

method was height deficit, meaning that the child was a certain amount shorter than he would have been had he continued to grow at a previous rate. Some studies used height z-scores.

The most sensitive studies were the longitudinal studies analyzing periodic observations taken before and after the initial period of treatment. Half of these studies (8 of 16) showed an attenuation of growth on the stimulants by at least 1 method, most reliably a change in height z-scores. The most scientifically rigorous study was one in which children with ADHD were randomly assigned to different treatment groups. This study showed a height deficit of 0.9 cm/yr in the first 14 months and 1.04 cm/yr from 14–24 months in children who received pharmacological treatment. Eight of the longitudinal studies used normative data as the controls, three of which showed an attenuation of height.

The studies of late adolescent and adult heights were mostly cross-sectional, and none showed any significant difference between those treated and the controls. The author stated that many of the studies were of poor quality. However, those of better quality demonstrated a significant association between treatment and attenuated height growth. The conclusion was that despite the large number of studies, most of those failed to detect any adverse affect on growth due to stimulant medication. Many did not stand up to any rigorous analysis. They further stated that it is reasonable to anticipate a reduction in height velocity when children are placed on stimulant medication, but that further studies should be performed in order to better understand the significance of this reduction.

Poulton A. Growth on stimulant medication; clarifying the confusion: a review. *Arch Dis Child*. 2005;90:801–806.

First Editor's Comment: *This paper is a welcome analysis of a large number of studies involving stimulant medications and the measurement of height in children with ADHD. Pediatric endocrinologists are often faced with the question of whether or not stimulant medication will adversely affect growth, and it is very difficult to*

reference opinions with well-conducted longitudinal trials. Thus, one is left with the conclusion that the results are uncertain. Poulton has shown that at least in those studies that were more rigorously performed, there did seem to be a significant height deficit in these children. However, he also points out that children often do not remain on stimulant medications for the duration of their linear growth. Thus, an overall effect on final height is difficult to discern. This review will hopefully encourage investigators to perform the kinds of studies needed to answer this question conclusively. Such studies need to be randomized, control trials with varying doses of stimulant medications. With so many children currently receiving these medications, such a trial seems feasible.

William L. Clarke, MD

Second Editor's Comment: *The efficacy of ADHD treatment and the growth of patients was also studied by the MTA Cooperative Group at the National Institutes of Mental Health¹ and reviewed in GGH.² It was clearly documented that there were behavioral benefits in treating ADHD patients, but there was decreased growth (–1.9 cm in height suppression in 24 months). As well, there were weight changes (–2.5 kg in the first 14 months and –1.22 kg in the following 20 months of treatment). These changes were more prominent in patients who adhered to the medication regimen. However, there were many who stopped taking the medication and thus, the effects were less marked. Suboptimal nutrition may play a role in the reduced growth and weight gain due to the effects of these medications. Thus, when these medications cannot be interrupted, physicians should attempt to overcome the decreased dietary intake and correct any nutrient deficits.*

Fima Lifshitz, MD

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Cardiovascular Effects of Adolescent Growth Hormone Deficiency

The metabolic effects of growth hormone (GH) led to FDA-approval of rhGH therapy for GH deficiency (GHD) in adults, even though they have no prospect of height benefits. These effects include improvements in body composition, serum lipid levels, and cardiac function, among others. Lanes and colleagues sought to determine whether cardiovascular function is already altered in adolescents with GHD. These authors compared 10 adolescents with GHD on GH treatment (0.03 mg/kg/d for a mean of 3.8 ± 1.1 yr), 12 adolescents with untreated GHD (4 of whom had previously

received 1.6 ± 0.2 yr of treatment but had been off GH treatment for 3.4 ± 1.2 yr due to financial reasons) and 14 healthy adolescent controls. The 3 groups were similar in chronologic age, bone age, height (but not height z-score), BMI, pubertal distribution (65–70% Tanner stages 2–4; remainder prepubertal), blood pressure, and pulse. GHD was defined by abnormally low serum IGF-I and IGFBP-3 concentrations plus failure on clonidine/L-DOPA stimulation testing (peak GH concentrations were 3.2 ± 2.4 and 3.0 ± 2.3 $\mu\text{g/L}$ with a range of 0.9–5.6 $\mu\text{g/L}$).

A pediatric cardiologist and his technician, blinded to the GH status of the adolescents, performed echocardiography, carotid sonography, and measurement of endothelium-dependent vasodilation. For this last measurement, Doppler ultrasonography was used to quantify right brachial artery blood flow and brachial artery diameter before and 45 to 60 seconds after release of 5 minutes of 300 mm Hg applied by a standard sphygmomanometer cuff to the forearm (to induce hyperemia). They also measured, during echocardiography, the epicardial adipose tissue on the right ventricle, which was described in 2003 as a correlate with MRI measurement of abdominal visceral fat, clinical parameters of metabolic syndrome, and hence, cardiovascular risk in adults.¹

Left ventricular mass was significantly lower in the untreated and treated GHD groups than the normal controls, although left ventricular posterior wall and interventricular septal thicknesses were both similar across groups. Left ventricular ejection fraction (%) was also similar, but the controls had significantly larger end systolic and end diastolic volumes than the 2 GHD groups. Carotid artery intima-media thickness did not differ, but the hyperemia-induced increases in brachial artery diameter and blood flow were both related to GH status; vasodilation was lower in the untreated GHD group than in the treated and control groups, and blood flow was greatest in the treated GHD group. Epicardial adipose tissue, which correlated positively with BMI in all 3 groups, was significantly greater in the untreated GHD adolescents than the other groups. Thus, GHD has been associated with decreased cardiac size, increased large-artery stiffness (IGF-I has a direct releasing effect on nitric oxide, an endothelial relaxing factor), and increased epicardial adipose tissue (a correlate of cardiovascular risk factors in adults).

Lanes R, Soros A, Flores K, Gunczler P, Carrillo E, Bandel J. Endothelial function, carotid artery intima-media thickness, epicardial adipose tissue, and left ventricular mass and function in growth hormone-deficient adolescents: Apparent effects of growth hormone treatment on these parameters. *J Clin Endocrinol Metab.* 2005;90:3978–3982.

Editor's Comment: *Quite extensive data have been accumulating on the cardiovascular effects of GH and GHD. I refer the reader to references 2 and 3 for reviews of GH effects and reference 4 for review of IGF-I effects on cardiovascular system. Growth hormone replacement therapy for GHD in adults is too new to allow analysis of the ultimate question; that is, if rhGH can significantly ameliorate the increased cardiovascular mortality seen in adults with GHD. The interim markers are encouraging; however, most of the work has examined adults.⁵ Lanes and colleagues alert us that potentially detrimental cardiovascular changes can be seen in patients with GHD as early as adolescence. Thus, cardiovascular health joins body composition issues (muscle mass and bone mineralization) as factors to consider in optimizing GH treatment during the transition period, the time between cessation of linear growth and attainment of full adult body maturity.⁶*

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