

## GROWTH HORMONE FOR THE ELDERLY?

IN addition to promoting linear growth in prepubertal children, growth hormone is often described as having anabolic, lipolytic, and diabetogenic properties. These descriptions are based on the results of diverse short-term studies of humans, animals, and isolated tissues, many of which involved the use of large doses of growth hormone. Until the production of growth hormone by recombinant-DNA methods began, the small supply of pituitary-derived human growth hormone limited its use to the treatment of children with growth hormone deficiency. The wide availability of synthetic human growth hormone has made possible long-term studies of other potentially beneficial uses of growth hormone and its more physiologic actions.

Growth hormone secretion (and secretion of the other anterior pituitary hormones) is both pulsatile and diurnal, so that serum growth hormone concentrations in young adults range between 0.1 and 30  $\mu\text{g}$  per liter, or even higher. Thus, a single measurement is not sufficient to assess overall growth hormone secretion. Growth hormone acts on the liver and other tissues to stimulate the production of insulin-like growth factor I (IGF-I, also known as somatomedin C), which is responsible for the growth-promoting effects of growth hormone and which serves as an indicator of overall growth hormone secretion. Serum IGF-I concentrations increase in response to both endogenous and exogenously administered growth hormone, are low in cases of growth hormone deficiency, and have little diurnal variation. The production of IGF-I also depends on adequate nutrition and normal hepatic, renal, and thyroid function. There is a linear correlation between integrated 24-hour serum growth hormone concentrations (measured at 20-minute or hourly intervals) and the serum IGF-I concentration in normal subjects.<sup>1,2</sup> Integrated 24-hour growth hormone concentrations decline with increasing age and are approximately one-third lower in healthy men and women more than 55 years old than in men and women 18 to 33; IGF-I concentrations are similarly reduced.<sup>1</sup> As indicated by serum IGF-I measurements, however, the decline in growth hormone secretion with age is not universal. The prevalence of serum IGF-I concentrations below the range found in 20-to-29-year-old men and women was 11 percent in the fourth decade of life, 20 percent in the fifth, 22 percent in the sixth, 42 percent in the seventh, and 55 percent in the eighth and ninth. At all ages, the serum level of IGF-I was inversely correlated with adiposity.<sup>2</sup>

The declines in growth hormone and IGF-I production and the decrease in muscle mass and increase in adiposity that occur in healthy elderly subjects, and presumably in adults with growth hormone deficiency, have led to attempts to determine whether the administration of growth hormone is beneficial in such people. In this issue of the *Journal*, Rudman and colleagues report the effects of the administration of

growth hormone three times a week for six months on body composition in healthy 61-to-81-year-old men who had serum IGF-I concentrations below those of healthy younger men.<sup>3</sup> In this study and in similar studies of men and women with growth hormone deficiency,<sup>4,5</sup> the administration of growth hormone increased the serum IGF-I concentrations to within the range found in young (less than 30 years old) healthy adults. The healthy older men and the men and women with growth hormone deficiency had increases in lean body mass of 8.8 and 10 percent and decreases in the mass of adipose tissue of 14.4 and 16 percent, respectively, after six months of growth hormone administration.<sup>3,4</sup> Growth hormone-deficient men and women given growth hormone for four months had a 5 percent increase in muscle volume in the thigh and a 7 percent decrease in adipose-tissue volume in the thigh.<sup>5</sup> Other effects of long-term administration of growth hormone on body composition included a 1.6 percent increase in vertebral-bone density<sup>3</sup> and 6.6 and 7 percent increases in skin-fold thickness.<sup>3,5</sup> Left-ventricular-wall mass, measured by echocardiography, did not change.<sup>5</sup> Functional assessments in the men and women with growth hormone deficiency revealed small increases in exercise capacity, isometric strength, and basal metabolic rate.<sup>4,5</sup> These measurements were not performed in the healthy older men. The metabolic effects of growth hormone were less well characterized; however, fasting serum glucose<sup>3,4</sup> and insulin<sup>4</sup> concentrations increased significantly. Fasting serum cholesterol concentrations decreased in the subjects with growth hormone deficiency<sup>4</sup> and did not change in the older men<sup>3</sup>; triglyceride concentrations did not change in either group.

These studies extend our understanding of the potential benefits of growth hormone administration to body composition and, to a lesser extent, to muscle and metabolic function in adults with an age-related decline in growth hormone secretion and in those with disease-related growth hormone deficiency. In assessing a possible role for the administration of growth hormone in older adults, however, these studies should be considered preliminary. Growth hormone can affect carbohydrate metabolism adversely (producing hyperinsulinemia, glucose intolerance, and diabetes mellitus), the musculoskeletal system (producing arthritis and arthralgia), and the cardiovascular system (producing hypertension, edema, and congestive heart failure), as exemplified by acromegaly. Therefore, before the use of growth hormone in healthy older adults can be contemplated, the following questions should be considered.

