

Effects of an Oral Ghrelin Mimetic on Body Composition and Clinical Outcomes in Healthy Older Adults

A Randomized Trial

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Background: Growth hormone secretion and muscle mass decline from midpuberty throughout life, culminating in sarcopenia, frailty, decreased function, and loss of independence. The decline of growth hormone in the development of sarcopenia is one of many factors, and its etiologic role needs to be demonstrated.

Objective: To determine whether MK-677, an oral ghrelin mimetic, increases growth hormone secretion into the young-adult range without serious adverse effects, prevents the decline of fat-free mass, and decreases abdominal visceral fat in healthy older adults.

Design: 2-year, double-blind, randomized, placebo-controlled, modified-crossover clinical trial.

Setting: General clinical research center study performed at a university hospital.

Participants: 65 healthy adults (men, women receiving hormone replacement therapy, and women not receiving hormone replacement therapy) ranging from 60 to 81 years of age.

Intervention: Oral administration of MK-677, 25 mg, or placebo once daily.

Measurements: Growth hormone and insulin-like growth factor I levels. Fat-free mass and abdominal visceral fat were the primary end points after 1 year of treatment. Other end points were body weight, fat mass, insulin sensitivity, lipid and cortisol levels, bone mineral density, limb lean and fat mass, isokinetic strength, function, and quality of life. All end points were assessed at baseline and every 6 months.

Results: Daily administration of MK-677 significantly increased growth hormone and insulin-like growth factor I levels to those of healthy young adults without serious adverse effects. Mean fat-free mass decreased in the placebo group but increased in the MK-677 group (change, -0.5 kg [95% CI, -1.1 to 0.2 kg] vs. 1.1 kg [CI, 0.7 to 1.5 kg], respectively; $P < 0.001$), as did body cell mass, as reflected by intracellular water (change, -1.0 kg [CI, -2.1 to 0.2

kg] vs. 0.8 kg [CI, -0.1 to 1.6 kg], respectively; $P = 0.021$). No significant differences were observed in abdominal visceral fat or total fat mass; however, the average increase in limb fat was greater in the MK-677 group than the placebo group (1.1 kg vs. 0.24 kg; $P = 0.001$). Body weight increased 0.8 kg (CI, -0.3 to 1.8 kg) in the placebo group and 2.7 kg (CI, 2.0 to 3.5 kg) in the MK-677 group ($P = 0.003$). Fasting blood glucose level increased an average of 0.3 mmol/L (5 mg/dL) in the MK-677 group ($P = 0.015$), and insulin sensitivity decreased. The most frequent side effects were an increase in appetite that subsided in a few months and transient, mild lower-extremity edema and muscle pain. Low-density lipoprotein cholesterol levels decreased in the MK-677 group relative to baseline values (change, -0.14 mmol/L [CI, -0.27 to -0.01 mmol/L]; -5.4 mg/dL [CI, -10.4 to -0.4 mg/dL]; $P = 0.026$); no differences between groups were observed in total or high-density lipoprotein cholesterol levels. Cortisol levels increased 47 nmol/L (CI, 28 to 71 nmol/L [1.7 μ g/dL [CI, 1.0 to 2.6 μ g/dL]) in MK-677 recipients ($P = 0.020$). Changes in bone mineral density consistent with increased bone remodeling occurred in MK-677 recipients. Increased fat-free mass did not result in changes in strength or function. Two-year exploratory analyses confirmed the 1-year results.

Limitation: Study power (duration and participant number) was insufficient to evaluate functional end points in healthy elderly persons.

Conclusion: Over 12 months, the ghrelin mimetic MK-677 enhanced pulsatile growth hormone secretion, significantly increased fat-free mass, and was generally well tolerated. Long-term functional and, ultimately, pharmacoeconomic, studies in elderly persons are indicated.

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Aging is an inevitable process across all species. In humans, muscle mass declines after reaching its peak in the third decade of life. Muscle mass is important for physical fitness and metabolic regulation; sarcopenia is a major risk factor for frailty, loss of independence, and physical disability in elderly persons (1) and is associated with shortened survival in critically ill patients (2). As lifespans increase, more adults are becoming frail and dependent on others, which creates challenges for them, their families, and society.

