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Mechanisms of Glucocorticoid Action in Bone: Implications to Glucocorticoid-Induced Osteoporosis*

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Bone remodeling is regulated by systemic hormones and locally produced factors acting in concert to maintain bone mass (1). In the adult skeleton, bone remodeling is a tightly controlled process that occurs in the bone surface and results in bone turnover. Bone formation occurs only in areas of previously resorbed bone. The remodeling cycle consists of an activation phase, followed by bone resorption, a reversal phase, followed by bone formation, and a resting phase (2). Normally, bone formation and resorption are coordinated and in balance, but in conditions of persistently increased bone resorption or decreased bone formation, osteoporosis occurs. Glucocorticoids have marked effects on bone metabolism, and continued exposure of skeletal tissue to excessive amounts of these steroids results in osteoporosis. Although the exact mechanism of action of glucocorticoids in bone is uncertain, recent investigations have enhanced our understanding of the actions of glucocorticoids on skeletal tissue. This information will prove helpful for the eventual understanding of the pathogenesis of glucocorticoid-induced osteoporosis and for the development of new strategies to prevent and reverse the catabolic actions of glucocorticoids on the skeleton. Although *in vivo* glucocorticoids have indirect actions on bone metabolism, there is sufficient evidence to believe that their direct actions on bone cells play a central role in determining their effects on bone mass and in the metabolic bone disease that follows glucocorticoid excess.

Effects of glucocorticoids on bone resorption and mineral metabolism

Glucocorticoids enhance bone resorption and decrease bone formation; consequently, they decrease bone mass and increase the risk of fractures (3) (Fig. 1). The increased bone resorption is in part due to direct effects of glucocorticoids on the skeleton and in part the result of a decrease in intestinal calcium absorption and an increase in the urinary excretion of calcium. *In vivo*, glucocorticoids inhibit intestinal calcium transport, opposing the effects of vitamin D, but the mechanism has not been established. Serum levels of vitamin D metabolites in patients receiving glucocorticoids are virtually normal, and glucocorticoids induce the expression of calbindin-D28K, a protein involved in intestinal calcium transport (4–6). Parathyroidectomy prevents the excessive bone resorption associated with glucocorticoids, suggesting that *in vivo*, a cause of excessive bone resorption is enhanced secretion or activity of PTH. Although some investigators have found increased serum levels of PTH, these are frequently reported to be in the normal range (4, 7). This would suggest that the cause of bone resorption is either a transient increase in PTH secretion or increased PTH activity, possibly in association with direct actions of glucocorticoids on skeletal cells. Glucocorticoids enhance the responsiveness of osteoblasts to PTH by increasing the expression of PTH receptors in these cells (8). As the bone-resorbing actions of PTH require the presence of osteoblasts, an increase in PTH receptors in osteoblasts by glucocorticoids could explain some of the results observed (9).

In vitro, glucocorticoids have an acute stimulatory effect on bone resorption, but in long term cultures, they are inhibitory (10). The stimulation may be due to an increase in osteoclast activity, and is in accordance with effects observed *in vivo*. The mechanism of this increased activity is not known, although it could involve the induction of interleukin-6 (IL-6) receptors in skeletal cells (11). IL-6 is a cytokine known to induce osteoclast recruitment and to play a central role in bone resorption (12). The inhibition of bone resorption appears to play a minor role *in vivo* and is due to a decrease in osteoclast number, an event that may be secondary to a suppression of IL-6 synthesis (13).

Effects of glucocorticoids on bone formation and osteoblastic cell function

An impairment in bone formation is a predominant result of glucocorticoid excess and is associated with a decrease in serum levels of osteocalcin, a marker of osteoblastic function (14). For the most part, the decreased bone formation is due to direct effects of glucocorticoids on cells of the osteoblastic lineage. An additional component could be due to indirect mechanisms, such as inhibition of gonadotropin and sex steroid production, because patients on glucocorticoids develop hypogonadism (3). Alterations in the GH/insulin-like

