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## Abstracts from the Literature

### Leptin-Replacement Therapy for Lipodystrophy

Severe lipodystrophy is known to be associated with leptin deficiency, insulin resistance, hypertriglyceridemia and hepatic steatosis. Thus, the authors assessed whether leptin-replacement would ameliorate this condition and its complications. Nine female patients (ages 15 to 42 years; 8 with diabetes mellitus) with lipodystrophy of various types, with serum leptin levels of less than 4 mg/ml, and with high insulin levels received recombinant methionyl human leptin subcutaneously twice a day for four months in escalating dosages (0.03 mg to 0 – 0.4 mg/kg/day) to obtain low, intermediate, and high physiologic serum levels of leptin. During the treatment, the serum leptin levels increased from a mean of 1.3 +/- 0.3 mg per ml to 11.1 +/- 2.5 mg per ml.

The glycosylated hemoglobin values in the diabetic patients decreased, a mean reduction of 1.9%. After four months of therapy, the average triglyceride levels decreased by 60% and the liver volume diminished in size by an average of 28% in all patients. Leptin also led to a discontinuation or a large reduction in the anti-diabetes therapy. The self-reported daily caloric intake also decreased significantly. No major problems or side effects occurred. The authors concluded that leptin replacement improved glycemic control and decreased triglyceride levels in patients with lipodystrophy and leptin deficiency.

Elif AO, et al. *N Engl J Med* 2002;346:570-578.

**Editor's Comment:** *These investigators demonstrated that leptin deficiency contributes to insulin resistance and other metabolic abnormalities associated with severe lipodystrophy. The reduction of glycosylated hemoglobin associated with leptin therapy is important, reflecting improved diabetic control. This could lead, if the effect persists, to a decrease in the relative risk of retinopathy and/or nephropathy in the diabetic population. The decreased triglyceride levels may reflect a reduced relative risk of adverse cardiovascular events. The alterations that characterize lipodystrophy are known to be refractory to other treatments, and, therefore, this paper reports a novel action of this hormone in addition to its known role in the control of energy homeostasis.*

*For those readers wishing more information regarding leptin, consult the article in the last issue (GGH 2002 Vol 18:2), which is entitled "The Endocrine Function of Adipose Tissue" and the article entitled "Molecular Physiology of Leptin and Its Receptor" (GGH 1998 Vol 14:2). Several articles from the literature concerning leptin have been abstracted in GGH since 1998.*

Fima Lifshitz, MD

### Effect of Growth Hormone Therapy on Height in Children with Idiopathic Short Stature: A Meta-Analysis

The authors reviewed all published (English language) manuscripts and manually searched all issues of the *JAMA*, *Journal of Pediatrics*, *Pediatrics*, and *Acta Paediatrica*, and the meeting abstract books of the *Lawson Wilkins Pediatric Endocrine Society* and the *Endocrine Society* between 1985-2000 for publications (N=761) that reported primary effects of recombinant human growth hormone (rhGH) on the growth of children. From this group, the authors culled those

papers reporting adult stature in more than 5 healthy children with "idiopathic" short stature treated with rhGH whose heights were below the 10th percentile at the initiation of treatment and who had "normal" GH secretion ( $\geq 10$  ng/mL during provocative testing) and in which more than 50% of the starting population completed the study. From this pool, 19 articles describing 10 controlled studies (N=434) and 34 articles reporting 28 uncontrolled studies (N=655) were selected

for more thorough analysis. In both groups the mean age at the beginning of treatment was 10-11 years, baseline growth rates were approximately 4.3 cm/year, and therapy with rhGH was maintained for approximately 5 years.

