Aging is associated with progressive and substantial decreases in growth hormone secretion and in circulating concentrations of insulin-like growth factor I (IGF-I) (1). Increasing evidence suggests that these hormonal changes, coupled with estrogen deficiency in menopausal women and reduced total and bioavailable testosterone in men, contribute to age-related decreases in skeletal muscle mass and strength (sarcopenia), increased total and intra-abdominal fat, loss of bone mass (osteopenia), insulin resistance, dyslipidemias, and enhanced risks for type 2 diabetes mellitus and cardiovascular disease (1–5). Taken together, these changes in body composition and function are precursors of musculoskeletal frailty, disability and reduced physical function, falls, bone fractures and subsequent nursing home admissions, and mortality (6).

Numerous reports indicate that growth hormone treatment improves body composition, muscle strength, metabolic and physical function, bone density, and quality of life in nonelderly adults with pathologic growth hormone deficiency (7). In contrast, relatively few randomized, controlled trials of recombinant human growth hormone have been conducted in older people, and the results of such studies have been equivocal or disappointing in terms of clinical benefits (8). In particular, administration of growth hormone to healthy older persons has consistently resulted in improvements in body composition (increases in lean body mass; decreases in total and abdominal fat mass; and, less frequently, augmented bone mineral density) and some metabolic parameters (lowering low-density lipoprotein cholesterol), without significantly affecting muscle strength, physical performance, or quality of life. Moreover, side effects of growth hormone treatment, such as peripheral edema, arthralgias, myalgias, glucose intolerance, and loss of insulin sensitivity, are especially common in older persons (8). Development of insulin resistance is of concern because it predisposes a patient to diabetes mellitus and vascular disease.

Injections or infusions of growth hormone–releasing hormone (GHRH) and parenteral or oral administration of a ghrelin-mimetic growth hormone secretagogue (GHS) have been shown to restore levels of growth hormone and IGF-I in older persons to those of young adults (9–11), indicating that the aging pituitary is capable of enhanced growth hormone secretion if appropriate stimuli are supplied and suggesting that older adults with relative growth hormone deficiency might also benefit from growth hormone stimulation.

Why use GHRH or a GHS in older persons? Growth hormone is released in episodic pulses by cells of the anterior pituitary gland and is an important hormone that increases muscle and bone mass and decreases body fat (1). Most circadian growth hormone release occurs at night, especially during slow-wave sleep. Growth hormone secretion is principally regulated by 2 stimulatory peptides—hypothalamic GHRH and ghrelin, which is produced in the stomach, small intestine, and hypothalamus—and the inhibitory peptide somatostatin. Biologically active GHRH is a 40– or 44–amino acid peptide that stimulates growth hormone production via the GHRH receptor (1). Ghrelin, an octanoylated 28–amino acid peptide, stimulates growth hormone secretion via a distinct, endogenous GHS receptor (12, 13). MK-677 is an orally active GHS and ghrelin mimetic that stimulates GHS-1α receptors. Ghrelin exerts considerable appetite-stimulating and growth hormone–releasing effects; thus, the clinical effects of a ghrelin mimetic might be expected to differ from those of GHRH or growth hormone (14). The availability of an orally administered GHS that enhances pulsatile release of growth hormone provides a practical opportunity to test the notion that chronic stimulation of growth hormone release can improve physical function in older adults.

Evidence suggests that GHRH or a GHS, like growth hormone, can increase lean body mass and decrease fat mass in older persons, but effects on muscle strength and physical performance have been less consistent. Two studies that reported improvements in physical function (15, 16) provided no placebo comparison, were of short duration (≤3 months), and had small sample sizes. The former, which used the oral GHS and ghrelin mimetic MK-677, was conducted in obese participants, and the latter, which used GHRH, was conducted in healthy postmenopausal women.

