

mean bone age delay of  $4.3 \pm 2.7$  years, and peak GH response in 2 stimulation tests ranging from  $<0.1$  to  $3.3$  mcg/L). All children were prepubertal with a mean age of  $8.6 \pm 4.1$  years, and treated exclusively with GH at a mean dose of  $32$  mcg/kg/day adjusted to weight every 3 to 4 months. Seventeen percent of subjects had a defined genetic etiology for GH deficiency, 63% had ectopic posterior pituitary and 25% had interrupted stalk on MRI imaging; only 8% had idiopathic GH deficiency, and patients with central nervous system tumors, meningoencephalocele or previous radiation therapy were excluded from the study.

Among the 71 subjects, 21% had  $-202$  IGFBP3 genotype of AA, 54% had AC, and 25% had CC. The genotype subgroups did not differ clinically at the start of treatment, nor in mean GH treatment doses. Mean circulating IGFBP-3 levels also were not significantly different at baseline, they gained significance with GH treatment; AA subjects had higher IGFBP-3 levels than C allele carriers in codominant ( $P<0.005$ ) and recessive models ( $P<0.001$ ), and developed greater increases in IGFBP-3 z-scores with treatment. The IGFBP3 polymorphism accounted for 19% of variability in circulating IGFBP-3 levels ( $P<0.001$ ) and 54% of variability when combined with age and gender.

The IGFBP3 polymorphism did not associate with IGF-I levels either at baseline or during GH treatment, but it did affect growth response to treatment. Mean first year growth velocity was  $13.0 \pm 2.1$  cm/year in AA subjects,  $11.4 \pm 2.5$  cm/year in AC subjects, and  $10.8 \pm 1.9$  cm/year in CC subjects ( $P<0.05$ ). Single and multiple linear regression analyses found the effect of IGFBP3 polymorphism independent of other variables in associating with growth velocity. It accounted for 10% of variability in growth velocity ( $P<0.005$ ) and 29% of variability when combined with height z-score and age at start of treatment.

This is the first study of the  $-202$  A/C IGFBP3 polymorphism in children. Because the genotype was significantly associated with circulating IGFBP-3 levels in healthy adults and in children with severe GH deficiency only after GH treatment but not at baseline, the authors concluded the effect is at least in part dependent on GH action.

Costalonga EF, Antonini SR, Guerra-Junior G, Mendonca BB, Arnhold IJ, Jorge AA. The  $-202$  A allele of insulin-like growth factor binding protein-3 (IGFBP3) promoter polymorphism is associated with higher IGFBP-3 serum levels and better growth response to growth hormone treatment in patients with severe growth hormone deficiency. *J Clin Endocrinol Metab.* 2009;94:588-595.

**Editor's Comment:** *This study conveys 2 important lessons. First, the results may seem counter-intuitive: the genotype associated with the highest IGFBP-3 levels had the greatest growth response to GH treatment. The IGFBP3s were defined by their high-affinity IGF binding that renders them competitive inhibitors for IGF binding to the type 1 IGF receptor (IGF1R), and hence inhibitors of IGF action.<sup>3</sup> This is an isolated effect. The situation in vivo and some in vitro cell models is more complex, because the balance of ligand binding protein receptor and post-receptor signaling pathways is modulated by multiple factors. Such factors include, but are not limited to, changes in ligand half-life, local IGFBP proteases that convert the high-affinity IGF binders to lower affinity IGFBP fragments, IGF1R trafficking and down-regulation, and interactions with other cell signaling systems. Plus, we now appreciate that the IGFBP3s exert IGF-independent actions of their own.*

*Secondly, this study highlights yet another factor that influences patient responsiveness to GH treatment. I applaud the authors' focus on clearly defined subjects with severe GH deficiency, rather than opening up their sample size to less severe and thus, heterogeneous, patients who may harbor other alterations in their GH/IGF axis function. The authors concluded their paper with the suggestion that future pharmacogenetic studies may support adjusting GH treatment to genotype in order to individualize and thereby optimize therapy. Before moving to genotyping—which is expensive and not readily available—clinicians already have tools to individualize therapy. For example, titrating GH dose to achieve desired IGF-I z-scores, as the principle mediator and biomarker of GH effects, is akin to titrating l-thyroxine dose to thyroid function tests when treating patients with hypothyroidism.<sup>4</sup> This paper provides additional data supporting the notion that the traditional, cookie cutter, one-size-fits-all, weight-based dosing of GH therapy can be improved by individualized approaches to optimize treatment efficacy and safety.*

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## References

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## GH Treatment for Growth Failure in Pediatric Patients with Crohn's Disease

