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Skeletal Effects of Growth Hormone and IGF-I in Adults

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Introduction

This symposium was organized around a general appreciation that the growth hormone/insulin-like growth hormone (GH/IGF-I) axis undergoes a decline in function during the course of normal human aging. The apparent temporal relationship of these declines to such characteristic somatic changes as increasing adiposity and reductions in muscle and bone mass, changes that also typify adults with acquired GH deficiency, led Rudman *(1)* to propose that some age-related changes in body composition directly reflect diminished GH status, and, further, that GH replacement therapy might be clinically useful in reversing them. The focus of this presentation will be the effects of GH/IGF-I on the adult skeleton. To examine this issue, the author will discuss separately the problem of adults with GH deficiency based on organic pituitary disease and that of GH status of healthy older men and women. The role of the GH/IGF axis on skeletal growth in children is well-described and will not be reviewed.

GH Effects on Bone

The possibility that GH might provide an anabolic stimulus to achieve increased bone mass in adults has been attractive because GH directly stimulates IGF production, and stimulates type-I collagen synthesis in osteoblastic cells *(2–4)*. In a classic experiment *(5)* administration of GH to adult dogs increased bone mass, and recombinant human GH has been shown to maintain trabecular bone mass in primates rendered hypogonadal by a gonadotrophin releasing hormone analog *(6)*. Thus, a combination of in vitro and in vivo evidence invites the conclusion that GH or IGF-I might represent an effective strategy to improve bone mass.

Before describing studies relating to this conclusion, however, it may be useful to review a few points about bone remodeling. It should be remembered that remodeling is a coupled process, that is, resorption events are coupled to and followed over time by bone formation. However, remodeling is not a completely efficient process; at completion of each remodeling cycle, small deficits in bone mass are accrued. It appears that the degree of remodeling inefficiency increases with progressive age, and it is this inefficiency that underlies the process of age-related bone loss *(7)*. Several points directly relevant to skeletal therapeutics can be inferred from this fact: Agents that decrease either the activation of remodeling osteons or the formation of osteoclasts eventually reduce overall bone formation rate, so that it becomes very difficult to achieve substantial gains in bone mass by drugs whose actions are exclusively antiresorptive; there exists at any given time a transient deficit in bone mass representing bone that was previously resorbed, but has not yet been replaced. Agents that activate remodeling expand the remodeling space and transiently decrease bone mass. Any drug that stimulates osteoblast proliferation or function may not increase bone mass in the early months of therapy if it simultaneously increases the remodeling space through a concurrent effect on activation of new remodeling units. These considerations are of particular importance for understanding the skeletal effects of GH or IGF-I, since both can be shown to initiate remodeling activity.

Skeletal Consequences of GH Deficiency in Adults

Deficits in bone mineral density (BMD) compared to age-matched controls have been frequently observed in GH-deficient adults *(8–14)*. Such deficits are particularly striking when GH deficiency emerged during childhood. Three reasons may underlie this fact. First, the consequences of onset of GH deficiency after peak bone mass has been achieved can be manifest only through an increase in the rate of bone loss. Prior to that time, however, deficient bone mass will reflect failure of bone accrual as well as possible superimposition of bone loss, and differences from age-related normative values will be more striking. Second, concomittant deficiencies in other pituitary axes during adolescence may contribute independently to inadequate bone acquisition. These mechanisms have been considered by most reviewers of this topic. However, an additional important feature has received little attention, and reflects the fact that, with the exception of Quantitative

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Computed Tomography, a technique that truly does measure volumetric BMD, most studies have employed dual energy X-ray absorptiometry (DXA) or related planar techniques that do not adequately account for differences in bone size *(15)*. At any given true volumetric bone density, DXA BMD measurements will increase with increasing bone size. Since final adult height may be jeopardized by preadult onset of GH deficiency, the deficits in BMD may be artifactually exaggerated when DXA is employed. Methods to correct for size have been proposed *(15,16)*.

Uncertainty persists over the BMD response to GH-replacement by adults with acquired GH-deficiency. In part, this reflects the timing of BMD measurements. Since GH increases the overall remodeling rate, measurements taken within the first several months of starting therapy predictably show a decrease in BMD, indicative of an expanded remodeling space that has not yet filled in *(17)*. However, some, but not all recent studies indicate eventual increases in BMD with GH replacement *(18–20)*, sometimes to a substantial and clinically meaningful degree *(20)*.

Skeletal Response to GH Administration in Healthy Older Men and Women

Limited experience with human pituitary GH gave interesting results suggesting a possibly useful clinical role for this hormone *(21,22)*. In a 2 yr study, Aloia et al. *(22)* compared the effect of GH followed by calcitonin to that of calcitonin alone in 14 osteoporotic women. GH plus calcitonin increased whole body bone mineral by 2.3% per year, whereas calcitonin alone produced no change. The effect of GH in this limited study seemed to be progressive, that is, without a plateau effect that would have occurred if treatment merely condensed the remodeling space. Unfortunately, the authors did not measure circulating IGF-I, so they could not judge dose adequacy.