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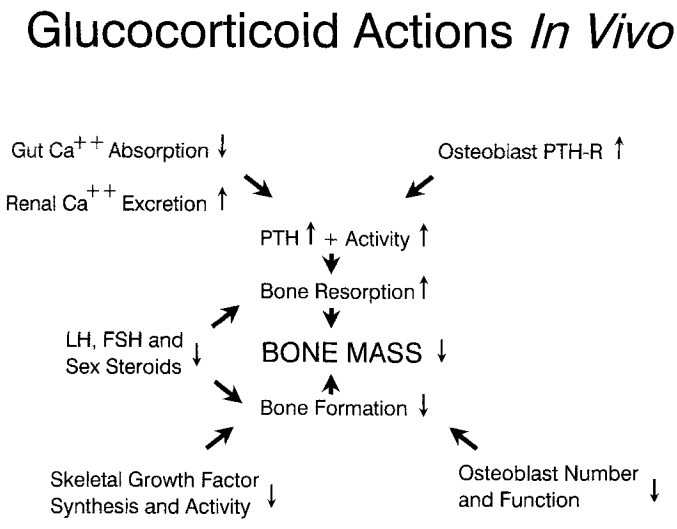

FIG. 1. Mechanisms of glucocorticoid action on the skeleton *in vivo*.

growth factor (IGF) axis have been proposed, but serum levels of these hormones are normal (3).

Glucocorticoids have complex actions on gene expression in skeletal cells, and they are dependent on the stage of osteoblast growth and differentiation (Table 1). Glucocorticoids have seemingly paradoxical effects on bone cell function, inducing the differentiation of preosteoblastic cells and inhibiting specific aspects of the differentiated function of the osteoblast. Glucocorticoids induce the differentiation of cells of the osteoblastic lineage into mature cells and the formation of multilayered bone nodules that eventually mineralize (15). As the cells differentiate, they express osteocalcin and alkaline phosphatase, genes that characterize the osteoblastic phenotype (15–17). In addition to their effects on differentiation, glucocorticoids decrease cell replication, depleting a cell population capable of synthesizing bone collagen, and repress type I collagen gene expression by the osteoblast by decreasing the rates of transcription and destabilizing α_1 I collagen messenger ribonucleic acid (18). Glucocorticoids have complex and unique effects on collagen degradation and regulate the synthesis of matrix metalloproteinases. These are a family of related proteolytic enzymes that include collagenases, gelatinases, and stromelysins (19–21). Collagenases cleave fibrillar collagen at neutral pH and are considered important in matrix remodeling. Three collagenases have been described: collagenase 1, secreted by stimulated human fibroblasts and osteoblasts; collagenase 2, secreted by neutrophils; and collagenase 3, secreted by human breast carcinoma cells and rat osteoblasts (20, 22, 23). Glucocorticoids increase collagenase 3 messenger ribonucleic acid and protease levels in rat osteoblasts, an effect that is in accordance with their actions on bone resorption (23). The stimulation of collagenase expression by glucocorticoids is specific to the osteoblast and is secondary to an increase in transcript stability without an increase in the rate of transcription (20). Glucocorticoids also decrease the expression of tissue inhibitor of metalloproteinase-1 by the osteoblast, and the combined increase in collagenase and decrease in tissue inhibitor of metalloproteinase-1 may play a role in type I collagen degradation and contribute to a decrease in the bone collagen matrix. As type I collagen is the major structural protein of the bone matrix, a decrease in its expression and an increase in its degradation are critical to the inhibitory actions of glucocorticoids on bone matrix and bone mass, and explain many of the inhibitory actions of glucocorticoids on bone formation observed *in vivo* (Fig. 2).

TABLE 1. Effects of glucocorticoids on osteoblastic function

1.	Decrease replication of preosteoblastic cells
2.	Induce differentiation of preosteoblasts to osteoblasts
3.	Decrease differentiated function of mature osteoblasts
	Decrease osteocalcin transcription
	Decrease α_1 I collagen expression by transcriptional and posttranscriptional mechanisms
4.	Increase collagenase expression by posttranscriptional mechanisms and decrease TIMP 1 expression