In this issue, Nass and colleagues (17) report the effects of MK-677 on age-associated decreases in lean body mass and increases in body fat. The investigators conducted a 2-year, double-masked, placebo-controlled, modified-crossover, General Clinical Research Center–based clinical trial in which 65 healthy men and women (of whom some were receiving hormone replacement therapy) 60 to 81 years of age received 25 mg of MK-677 each morning. The primary outcome measures at 1 year included 24-hour growth hormone secretory profiles, morning IGF-I serum concentrations, fat-free mass (determined by a 4-compartment model), and abdominal visceral fat. The study was powered on the 12-month change comparison between the MK-677 and placebo groups and did not evaluate possible effects of sex or hormone replacement therapy. Secondary outcome measures included various other body composition, endocrine–metabolic, strength, physical performance, and quality-of-life measures. After 1 year, circadian pulsatile growth hormone secretion and morning IGF-I concentration were augmented to those of
healthy young adults. Fat-free (total body and limb lean) mass and intracellular water increased significantly, the latter being a biomarker of fat-free mass. Total and abdominal fat, muscle strength and function, and quality of life did not change. Low-density lipoprotein cholesterol levels decreased slightly, whereas cortisol, fasting blood glucose, and hemoglobin A\textsubscript{1c} levels increased. The Quicki index of insulin sensitivity decreased slightly. MK-677 was generally well tolerated. Appetite and body weight increased somewhat, but peripheral edema, joint or muscle pains, newly detected malignant disease, and other adverse outcomes did not significantly increase in women or men. Analysis of the 2-year outcome data in a subset of 53 of the 65 participants revealed that the growth hormone IGF-I and fat-free mass changes persisted. In participants treated for 2 years with MK-677, fasting blood glucose values were no longer elevated. Concentrations of IGF-I returned to normal 1 month after crossover and by 6 months after study completion. Nass and colleagues concluded that long-term functional and, ultimately, pharmacoeconomic studies are indicated in older adults.

Is there a role for MK-677 or another GHS in attenuating age-related alterations in body composition and losses of function that lead to disability and loss of independence? Nass and colleagues, in their rigorously conducted study, clearly found that sustained use of an oral GHS for 1 to 2 years will maintain a youthful growth hormone and IGF-I hormonal profile and augment fat-free (lean body) mass. However, as with other published studies using growth hormone, GHRH, or MK-677, no functional or quality-of-life benefits and some unwanted and worrisome adverse effects (such as increased insulin resistance and decreased glucose tolerance) were observed. Possible reasons for Nass and colleagues’ findings include the relatively small number of participants studied; their general good health (questionable ceiling effect); their uncertain pretreatment growth hormone, IGF-I, and sex-steroid status; the combination of data from men and women, and from women receiving and not receiving hormonal replacement (estrogen with or without progestin); and the relatively short duration of the intervention. Given that men and women respond differently to manipulation of the growth hormone–IGF-I axis, and that such responsibility is further modulated by endogenous or exogenous gonadal steroids, it is important to design studies so that possible qualitative and quantitative sexual dimorphic effects can be discerned.

Dose–response relationships of MK-677 and other GHS have been characterized with regard to their effects on growth hormone secretion and IGF-I, but little knowledge exists regarding dose–response effects on body composition and other outcome measures. In a recent, preliminary series of reports of 12-month data from a multicenter study that used a different orally active GHS in older persons at risk for mild functional decline (19, 20), dose-responsive increases in IGF-I and changes in body composition were accompanied by small but significant improvements in some measures of physical function. These findings suggest that evaluating growth hormone axis manipulation may have more benefit for older persons who are at increased risk for frailty. Moreover, because ghrelin and its mimetics also act by non–growth hormone mechanisms, such as by affecting appetite and caloric balance and the thymus and proinflammatory cytokine pathways (14), it seems prudent to investigate the effects of a GHS on multiple target tissues in addition to muscle, fat, and bone, such as the heart, brain, and immune system.

Clearly, many questions about the potential utility and safety of an oral GHS in older persons remain unanswered. What might be the optimal intervention paradigm, for what clinical outcomes, and in what populations? Would long-term administration of MK-677 or other secretagogues improve physical and psychological functions and quality of life; have different effects according to age or racial or genetic predisposition; overstimulate the pituitary gland or central nervous system, with increased risk for pituitary neoplasms or neurobehavioral dysfunction; increase cancer frequency in older individuals, who are already at greater risk for malignant diseases; or supplant the less physiologic and more costly use of recombinant growth hormone or injectable GHRH or its analogues? At present, the clinical use of growth hormone axis manipulation in aged persons should be restricted to carefully controlled clinical studies and is not ready for prime time. However, Nass and colleagues’ findings raise many questions that we need to address.

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