With the availability of recombinant human GH (rhGH), therapy of adults became feasible, albeit expensive. The author's research group *(23)* reported the effects of 7 d of rhGH administration to 16 healthy men and women over 60 yr of age. rhGH produced a brisk rise in circulating IGF-I that was associated with striking increases in nitrogen and sodium retention, and a marked increase in urine calcium excretion. Significant increases were observed in circulating osteocalcin and in urinary hydroxyproline, suggesting that bone remodeling had been activated. In this regard, Brixen et al. *(24)* also showed that several daily injections of rhGH in young men initiated a prompt and very sustained elevation in circulating concentrations of osteocalcin.

The most widely publicized clinical trial of growth hormone to date was reported by Rudman et al. *(25)*. In this 6-mo randomized, placebo-controlled trial in 21 elderly men, GH (0.03 mg/kg three times per wk), bone density was assessed at nine different sites by dual photon absorptiometry. A 1.6% increase in lumbar spine mineral density was reported, with no significant changes elsewhere in the skeleton. This marginally significant result, poses methodological questions, as the analysis was conducted without adjustment for multiple comparisons. Papadakis et al. *(26)* conducted another 6 mo trial of GH in older men, and observed only a 0.9% average rise in lumbar spine BMD. These two studies provide little evidence for an anabolic effect of GH, although one must keep in mind that the BMD response was limited by the short duration of treatment.

The author's group has reported a randomized, placebo-controlled 1-yr clinical trial of rhGH (0.025 mg/kg/d) in 23 healthy elderly women *(27)*. GH stimulated a persistent increase in bone turnover. In the treatment group, sustained elevations were observed in circulating IGF-I, osteocalcin, type I procollagen peptide, and bone alkaline phosphatase, as well as in urinary excretion of hydroxyproline. These changes associated with rhGH reverted to baseline values by 3 mo after stopping treatment. Despite clear changes in markers of bone turnover, no significant changes were observed in bone mineral density at either the lumbar spine or the proximal femur. However, BMD at the femoral trochanter and Ward's triangle decre-ased significantly in the placebo group. Thus, although rhGH did not increase bone mass, it may have been responsible for maintaining bone mineral density at the hip.

Recently, Rosen et al. (personal communication) described an interim 12-mo analysis of a 2-yr GH trial in elderly individuals. Using a lower GH dose than had been given in any of the published trials, results gave no evidence that anabolic effects on bone had been achieved. In fact, BMD was significantly lower than baseline in treated subjects. This result probably indicates an expanded remodeling space, as has been reported for brief duration treatment by Holmes et al. *(17)* in adults with GH deficiency.

One may ask why healthy older subjects have shown such a meager response to GH, given the sometimes exuberant findings in younger adults with GHD. Since bone remodeling indices are powerfully affected by GH, even in very old individuals, it seems very unlikely that the hormone is unable to initiate remodeling events. It may be that beyond age 65 substantial loss of remodeling efficiency has occurred, so that any bone formative response to a resorption event becomes obscured. It is also likely that younger adults with organic GH deficiency have, on an absolute basis, greater deficits in GH secretory status than do healthy older individuals. If this were the case, organ sensitivity to hormone replacement would predictably increase.

As mentioned above, Aloia et al. *(22)* explored the possibility that addition of the antiresorptive hormone, calcitonin, to GH, could achieve more substantial increases in bone mass. Features of those studies may have limited the treatment effect. The study drug was human pituitary-derived GH of uncertain potency, and a limited supply of hormone jeopardized statistical power by restricting the

size of treatment groups. The author and his colleagues have now reported the results of a placebo-controlled randomized clinical trial, in which 2-mo cycles of 7 d of GH followed by 5 d of salmon calcitonin (CT) (or their respective placebos) were maintained for two years, with follow-up bone density assessment at 3 yr *(28)*. GH treatment increased IGF-I concentrations from low values at baseline to the young normal range. Groups receiving GH + CT or GH + placebo significantly increased lumbar spine BMD at 2 yr by 2.70 and 1.72 ± 0.74 %, respectively. Significant increases in total hip BMD measurements of 1–2% were observed for the GH groups, but no significant change in femoral neck BMD was observed. Women taking replacement estrogen had the same BMD response as those who were estrogen-deficient. No signifcant increase in BMD was observed between 24 and 36 mo in the 62 women who returned for a 3 yr measurement.

Based on this cumulative experience, it is difficult to justify optimism that any tolerable dose of GH, given as monotherapy or in combination with antiresorptive medication, will provide a major skeletal anabolic effect in elderly men and women. Although a small rise in lumbar BMD or maintenance of BMD at the hip may occur, several antiresorptive agents currently offer even greater protection, and it would be hard to justify the use of an expensive, injectable protein hormone to achieve a poorer result. Since the doses employed are close to maximally tolerated levels, it is unlikely that an upwards adjustment of dose will make the therapy more attractive. However, other strategies involving the somatotropic axis warrant further evaluation. Administration of GH releasing hormone, or GHRH analogs, may permit a more physiologic, pulsatile release of endogenous GH, which might conceivably provide a superior skeletal response. Even more interesting is recent evidence that IGF-I is skeletally anabolic. Ebeling et al. *(29)* and the author's own group *(30)* have both reported that low doses of recombinant IGF-I substantially increase bone formation activity and only slightly increase bone resorption activity in older women. These results suggest the rationale for a clinical trial of IGF-I in osteoporotic postmenopausal women.

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