Molecular mechanisms of glucocorticoid action

Glucocorticoids can affect gene expression by transcriptional and posttranscriptional mechanisms. Although information about glucocorticoid responsive elements (GRE) necessary for transcriptional activation is available, information about sequences operational in genes expressed by the osteoblast is limited. Furthermore, sequence requirements for possible negative GREs are loosely defined (24). In fact, negative regulation by glucocorticoids may be due to indirect mechanisms, such as transcriptional interference. This may be secondary to binding of the ligand-activated receptor to promoter sequences overlapping with binding regions for positive transcriptional factors or to competition with an activator for the transcription initiation unit (24–27). Negative regulation may also involve other protein-protein interactions essential for transcriptional control, including squelching and the degradation of transcription factors into inactive forms either directly or by induction of other nuclear proteins (26). Interactions of glucocorticoid receptors with transcription factors may result in increased gene activation. Occasionally, the response to glucocorticoids is cell specific and secondary to a composite GRE that depends not only on the binding of the activated glucocorticoid receptor to DNA, but also on the presence of additional elements (27). For example, the response of the proliferin gene to glucocorti-

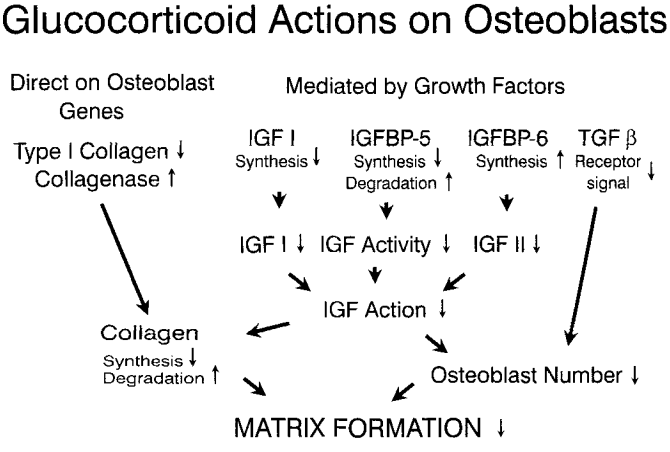

FIG. 2. Mechanisms of glucocorticoid action on the skeleton *in vitro*.

coids is cell specific and depends on the cell content of AP-1 subunits. Glucocorticoid receptors can interact in a positive or negative fashion with a variety of nuclear factors, and studies on the osteocalcin gene have revealed multiple glucocorticoid receptor-binding sites. Some of these sites overlap with DNA sequences important for the 1,25-dihydroxyvitamin D_3 stimulation of osteocalcin gene transcription (28).

Regulation of skeletal growth factors by glucocorticoids

In addition to direct actions on the collagen and collagenase gene, selected effects of glucocorticoids on skeletal cells may be more indirect and involve intermediate modifications in the synthesis, release, receptor binding, or binding proteins of locally produced growth factors (Table 2 and Fig. 2). Skeletal cells synthesize IGF-I, IGF-II; transforming growth factor-β1 (TGFβ1), -2, and -3; acidic and basic fibroblast growth factors (FGF); platelet-derived growth factor Δ (PDGF-Δ); PDGF-β; bone morphogenetic proteins; and additional cytokines (29). Growth factors modify the replication and differentiated function of cells of the osteoblastic lineage, although they may also affect the bone-resorbing process.

IGF-I and IGF-II are among the most important local regulators of bone cell function because of their abundance and their anabolic effects on the skeleton. IGF-I and IGF-II are weak mitogens that increase the replication of cells of the osteoblastic lineage, probably preosteoblasts, which eventually differentiate into osteoblasts (30). Independent of this effect, IGF-I and IGF-II increase type I collagen synthesis by the osteoblast, matrix apposition rates, and bone formation (30). In addition, IGF-I and IGF-II decrease collagenase expression and collagen degradation in calvariae (31). As a consequence of these effects, IGFs play an autocrine role in the maintenance of bone matrix (32). As IGFs and glucocorticoids have opposite effects on bone formation, it is plausible to propose that changes in the IGF axis are central to the inhibitory actions of glucocorticoids on bone formation *in vitro* and *in vivo*. In osteoblasts, glucocorticoids decrease IGF-I synthesis by transcriptional mechanisms, and a glucocorticoid-responsive region of the rat IGF-I exon 1 promoter was localized, but the exact transcription factor responsible for the effect has not been defined (33, 34). Glucocorticoids have inconsistent inhibitory effects on IGF-II synthesis.

