INTRODUCTION

Since the first demonstration of the activity of human and monkey pituitary growth hormone (GH) extracts in humans (1, 2), research regarding the effect of GH on bone have focused primarily on the hormone’s promotion of linear growth. In the last decade, however, the importance of the role of GH in bone metabolism has become increasingly apparent. Recent research has demonstrated that GH administration stimulates osteoblast proliferation and promotes bone formation in vitro and in vivo, and that GH deficient states are associated with osteoporosis. In addition, normal aging has been shown to be associated with both declining GH secretion and declining bone density, suggesting a possible link between GH and senile osteoporosis. A number of technical advances have aided this work. In vitro studies have been advanced by new cell-culture techniques and recombinant DNA technology. Studies of bone metabolism in humans have assessed bone turnover with a widening array of serum and urine markers. These include osteoblast markers, byproducts of bone formation, and urine markers of bone resorption. Furthermore, refinements in the measurement of bone mineral content and bone density have permitted long term studies of the effect of GH administration on bone mass. This chapter will address the relationship between GH and osteoporosis by reviewing in vitro studies of GH and bone cells, studies of patients with GH deficiency, and studies of GH administration using different model systems.
MOLECULAR, CELLULAR, AND HISTOLOGIC EFFECTS OF GH

The effects of GH on longitudinal bone growth at the cellular level are well-established. GH acts at the growth plate, where it binds to chondrocytes and promotes local synthesis of insulin-like growth factor (IGF-1) (3–5). GH stimulates the differentiation of growth-plate precursor cells and increases the responsiveness of these cells to IGF-1. Clonal expansion of differentiating chondrocytes, and thus longitudinal bone growth, is stimulated primarily by locally produced IGF-1, though GH and circulating IGF-1 may also have a role (3).

An effect of GH on bone density, however, especially in patients whose epiphyses have fused, depends on the ability of GH to affect bone formation by osteoblasts, rather than simply to promote proliferation of growth-plate chondrocytes. GH has been shown to stimulate the proliferation of osteoblast-like cells cultured from fetal rat calvaria, and this effect is dependent on local synthesis of IGF-1 (6). GH stimulates DNA synthesis as measured by labeled thymidine incorporation in fetal chicken osteoblasts, an effect which is enhanced by a serum factor, presumably IGF-1 (7). In addition to promoting cell division, GH also stimulates collagen production and inhibits collagen breakdown in fetal rat osteoblasts (8,9), suggesting a positive effect of GH on bone formation. Specific GH and IGF-1 receptors have been identified on rat osteoblasts (10,11), supporting the hypothesis that effects of GH and IGF-1 on osteoblasts are receptor-mediated. IGF-1 enhancement of cell replication and collagen gene expression may depend on GH-induced local production of IGF binding protein 3 (IGFBP-3). IGF-1 effects on osteoblasts in cell culture are less pronounced when GH and the resultant synthesis of IGFBP-3 are absent and when IGF-1 binding to IGFBP-3 is blocked (12).

GH may also influence bone density through effects on vitamin D metabolism. Hypophysectomized rats demonstrate a marked fall in plasma levels of 1,25 dihydroxyvitamin D, which is not explained by a change in circulating parathyroid hormone (PTH), calcium, or phosphorus levels (13). Furthermore, hypophysectomy eliminates increases in plasma levels of 1,25 dihydroxyvitamin D as well as in vitro production of the vitamin by kidney slices ex vivo normally seen with phosphate deprivation. GH treatment of these animals restores normal 1α-hydroxylase activity (14). Such GH effects on vitamin D metabolism could theoretically mediate increases in bone density through increased calcium absorption or local effects on bone mineralization.

Positive effects of GH on bone accretion have been characterized histologically in studies of GH administration in dogs (15,16). Harris and Heaney published two studies in which dogs received pharmacologic doses of GH for 12 wk, and bone formation rates were determined using tetracycline labeling. Examination of cortical bone specimens from several skeletal sites showed that the formation of endosteal bone was markedly accelerated by GH administration, with significantly increased bone mineral accretion and a 30% decrease in fecal calcium loss owing to increased absorption (15). However, these experiments have not been replicated, and their applicability to humans remains uncertain.

Extensive experimental evidence in vitro and in vivo therefore indicates that GH plays an important role in maintenance of the skeleton. These data have also provided a rationale to explore the possible therapeutic benefit of GH on bone density in states of GH deficiency and osteoporosis. In humans, however, these issues are complex, because GH deficiency (GHD) may vary in timing, etiology, and severity. Because GH is administered as an injection, whereas endogenous GH secretion occurs in pulses,