

Advances in Recombinant Human Growth Hormone Replacement Therapy in Adults

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Acquired growth hormone (GH) deficiency results from the destruction of normal pituitary and/or hypothalamic tissue, usually from a tumor or secondary to surgical and/or radiation therapy. Diagnostic criteria and clinical sequelae of GH deficiency, although well established in children, are currently areas of active investigation in the adult. It is now apparent that acquired GH deficiency is associated with significant changes in body composition, bone density, lipid metabolism, cardiovascular function and physical performance. In addition, new information is now available on the use of low doses of recombinant human growth hormone (rhGH) to reverse the sequelae of GH deficiency in adults.

The Growth Hormone Deficiency Syndrome

Acquired GH deficiency is characterized by weight gain, increased fat mass and decreased lean body mass. In one recent study, total body fat was shown to be increased by 7% in this population while lean body mass was decreased to a similar degree (1). The increased fat mass is found in a truncal distribution, thereby increasing the waist:hip ratio. In addition, triglyceride levels are increased and HDL levels decreased. The increased lipid levels may explain, in part, the observation of increased vascular wall thickness, as measured by carotid ultrasonography, in this population. These factors all likely contribute to the increased incidence of cardiovascular mortality seen in patients with GH deficiency (2).

Muscle mass and muscle strength are diminished in GH-deficient patients. In the heart, these changes are manifested by a reduced left ventricular mass, decreased fractional shortening of cardiac myocytes, and decreased cardiac output. Such abnormalities may contribute to the striking decline in exercise capacity in this population. In one recent study, exercise capacity, as assessed by cycle ergometry was decreased by 20-25% compared to normal controls (3). Bone density is also known to be reduced in the GH-deficient patient. In a recent study, cortical bone density and spinal (trabecular) bone density were 2.8 and 1.5 standard deviations below the mean for age and sex matched controls (4).

Finally, patients with GH deficiency appear to have impaired psychological well being and potentially significant neuropsychiatric manifestations, such as lack of concentration and memory impairment. Self rating questionnaires consistently demonstrate reduced vitality, fatigue, social isolation and de-

pression (5). However, it is unknown whether this impairment in psychological well being is associated specifically with GH deficiency or is due to another factor associated with hypopituitarism.

Recombinant Human Growth Hormone Therapy

Recombinant human growth hormone may become a novel therapeutic option for adults with acquired GH deficiency. Recent studies indicate that many of the metabolic and psychological abnormalities associated with GH deficiency can be reversed with GH replacement, even at low doses which are not associated with side effects.

Body Composition

GH therapy results in profound changes in body composition: fat mass is reduced while lean body mass increases. Growth hormone, at the relatively low dose of 0.003 mg/kg was shown to normalize lean body mass over 6 months in 24 adults with GH deficiency (1). The improvement in lean body mass is associated with increased protein synthesis, muscle mass and muscle function. Total body fat mass also decreases after 6 months of GH administration. The decline in fat mass is most significant in visceral and trunk locations as compared to the arms, neck and legs, suggesting that GH replacement therapy will reverse the truncal redistribution of fat mass associated with GH deficiency and impact on cardiovascular risk (6).

Lipid Metabolism

GH replacement in adults may have a beneficial effect on lipids. In a recent study, it was reported that short courses of GH reduced LDL cholesterol and this reduction correlated with increased mRNA expression of the LDL receptor in the liver (7). The potential benefit of this interaction has yet to be investigated in longer term clinical trials, but it must be noted that dramatic changes in serum lipid levels are not consistently seen with GH administration.

Bone Density

The potential role of GH in the maintenance of the skeleton has recently been investigated. GH is known to stimulate osteoblast proliferation and thymidine incorporation in vitro. Furthermore, GH stimulates systemic and local production of Insulin Like Growth Factor I, another known bone mitogen. In a recent study, GH replacement was shown to increase significantly bone Gla-protein, a sensitive indicator of osteoblast function (8). Less consistent changes in bone density have

been demonstrated with GH administration. However, in a recent study using the sensitive techniques of quantitative tomography and single photon absorptiometry, significant increases of 5% and 4% were demonstrated in spinal and cortical bone density over 12 months of therapy in GH-deficient adults (4). It thus appears that GH administration may act to reverse the osteopenia present in the GH-deficient patient.

Cardiovascular Function

Improvements in exercise capacity and cardiac function have been demonstrated among GH-deficient patients receiving GH replacement in several recent studies. Such patients show increased oxygen uptake and power output during cycle ergometry associated with increased skeletal muscle mass and improved cardiac function. Echocardiography has shown that left ventricular mass index, fractional shortening and fiber shortening velocity all improve after 6 months of low dose GH therapy (8).

Side Effects Associated with Low-Dose GH Replacement

The dose of rhGH is an important consideration in the therapy of acquired GH-deficiency. Large, pharmacological doses of GH are often associated with the clinical sequelae of GH excess, including fluid retention and hypertension. However, increasingly smaller, physiological, doses of rhGH are currently being used for replacement in GH-deficient patients without such sequelae. At a dose of 0.03 mg/kg/week, Bengtsson et al. demonstrated only minor side effects including fluid retention and mild arthralgias in the majority of patients but did report carpal tunnel syndrome in one patient (6). In all cases, further reduction of the GH dosage resulted in amelioration of side effects. In another recent study in which a smaller dose of GH was used, 0.01 mg/kg was administered three times per week without any reported side effects (8). It remains unknown, however, whether chronic administration of GH at doses which keep IGF-I levels within the normal range will also improve key metabolic variables.

Future Directions

Growth hormone deficiency is an important cause of excess morbidity and even mortality. Evidence from a number of smaller studies indicates that GH replacement will improve body composition, lipid metabolism, bone density, cardiovascular function and psychological well being. Important issues remaining are the precise clinical definition of partial vs. complete GH deficiency in such patients and clarifying the best tests to make this diagnosis. In addition, it is unclear whether some of the observed beneficial effects reflect pharmacological GH therapy rather than physiologic GH replacement. Nevertheless, it is apparent that small doses, unassociated with

sequelae of GH excess, may suffice to achieve the desired metabolic results. Definitive recommendations on dosage and the long term effects of GH therapy, particularly on cardiovascular morbidity and mortality, will be determined by the prospective studies now underway at the MGH and other centers around the country.

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