

Growth Hormone Sensitivity in Obesity

These authors sought to explore the observation that insulin-like growth factor (IGF)-I levels remain normal in obesity despite reduced growth hormone (GH) levels. Ninety-one healthy adults (mean age about 50; range 21-82 years) were subdivided by body mass index (BMI) and gender; there were 19 normal weight men, 23 normal weight women, 15 obese men and 34 obese women (obesity defined as BMI > 30). Fat mass and percent body fat were measured by bioimpedance. GH sensitivity was assessed by an IGF-I generation test, with IGF-I levels measured before and 24 hours after a single, standard 7mg dose (21IU) of GH. The increment in IGF-I was greater in obese than normal-weight equivalents, negatively correlated with baseline IGF-I concentration, positively correlated with GH binding protein (GHBP) level, and seen in both men and women (pre- and post-menopausal). GHBP concentrations were higher in obesity, and also correlated with BMI, fat mass and percent body fat. The authors concluded that their study provides evidence of increased GH sensitivity in obesity. The fact they used a single, standard GH dose makes the result cleaner than earlier studies that employed a weight-based GH dosing scheme; IGF-I levels were higher in obese subjects, but in those studies, the obese subjects also received a greater GH dose. Because GHBP is the extracellular domain of the GH receptor (GHR), it is sometimes used as an indirect measure of GHR number. The finding of a positive association between GHBP level, markers of obesity and IGF-I increment led the authors to hypothesize that the enhanced GH sensitivity of obesity may be due to increased GHR density, itself resulting from the lower GH levels. Because the data are all associative, further studies are needed to test this hypothesis.

Gleeson HK, Lissett CA, Shalet SM. IGF-I response to a single bolus of growth hormone is increased in obesity. *J Clin Endocrinol Metab* 2005;90:1061-7.

Editor's Comment: *This paper clearly showed increased*

hepatic sensitivity to GH in obesity, at least in terms of IGF-I generation, which helps to explain the discordance between the low GH but normal IGF-I levels seen in obesity. The pediatric correlate of this adult study is the enhanced growth frequently experienced by obese children who continue growing despite GH deficiency (classically, craniopharyngioma patients who develop hypothalamic obesity and GH deficiency); the growth without GH phenomenon is reviewed in Reference 1. Proposed mechanisms include hyperinsulinism-stimulated growth, decreased IGFBP-1 levels resulting in increased bioavailable (free) IGF-I, and increased growth plate stimulation by sex steroids (increased aromatization by the greater adipose mass). An interesting finding came from studies of a model of endochondral ossification, the chondrocyte population of the skeletal growth centers in the mouse mandibular condyle. The growth center chondrocytes expressed leptin receptors and when stimulated by leptin, increased expression of IGF-I receptor, increased both proliferation and differentiation processes, and had larger growth plate growth.² Furthermore, when mice were calorie-restricted by 40%, circulating IGF-I levels dropped by 70% and tibial growth decreased by 5%; leptin treatment corrected the growth deficit despite further reductions in circulating IGF-I levels.³ Thus, the growth-promoting consequences of obesity are multi-factorial, and it will be interesting to see if enhanced hepatic GH sensitivity, perhaps due to increased GHR density, also plays a role in the growth of obese children.

Adda Grimberg, MD

References

1. Phillip M, Moran O, Lazar L. *J Pediatr Endocrinol Metab* 2002;15 Suppl 5:1267-72.
2. Maor G, Rochwerger M, Segev Y, Phillip M. *J Bone Miner Res* 2002;17:1034-43.
3. Gat-Yablonski G, Ben-Ari T, Shtaf B, et al. *Endocrinology* 2004;145:343-50.

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