Skeletal cells express IGF-I and IGF-II receptors. The IGF-I receptor mediates most of the anabolic functions of IGF. Glucocorticoids have been reported to increase IGF-I receptors in osteoblasts, but the effect was cell number dependent and not consistently found by all investigators (35, 36). The function of the IGF-II receptor in skeletal cells has remained elusive, but glucocorticoids inhibit its expression in osteoblasts by transcriptional mechanisms (36). There is evidence that the IGF-II receptor targets and transports lysosomal enzymes bearing mannose-6-phosphate recognition sites, and consequently, it could play a role in bone resorption (37). The IGF-II receptor binds IGF-II acting like an IGF-binding protein (IGFBP), so that changes in its expression may modify the amount of available IGF-II (38). Its inhibition by glucocorticoids could result in higher levels of available growth factor, but could also result in faster degradation of IGF-II.

TABLE 2. Glucocorticoid regulation of skeletal growth factors

1.	Decrease IGF I transcription
2.	Decrease IGF II receptor transcription
3.	Decrease IGFBP-3, -4, and -5 expression
4.	Increase IGFBP-6 transcription
5.	Activate TGFβ
6.	Shift binding of TGFβ to nonsignal-transducing betaglycan
7.	Increase SPARC to bind PDGF-B

The activity of IGFs is regulated by six IGFBPs, all of which are expressed by osteoblasts (39, 40). The exact function of IGFBPs in skeletal cells is not known, although they are considered important in the storage and transport of IGFs locally. IGFBP-1 is important in glucose homeostasis, and its expression in bone is limited (40). IGFBP-2 is abundant in bone, although little is known about its function. IGFBP-3, the most prevalent circulating IGFBP in serum, transports IGFs to target tissues (39). IGFBP-4 inhibits and IGFBP-5 stimulates bone cell growth (41, 42). Glucocorticoids decrease the expression of IGFBP-3, -4, and -5 in osteoblasts (40, 43). The inhibitory effect of cortisol on the IGFBP-5 gene occurs through transcriptional mechanisms and is mediated by Myb consensus sequences (43). Cortisol increases the levels of collagenase 3, an enzyme known to degrade IGFBP-5, and may modify the stability of the binding protein in osteoblasts (44). As IGFBP-5 stimulates bone cell growth and enhances the effects of IGF-I, the reduced level of IGFBP-5 in the bone microenvironment may be relevant to the inhibitory actions of glucocorticoids on bone formation. IGFBP-6 binds IGF-II with 20–100 times higher affinity than IGF-I, whereas other IGFBPs display similar affinities for IGF-I and IGF-II (45). IGFBP-6 inhibits the effects of IGF-II on DNA and glycogen synthesis in osteoblasts, but it causes only a small inhibition of IGF-I-mediated actions (46). Cortisol increases IGFBP-6 transcription and synthesis in osteoblasts causing a decrease in the amount of free IGF-II (47). Although acting through different mechanisms, a decrease in IGF-I synthesis and an increase in IGFBP-6, glucocorticoids decrease the amounts of IGF-I and IGF-II available to bone cells. These actions as well as a decrease in IGFBP-5 levels, cause a decrease in the replication and differentiated function of osteoblastic cells and contribute to the inhibitory effects of glucocorticoids on bone formation.

TGFβ1, -2, and -3 genes are expressed by skeletal cells (29). TGFβ stimulates bone collagen synthesis and matrix apposition rates and modifies bone cell replication, although the effect varies with the cell line studied (48). TGFβ inhibits selected aspects of the differentiated function of the osteoblast. Glucocorticoids do not modify the expression of TGFβ1 in osteoblasts, but induce the activation of its latent form by increasing the levels of proteases in bone (49). Osteoblasts express two signal-transducing TGFβ receptors, and cortisol shifts the binding of TGFβ from these receptors to betaglycan by increasing the synthesis of this proteoglycan (50). As a consequence, cortisol opposes the effects of TGFβ on cell replication in osteoblastic cells. Whereas the actions of glucocorticoids on the IGF/IGFBP axis and possibly TGFβ appear central to their effects on bone formation, other growth factors do not seem to play a role mediating the actions of corticosteroids in bone. FGF and PDGF have important mitogenic effects for skeletal cells, but do not increase the dif-

