (particularly pamidronate); and in women hormone replacement therapy (which may also have a direct effect on the osteoblasts). Again the evidence for the usefulness of these forms of treatment in corticosteroid osteoporosis is usually restricted to studies lasting a year or less. Although all show the increase in bone mass expected from the known physiology of bone over this period, long term benefits in corticosteroid osteoporosis have yet to be proved.

Although the reduced absorption of calcium produced by corticosteroids appears to bypass any effect on vitamin D, there is some evidence that giving 25-hydroxyvitamin D (in an average daily dose of 40 μg) with 500 mg of calcium can reduce osteoclast numbers after 12 months and increase metaphyseal and diaphyseal radial bone mass. These changes are associated with improved calcium absorption and a fall in serum parathormone concentrations.[11] Similar short term studies with 1α-hydroxycholecalciferol or 1,25-dihydroxycholecalciferol showed a reduction in cancellous osteoclast surface, without any change in forearm bone mass. Thus, although 25-hydroxyvitamin D taken with calcium rather than calcium alone may confer some benefit, the evidence for this is not convincing,[6] and the potential toxicity of vitamin D and its metabolites cannot be disregarded.

The evidence that calcium on its own has a beneficial effect on corticosteroid induced osteoporosis is also fragmentary. Certainly oral calcium increases the amount absorbed and decreases bone resorption, as assessed by urinary total hydroxyproline excretion; but this is not a particular feature of steroid induced osteoporosis. As in other forms of osteoporosis, there is no consistent or long term evidence that giving additional calcium alone significantly reduces the rate of bone loss.

Calcitonin rapidly inhibits bone resorption by the osteoclast and is therefore a potentially useful agent in preventing bone loss. Its effects are only temporary, however, it has considerable side effects, and it is expensive; and until recently it had to be given by injection. Now that apparently effective intranasal preparations are available its effects in corticosteroid induced osteoporosis are likely to be investigated further.

In contrast, the new bisphosphonates, particularly 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD; pamidronate) are effective orally and have no appreciable side effects. They have been shown to reduce both resorption and formation of bone, and to produce a sustained increase in the bone mineral density of patients with steroid induced osteoporosis for up to two years.[27 28]

In perimenopausal or postmenopausal women with corticosteroid induced osteoporosis treatment with oestrogen (and progestogen unless a hysterectomy has been performed) would seem logical for preventing continuing bone resorption. A case could also be made for hormone replacement therapy in the earlier years as such patients are deficient in adrenal derived oestrogen. This has led to some controversy, however, and it has been suggested that the proved effectiveness of percutaneous hormone implants (containing both oestrogen and testosterone) is due to the anabolic effects of testosterone rather than any effect of

oestrogen.[29] Nevertheless, in six patients with corticosteroid osteoporosis who received such implants there was an increase in vertebral bone density of 12·5% and of proximal femoral density of 7·5% in one year. Oestrogen may have an anabolic effect, stimulating collagen synthesis, as well as its antiresorptive action.[30]

Finally, the use of thiazide diuretics should be mentioned. These agents reduce the urinary excretion of calcium by increasing its renal tubular reabsorption and have been shown to slow postmenopausal bone loss. Patients taking thiazides also have a reduced rate of femoral neck fracture.[31] One way in which thiazides could prevent bone loss is by conserving calcium and reducing bone resorption. As one of the minor effects of glucocorticoids is to produce hypercalcuria thiazide treatment would seem very logical in corticosteroid osteoporosis, but long term studies of bone density have yet to be done.

COMBINED REGIMENS

Clearly anabolic and antiresorptive regimens can be combined. This has been done in an apparently haphazard manner—for instance, the anabolic steroid nandrolone has been given with oral calcium in the form of microcrystalline hydroxyapatite to produce an appreciable increase in total body calcium in the first year and a temporary increase in osteocalcin.[32] Cyclical treatment may be more logical and attempts have been made to manipulate the remodelling cycles by alternating periods of cellular activation (A) with periods of cellular depression (D) and with periods free of treatment (F) and using repeated cycles (R)—an ADFR regimen. A regimen using phosphate as an activator and etidronate as a depressor has been used cyclically in the treatment of postmenopausal osteoporosis. ADFR regimens have been investigated for only a short time and all results must be regarded as preliminary. The time for which these cycles are given is variable and depressors such as etidronate may be used intermittently on their own.