Heyman and colleagues studied the effects of growth hormone (GH) treatment ( $0.043$  mg/kg/day;  $0.3$  mg/kg/week) on height velocity, body composition,

and disease activity in a group of children and adolescents (mean age  $12.6 \pm 4.5$  years; 6 males) with Crohn's Disease (CD) and growth failure. All

subjects had a confirmed endoscopic, histological, and/or radiographic diagnosis of CD and height below the 5<sup>th</sup> percentile for age with no evidence of catch-up growth (increase in height z-score of 0.5) for the year prior to GH therapy. Exclusion criteria included hepatic abnormalities, renal disease, history of non-compliance, and pre-existing scoliosis. Subjects were seen at baseline and every 3 months for 12 months for a history, physical assessment of anthropometric measurements, calculations of BMI and body fat mass, as well as laboratory studies to evaluate disease activity. Nutritional state, serum vitamin B12, iron levels, red blood cell folate, plasma insulin-like growth factor (IGF)-I and IGF binding protein (IGFBP)-3 were measured at each visit and the CD activity was characterized using the Pediatric CD Activity Index (PCDAI). Bone age was determined by wrist radiography. Bone density and body composition were assessed using DEXA at the lumbar spine (L1 to L4) and hips. Age adjusted values were used for comparison and variation of z-scores. The comparison control group was gathered from the PEDI IBD Consortium Registry which included consecutively enrolled patients from 6 sites with inflammatory bowel disease; 989 children were identified as having CD. For each subject receiving GH, 3 comparison subjects with CD were retrospectively matched by age, sex, race, and height (at baseline). The patients in the control group were receiving standard treatment and nutritional supplementation for CD.

The study group had a mean bone age of 10.7 years with an average diagnosis of CD for 2.7 years, PCDAI of 21.9, a height z-score of -2.48, and a weight z-score of -1.88 with a previous year's growth velocity of 2.8 cm/year. The control group had a similar age, and a mean height z-score of -1.8 with a mean weight z-score of -1.19. Each patient remained on his or her clinically indicated therapy for CD which included temporary total parenteral nutrition (TPN), elemental formula diet, or regular diet. All subjects consumed more than 85% of the RDA of calories for age. BMI did not increase significantly from baseline at 12 months, however DEXA scans at 1 year of GH treatment demonstrated an increase in mean lumbar z-scores and a decrease in mean percent body fat; the bone age increased by 0.97. IGF-I level increased from  $249.4 \pm 146.8$  to  $447.1 \pm 242.6$  at the end of treatment. Mean IGF-BP3 was within the range adjusted normal range. No significant changes in thyroid functions, or electrolytes were observed. Mean height velocity increased from  $3 \pm 1.39$  cm/year at baseline to  $8.32 \pm 3.2$  cm after 1 year of GH. Within the control group the mean height velocity was  $3.98 \pm 2.32$  cm/year at baseline and  $4.84 \pm 2.85$  cm/year after 1 year; this difference was significant. The height z-score increased by 0.76 and the weight z-score increased by 0.81 as compared with increases

of 0.16 and 0 in the control group. The mean PCDAI was 21.9 at baseline and 13.1 after 1 year of treatment. No subject experienced any adverse reaction to GH. Two patients were excluded from the comparison, one of whom had a disease exacerbation requiring 2 hospitalizations during the 12 month study period and the other due to a lack of a matched comparison.

The authors stated that their data suggest that children with CD treated with GH experience increased height velocity and improved bone mineral density. There have been 10 other pediatric inflammatory bowel disease uncontrolled GH trials. Results from these studies have varied, but they have included small numbers of subjects and no disease controls. The authors noted that despite the increase in growth, there was no consistent clinical improvement in CD activity. Thus, it would appear that GH is not a primary treatment strategy for CD. They also noted the limitations of having used a retrospective comparison group and the small size of their study, which prohibited controlling for concomitant medications, including corticosteroids and other supplements. They concluded that a larger randomized trial of GH therapy in CD is needed.

Heyman MB, Garnett EA, Wojcicki J, et al. Growth hormone treatment for growth failure in pediatric patients with Crohn's Disease. *J Pediatr*. 2008;151:651-658.

**Editor's Comment:** *The authors reported that growth impairment is seen in about 40% of pediatric patients with CD and that this often leads to short stature in adulthood. The possible etiology of this growth failure may include anorexia, inflammation, direct effects of cytokines on bone, GI nutrient losses, GH resistance with low IGF-I and other medications including corticosteroids. Of note, growth impairment may precede the onset of intestinal symptoms in CD.*

*Pediatric endocrinologists recognize the importance of looking for inflammatory bowel disease when evaluating children with short stature. Indeed CD is occasionally diagnosed during the evaluation for short stature prior to any GI symptoms. The authors clearly pointed out that other studies have shown variable results when GH is used to treat short stature and growth failure in CD and the limitations of those studies.*

*Studies of growth impairment in complex disease states such as CD may provide information on the importance of a variety of different disease processes associated with growth failure. In other words, are inflammatory processes critical or is the effect of cytokines on bones critical? Thus a study of a large number of individuals for whom assessments of these factors have been well characterized may lead to an important understanding of growth, not just in CD, but in other chronic disease processes.*

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