ferentiated function of the osteoblast (51, 52). Acidic and basic FGF are expressed by skeletal cells, but there is limited information about the regulation of their synthesis or binding by glucocorticoids. There is limited expression of the PDGF-A and -B genes by the osteoblast, and neither the synthesis nor the binding of PDGF is modified by glucocorticoids. Although there are no specific PDGF-A- or PDGF-B-binding proteins, SPARC (secreted protein acidic rich in cysteine) or osteonectin, an abundant protein in the bone matrix, binds and prevents the biological actions of PDGF-B chains (53). Glucocorticoids enhance osteonectin expression in osteoblastic cells; consequently, they may decrease the activity of PDGF-B chains in bone (54). As there is little PDGF expressed by skeletal cells, this effect may be relevant after platelet aggregation and release of systemic PDGF, as it occurs during the early phases of fracture healing.

Clinical features of glucocorticoid-induced osteoporosis

Glucocorticoid-induced osteoporosis is observed in patients chronically exposed to excessive amounts of glucocorticoids, and they may present with other clinical features of Cushing's syndrome. Analysis of biopsies from patients on glucocorticoids reveals decreased bone matrix apposition rates, decreased trabecular volume, and increased bone resorption (4, 55, 56). Histomorphometric analysis reveals a decline in all aspects of bone formation, except for the calcification front (57). An increase in resorption cavities is noted, but this is considered secondary to a prolonged reversal phase with inadequate filling of previously formed cavities. The function and number of osteoblasts are altered, and the cells are spindle shaped and attenuated. As a consequence, there is a decrease in trabecular bone volume, but not in trabecular number (57–59).

Patients exposed to glucocorticoids in excess have decreased bone mineral density, and 30–50% develop vertebral fractures (3, 55). The degree of bone loss is related to the duration of therapy and the dose used, but is probably not related to the underlying diagnosis, age, or sex of the individual. However, older women with other causes of osteoporosis are more likely to manifest the disease. Patients with glucocorticoid-induced osteoporosis lose more trabecular than cortical bone; consequently, they have greater bone mineral loss in the vertebral spine (3, 55). After initiation of corticosteroid therapy, there is a phase of rapid bone loss followed by a slower, but continuous, decline in bone mineral density. Therefore, the periodic assessment of bone mineral density is recommended. In fact, glucocorticoid therapy is a clear indication for bone mass measurements (60). Ideally, these should be performed before and 6 months after the initiation of therapy and then at yearly intervals. Serum levels of calciotropic hormones, such as PTH and vitamin D metabolites, tend to be within the normal range. Serum calcium and phosphorous are normal, and serum levels of osteocalcin and alkaline phosphatase activity are decreased (14).

Prevention of glucocorticoid-induced osteoporosis

It is difficult to prevent or treat glucocorticoid-induced osteoporosis, except by discontinuation of glucocorticoid therapy, which can result in partial or total restoration of bone mass (61, 62). As discontinuation of therapy is frequently not possible, the use of inhaled steroids for the treatment of bronchopulmonary disorders and the use of glucocorticoids with bone-sparing properties have been proposed. The effects of inhaled steroids on bone metabolism and their contribution to osteoporosis are difficult to assess because they are frequently administered to patients previously receiving oral glucocorticoids, and the number of subjects studied has been limited. There are two major inhaled glucocorticoids: budesonide, which is widely available in Europe but not in the United States, and beclomethasone. There is evidence that inhaled steroids are absorbed, as they suppress serum levels of cortisol, inhibit markers of osteoblastic function, and cause a decrease in bone mineral density, an effect proportional to the dose and duration of steroid therapy (63, 64).

Deflazacort is a synthetic glucocorticoid with antiinflammatory and antiimmune properties similar to those of prednisone. Deflazacort appears to have less detrimental effects on bone and mineral metabolism (65). However, *in vitro* studies have demonstrated comparable inhibitory effects of deflazacort and cortisol on bone DNA and collagen synthesis (66). The discrepancy between *in vitro* and *in vivo* studies may be due to a lesser effect of deflazacort on calcium absorption. However, investigations on the long term effects of deflazacort on bone metabolism and comparison with other steroids are warranted to determine its value in the prevention of glucocorticoid-induced osteoporosis.