Practical issues

How far does this knowledge of corticosteroid induced osteoporosis help the clinician? It provides an insight into the multiple effects of corticosteroids on the bone and its cells, and some understanding of how corticosteroid osteoporosis differs from other forms such as involutional osteoporosis. There does not appear to be a well defined threshold dose of corticosteroids, and recovery from corticosteroid osteoporosis appears to be most likely in young people, especially where there is potential for growth. It should be possible to put the management of corticosteroid induced bone loss on a more logical basis.

There are three important practical questions to which only partial answers can be given. The first is whether the amount of corticosteroid induced bone loss can be predicted (who will lose bone, and how much and how fast?). Secondly, how long can corticosteroids be given without ill effect? Thirdly, what practical therapeutic measures can be taken to prevent corticosteroid induced osteoporosis?

The first two questions are interrelated. Although there appears to be considerable variation in the susceptibility of the skeleton to corticosteroids, in general the amount of bone loss is related to the total amount of corticosteroids given, and the loss is greatest with a high total dose—that is, a high daily dose, prolonged treatment, or both. As the likelihood of fracture is broadly related to the amount of bone (the bone mineral density) is it important to measure bone density before starting corticosteroid treatment? Where a bone densitometer is available, preferably a dual x ray (DEXA) machine capable of measuring spinal bone density, the answer must be yes, as it will provide a pretreatment measurement of bone mass (which may be excessively low, as in an elderly woman), and when the measurement is repeated it will give an indication of the rate of bone loss with the patient taking corticosteroids. Unfortunately instruments capable of measuring spinal bone density are not widely available. Measurement of forearm bone density with a single isotope source provides an economic alternative that is better than having no measurement at all, especially when serial readings are made; but because corticosteroid osteoporosis preferentially affects trabecular bone and the vertebrae it provides a less sensitive measure. As Lukert and Raisz[6] point out, some patients taking glucocorticoids do not develop osteoporosis so it is important to identify those at risk to assess the effectiveness of prevention. They consider that patients most likely to develop osteoporosis (without reference to the amount of corticosteroids) have the lowest initial bone mass and muscle strength (because of the association between corticosteroid osteoporosis and myopathy) and, during corticosteroid treatment, the most serious impairment of calcium absorption, the highest urinary loss of calcium, the greatest degree of secondary hyperparathyroidism, and the most dramatic inhibitory effect of corticosteroids on their osteoblastic function. In practice this implies that, apart from normal physical examination, the initial assessment and subsequent follow up of patients taking corticosteroids should include measurement of spinal bone density, urine calcium, plasma parathormone, and osteocalcin. In addition, vitamin D deficiency should also be excluded by measuring plasma 25-hydroxyvitamin D because deficiency appears to augment the deleterious effects of corticosteroids.

The answer to the second question is that corticosteroid treatment should be given for the shortest time compatible with control of the illness for which it is prescribed. Clearly the decision will depend very much on the disorder and the individual. Giant cell arteritis and temporal arteritis provide a useful example.[33] Both are self limiting disorders, so there is a risk of continuing corticosteroids unnecessarily. From one fifth to a half of those treated have serious side effects unless the initial dose of prednisolone is 10 mg or less and the maintenance dose less than 7·5 mg. There appears to be no reliable way of telling which patients are at risk from side effects, apart from the clear relation to total dose. The authors conclude that treatment should normally continue for at least two years and that relapse should be monitored every six months thereafter. They advise using azathioprine as it has a modest corticosteroid sparing effect and reducing prednisolone to alternate day administration once the daily dose is less than 5 mg to make eventual drug withdrawal easier.

In answer to the third question, the practical (as opposed to the theoretical) therapeutic alternatives are limited. On the whole, physicians do not like to counteract the effects of one powerful drug with those of another. At present the use of injectable calcitonin and oral sodium fluoride, both of which have appreciable side effects, is not recommended. Nasal calcitonin remains a possibility for the future, as do phosphonates such as disodium etidronate (Didronel, EHDP) and pamidronate. It is sensible to recommend exercise and additional oral calcium, which have well tried but undramatic effects in preventing bone loss, for preventing corticosteroid osteoporosis. As such patients are often closely supervised, a case could be made for giving moderate doses of vitamin D to aid calcium absorption. Corticosteroid induced osteoporosis in postmenopausal women would seem to provide a firm indication for hormone replacement therapy despite recent controversy. Lukert and Raisz[6] provide a list of specific recommendations for managing patients along these lines.

In the future we should be able to take advantage of the new knowledge about the effect of corticosteroids on the skeleton and enable new bone to be built on the attenuated but intact trabeculae. In this respect newly isolated growth factors and osteogenic agents have considerable potential.[34]

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