What are the effects of long-term administration of growth hormone on carbohydrate, lipid, and protein metabolism? Numerous studies of growth hormone administration for a few hours or days have demonstrated both seemingly beneficial and harmful effects. They include impaired glucose uptake (carbohydrate intolerance), increased insulin secretion and insulin resistance, increased serum triglyceride and de-

creased serum cholesterol concentrations, a decrease in plasma urea levels and urinary nitrogen excretion, and positive nitrogen balance.<sup>6-8</sup> It is not clear whether the long-term administration of growth hormone produces similar effects, or whether the improved metabolism of nutrients observed in animals<sup>9</sup> given growth hormone also occurs in humans. This is probably the most important area of growth hormone research, since the more efficient use of substrate is the likely basis for the observed changes in body composition during the administration of growth hormone.

Does long-term treatment with growth hormone improve muscle function? Information on this subject is meager, but in 20 adults with growth hormone deficiency, exercise capacity increased in 11, was unchanged in 6, and declined in 3 after four months of treatment with growth hormone.<sup>5</sup> This aspect of the effects of growth hormone is also of interest to athletes, since pharmacologic doses of growth hormone produced a 12 percent decrease in body fat and a 4 percent increase in fat-free weight in highly conditioned exercising men and women 22 to 33 years of age.<sup>10</sup> Growth hormone is said to improve athletic performance, but this claim is far from proved.

If growth hormone is to be given to healthy older adults with diminished production of the hormone, when should its administration begin? If the purpose is to reverse the decline in growth hormone secretion that occurs with aging, then treatment would need to begin in the fourth decade of life in some people. If it is given, for how long should it be given? Since it is unlikely that the beneficial effects of growth hormone on body composition are lasting, lifelong use would probably be required.

What is the optimal dose and frequency of administration? The doses of growth hormone used in these studies raised IGF-I production to levels similar to those found in healthy young adults (and some healthy older adults); however, thrice weekly or even daily administration is not physiologic, since growth hormone secretion is pulsatile throughout the day and night. Although the doses of growth hormone used by Rudman et al. and other investigators raised serum IGF-I concentrations to those of young adults, the doses had to be increased or decreased in some subjects because the IGF-I response was suboptimal or because there were indications of excessive growth hormone action, including an increase in blood pressure, edema, and arthralgia.<sup>3,4</sup> Although an optimal dose of growth hormone can be readily established, it is possible that the pulsatile administration of growth hormone, which would require the use of a portable infusion device, would have additional benefits, fewer side effects, or both. An alternative method to increase endogenous growth hormone secretion is the long-term administration of growth hormone-releasing hormone, which produces normal pulsatile and diurnal growth hormone release.<sup>11</sup> An analogue of a long-acting growth hormone-releasing hormone or a depot preparation would be needed to make this practical.

Are there ethical issues relating to the administration of growth hormone to healthy older adults? Since the risk-benefit ratio has not been established, the answer to this question is a straightforward yes. The decline in growth hormone secretion with increasing age has led many investigators to suggest that there is a cause-effect relation between this decline and changes in body composition — increased adiposity and decreased muscle mass. This is an important issue, but is it an ethical one? If the changes in body composition in older adults are not directly related to the decline in growth hormone secretion, then it is an ethical issue, since growth hormone would be given to healthy subjects. An analogous situation would be administering growth hormone to short children who do not have growth hormone deficiency, a practice that cannot be recommended. In addition, it is not clear whether a growth hormone-induced increase in muscle mass of 10 percent or a 15 percent decrease in the mass of adipose tissue produces substantial improvement in muscle strength, mobility, or the quality of life. The cost of long-term treatment is also an obvious consideration. Currently, the cost of growth hormone therapy for a child with growth hormone deficiency ranges from \$10,000 to \$30,000 a year, depending on body weight. Treatment of a 70-kg adult with the regimen used by Rudman et al. would cost approximately \$13,800 a year. Thus, long-term growth hormone treatment in elderly adults with diminished growth hormone secretion would require a considerable personal and financial investment.

Because there are so many unanswered questions about the use of growth hormone in the elderly and in adults with growth hormone deficiency, its general use now or in the immediate future is not justified. A better use of scientific and financial resources would be to determine whether growth hormone is beneficial in patients with severe catabolic illnesses. Limited information suggests that growth hormone is beneficial in patients with burn injury, sepsis, or renal failure and during prolonged recovery after surgery. Ideally, short-term growth hormone therapy, in conjunction with optimal nutritional and other medical support, may reverse or ameliorate ongoing catabolism, aid in recovery, and shorten the duration of the illness.

Our understanding of growth hormone, its interrelations with other hormones, and its regulation of metabolism is considerable. Although its actions and benefits are fairly clear in children with growth hormone deficiency, they are not at all clear in adults. The studies of Rudman et al. and other investigators should be viewed as an important beginning in deciphering the actions of growth hormone in adults.

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