Glucocorticoids inhibit the intestinal absorption of calcium, and the use of vitamin D and calcium at 1 g daily in the prevention and treatment of glucocorticoid-induced osteoporosis is indicated. 25-Hydroxyvitamin D (calcifedol) or 1,25-dihydroxyvitamin D_3 (calcitriol) should be administered to increase calcium absorption and decrease bone resorption (4, 67). However, physicians should be cautious when using vitamin D supplementation and monitor patients for the possible development of hypercalcemia. This was reported to occur in about a quarter of patients taking glucocorticoids and receiving calcitriol at 0.6 μg daily and calcium supplementation (67).

Treatment of glucocorticoid-induced osteoporosis

A wide range of therapeutic agents have some effectiveness in glucocorticoid-induced osteoporosis, although most studies have examined a limited number of patients (Table 3). As glucocorticoids increase bone resorption *in vivo*, a therapeutic option is the use of antiresorptive agents such as calcitonin and bisphosphonates. Injectable and nasal spray calcitonin appear effective in the treatment of glucocorticoid-induced osteoporosis. Nasal spray calcitonin at a dose of 200 U daily for 2 yr prevented the decrease in bone mineral density of the lumbar spine and was more beneficial when combined with calcium and calcitriol (67, 68). However, there is no information about its effectiveness in the prevention of fractures. The intermittent use of etidronate, a bisphosphonate, at 400 mg daily for 2-week cycles every 3 months, with or without supplemental vitamin D, has been effective in preventing the bone mineral loss observed in the spine and

TABLE 3. Treatment of glucocorticoid-induced osteoporosis

A.	Currently available
	1. Vitamin D
	2. Calcium supplements
	3. Calcitonin
	4. Bisphosphonates
	5. Sex steroid replacement
	6. Sodium fluoride
B.	Experimental treatment
	1. GH
	2. PTH
	3. IGF

femur of postmenopausal women receiving glucocorticoids (69–71). Information about the effect of calcitonin or etidronate on fracture prevention in glucocorticoid-induced osteoporosis is lacking. Alendronate increases bone mineral density and decreases the incidence of fractures in postmenopausal osteoporosis, but data on its effectiveness in glucocorticoid-induced osteoporosis are not yet available (72). As glucocorticoids suppress gonadotropin secretion, it is reasonable to place hypogonadal patients on sex steroid replacement therapy. However, its efficacy has been documented in a limited number of patients. In a retrospective study, the administration of estrogens to individuals receiving low dose prednisone with amenorrhea resulted in an increase in bone mineral density (73).

Sodium fluoride enhances selected parameters of bone cell function *in vitro*. Therefore, its use in a disease of decreased osteoblastic function seems reasonable. A recent 18-month trial demonstrated that sodium monofluorophosphate and calcium increased the bone mineral density of the lumbar spine in patients taking glucocorticoids (74). Slow release sodium fluoride appears beneficial in the treatment of osteoporosis, and it may also be useful in management of the glucocorticoid-induced disease (75).

Experimental therapy of glucocorticoid-induced osteoporosis

The major effect of glucocorticoids on the skeleton is the inhibition of bone formation. Therefore, it is reasonable to expect that new agents that enhance bone formation could play a role in the therapy of glucocorticoid-induced osteoporosis. It is probable that the actions of glucocorticoids on the IGF axis have a significant impact on bone formation, particularly as IGF and glucocorticoids have opposite effects on bone matrix formation and degradation. One could speculate that the decrease in the synthesis of IGF-I and IGFBP-5 or the increase in the synthesis of IGFBP-6, with its consequential trapping of IGF-II, is central to the inhibitory effect of glucocorticoids on bone formation. Therefore, the restoration of normal concentrations of IGF-I, IGF-II, and IGFBP-5 in bone may be potential avenues to correct the effects of glucocorticoids in bone. IGF-I could be administered systemically and has been used for the treatment of catabolic states and insulin-resistant diabetes (76). Recently, its short term effects on bone metabolism were examined in humans (77–79). IGF-I increased serum levels of type I procollagen peptide, a marker of bone formation, and the urinary excretion of collagen cross-links, a marker of bone turnover. No changes in serum levels of calcium or calciotropic hormones were detected. Although these results are encouraging, it is important to note that the effects of IGF-I were not tested in patients taking glucocorticoids. Furthermore, there are potential problems with the systemic use of IGF-I. Side-effects such as hypoglycemia, edema, postural hypotension, and tachycardia have been reported, and the prolonged use of systemic IGF-I could result in nonspecific effects in nonskeletal tissues. Consequently, the use of IGF-I should be limited to short periods of time and the dose carefully adjusted to avoid side-effects and increases in bone remodeling. It is possible to prolong the half-life of the administered IGF-I by complexing it to IGFBP-3 (80). However, there is no information on the effects of IGF-I alone or with a binding protein on bone mass in humans or experimental animals with glucocorticoid-induced osteoporosis.