In the *controlled* studies, adult stature of rhGH-treated children exceeded that of the control group by 0.84 SD (5-6 cm) with the treated group achieving an adult stature of -1.51 SDs and the control group -2.29 SDs. The adult stature of the rhGH-treated group exceeded their pretreatment predicted adult height by 0.54-0.65 SDs (+3.6-4.6 cm). In the *uncontrolled* studies, the adult stature of the rhGH-treated group exceeded their pretreatment predicted adult height by 0.56-0.63 SDs (+3.8-4.5 cm). The authors concluded that administration of rhGH can modestly increase the adult stature of children with idiopathic short stature. They estimated the cost of treatment to be approximately \$14,170/cm (\$35,000/in). The authors discuss the limitations of this meta-analysis (such as the heterogeneity of the populations treated; absence of data on those children who did not complete the course of treatment with rhGH) and point out that there are no data demonstrating any beneficial effect of treatment on psychological well-being, educational achievement, or vocational advancement.

Finkelstein BS, et al. 2002 Arch Pediatr Adolesc Med 156:230-240.

**Editor's Comment:** The authors are to be complimented on the completion of an arduous task. Of concern to this reviewer is the inclusion criterion for short stature of height below the 10th percentile. This reviewer cannot imagine that there are any pediatric endocrinologists who prescribe rhGH for otherwise normal children with heights between the 3rd-10th percentiles. One would very much like to see the data reanalyzed to include only children with heights below the 3rd percentile (or -2 SD) at the initiation of therapy. Among the questions

that would be of interest to answer are: 1) Was the growth promoting effect of rhGH more apparent in those with the shortest stature? 2) Did the children with familial (intrinsic/genetic) short stature respond more/less favorably than did those with non-familial short stature? 3) Did pre-treatment skeletal maturation influence the linear growth response to rhGH?

In addition to the data analyzed by Finkelstein et al, two additional reports of the effect of rhGH on adult stature in children with idiopathic short stature have been published. Lopez-Siguero et al<sup>1</sup> observed a mean gain in adult height of 4.5 cm in 30 boys treated with rhGH compared to an historical control group of 42 lads. Wit and Rekiers-Mombarg<sup>2</sup> reported that treatment with rhGH (0.17-0.32 mg/kg/week for approximately 7 years) resulted in a gain in adult height SD score of 1.3 versus baseline height in 53 patients with idiopathic short stature (12 born small for gestational age) as compared to a gain of 0.7 SD in an historical control group of 64 subjects. There was an increment of 4 cm in adult height over pretreatment predicted adult height in those children receiving rhGH (+0.8 cm in controls). In children who received the highest dose of rhGH (0.32 mg/kg/week) throughout the study, the increment in adult stature over pretreatment predicted adult height was 7 cm. These authors concluded that higher doses of rhGH led to greater increments in gain in adult height. However, they also concluded that in the absence of proven benefit of greater stature on well-being, the ethical controversy about the administration of rhGH to healthy children, and the high cost of rhGH treatment, "rhGH treatment for (idiopathic short stature) cannot be advised in general." This reviewer would agree with this conclusion.

Allen W. Root, MD

1. Lopez-Siguero JP, et al. J Pediatr Endocrinol Metab 2000;13:1595-1602.
2. Wit JM, Rekiers-Mombarg LTM. J Clin Endocrinol Metab 2002;87:604-611.

## Centers for Disease Control and Prevention 2000 Growth Charts for the US: Improvements to the 1977 National Center for Health Statistics Version

The childhood growth charts used by most centers in North America are the charts produced by the National Center for Health Statistics (NCHS) in 1977. There are a number of problems with those charts that have been overcome in the newly produced charts from CDC. Specifically, the 1977 charts did not fully represent a cross-section of children living in the U.S. They were also deficient in including breast-fed infants. They did not make the transition well, using the recumbent lengths

on the infant charts and standing heights on the childrens-adolescents growth charts, and only heights up to 18 years of age were utilized. The new charts follow adolescents up to 20 years of age. The new charts also allow both percentiles and z-scores to be determined and provide body mass index for age charts and smooth the percentile curves.

The national data collection in a series of five surveys between 1963 and 1977 were used to develop the 2000