An alternative to the systemic administration of IGF-I would be the modification of its synthesis in skeletal tissue. GH enhances IGF-I synthesis in the liver, and circulating levels of IGF-I are GH dependent. However, the effect of GH on IGF-I synthesis in osteoblasts is modest. GH plays a central role in skeletal metabolism and patients with GH deficiency have decreased bone mass (81). Although GH is of benefit in the treatment of these patients, its usefulness in the treatment of idiopathic osteoporosis is less apparent, and it has failed to counteract glucocorticoid-induced osteoporosis in experimental animals (81, 82). Although PTH may be responsible for some of the deleterious effects of glucocorticoids by increasing bone resorption, PTH also induces the synthesis of IGF-I by the osteoblast. Intermittent, but not continuous, PTH could be a therapeutic alternative, as IGF-I mediates the stimulation of collagen synthesis by PTH *in vitro*, and the intermittent use of PTH has anabolic effects in bone *in vivo* (83–85). Although there is no information about the use of PTH in glucocorticoid-induced osteoporosis, PTH reverses the inhibitory effects of glucocorticoids on IGF-I synthesis (Fig. 3). One could postulate the suppression of endogenous, and possibly continuous, PTH secretion with calcium and vitamin D supplementation, followed by the administration of PTH intermittently. Caution will be needed, and potential hypercalcemic effects should be monitored carefully. Another possible experimental therapy could be the development of agents that increase the synthesis of IGFBP-5 or direct its distribution to the extracellular matrix, where it stimulates bone cell growth. Agents that inhibit the synthesis of IGFBP-6 in bone could play a therapeutic role by releasing IGF-II in the skeleton. Other possibilities could include the development of factors that enhance the affinity of IGF-I or TGFβ for their signal transducing receptors or increase the number of receptors. It is important to note that glucocorticoids have multiple effects on bone metabolism, and some are independent of their actions on skeletal growth factors. These include the stimulation of collagenase synthesis and the inhibition of collagen expression, and agents that directly oppose the effects of glucocorticoids on these genes could be therapeutically beneficial.

In conclusion, glucocorticoids have profound effects on skeletal tissue, and there is no ideal therapy for the bone disease caused by these steroids. However, one should consider the use of antiresorptive agents, such as estrogens,

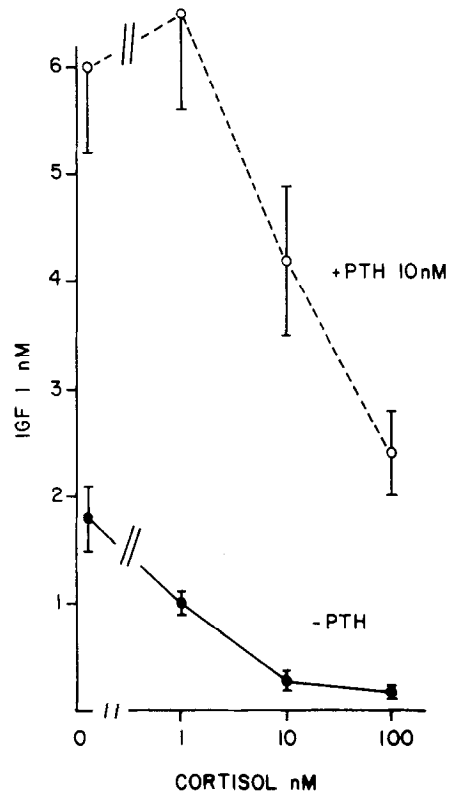

FIG. 3. Effect of cortisol, in the presence and absence of PTH, on IGF-I levels in cultured calvariae.

calcitonin, and bisphosphonates in addition to calcium supplementation and vitamin D. This is particularly important in postmenopausal women. As most of the bone loss occurs in the first 6 months after glucocorticoid administration, early therapy is advisable.

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