The decrease in fat-free mass correlates with the aging-associated decrease in growth hormone secretion (3, 4). Aging adults show decreases in fat-free mass and growth

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Context

The age-related decline of growth hormone secretion may play a role in sarcopenia and frailty.

Content

In this randomized trial, 65 healthy older adults were assigned to receive placebo or MK-677, an oral ghrelin mimetic that increased pulsatile growth hormone secretion to young-adult levels. Over 1 year, lean fat-free mass increased 1.1 kg with MK-677 and decreased 0.5 kg with placebo. MK-677 did not affect strength and function, but insulin sensitivity declined and mean serum glucose levels increased 0.28 mmol/L (5 mg/dL).

Caution

This short-term trial was underpowered to detect functional changes and adverse events.

Implication

An oral ghrelin mimetic increases pulsatile growth hormone secretion and alters body composition in healthy older adults.

—The Editors

hormone secretion similar to those seen in growth hormone-deficient young adults (5). By the eighth decade, men and women lose approximately 7 and 3.8 kg of muscle mass, respectively (3), and gain intra-abdominal fat (6, 7).

Previous trials in which growth hormone was administered to elderly persons were small, poorly controlled, or too short (8); in addition, growth hormone replacement does not restore pulsatile growth hormone secretion. MK-677, the first orally active ghrelin mimetic (a growth hormone secretagogue and growth hormone secretagogue-receptor agonist), increases pulsatile growth hormone secretion in older adults to levels observed in young adults (9, 10). Our primary objectives were to determine whether 25 mg of oral MK-677 daily would increase growth hormone and insulin-like growth factor I (IGF-I) levels in healthy older adults, prevent the decline in fat-free mass, and decrease abdominal visceral fat, with acceptable tolerability.

METHODS**Design**

The General Clinical Research Center (GCRC) and the University of Virginia institutional review boards approved this study. All participants gave written informed consent. We performed a 2-year, randomized, double-blind, modified crossover trial in which healthy older men, women receiving hormone replacement therapy, and women not receiving hormone replacement therapy received oral MK-677, 25 mg, or placebo (in a 2:1 ratio) daily. After 1 year, participants receiving MK-677 were

randomly assigned to continue receiving MK-677 (group 1) or change to placebo (group 2); participants receiving placebo were given MK-677 during year 2 (group 3). **Appendix Figure 1** (available at www.annals.org) shows the study design.

Setting and Participants

We recruited healthy volunteers older than 60 years of age from the general population by advertisement and screened them by medical history, physical examination, and laboratory testing to rule out underlying disease. Exclusion criteria were body mass index greater than 35 kg/m², strenuous exercise for more than 60 minutes per day, smoking, diabetes, history of cancer (other than some types of skin cancer), untreated hypertension or thyroid disease, or medications known to affect growth hormone secretion. We asked participants to maintain their typical diet and exercise throughout the study and to report any illnesses, medical procedures, or adverse effects. All participants were white, with the exception of 1 Hispanic and 1 African-American man.

At baseline and every 6 months for 2 years, we admitted participants to the GCRC for measurement of body composition, body water, lipids, and bone mineral density; frequent blood sampling; and completion of quality-of-life questionnaires. We also performed tests of strength and function. During GCRC admissions, we standardized meals for caloric and nutrient content. Blood samples for growth hormone were drawn through an indwelling venous cannula every 10 minutes for 24 hours; participants were allowed to sleep after 9 p.m.

Randomization and Intervention

MK-677 and placebo tablets were provided by Merck Research Laboratories (Rahway, New Jersey) in a blinded manner and stored by a research pharmacist and dispensed in a blinded manner according to a randomization table with stratification for sex and hormone replacement therapy. Ten-mg tablets were provided for blinded back-titration. Participants were instructed to take the placebo or MK-677 tablets once daily between 7:00 and 9:00 a.m. (or at 9:00 a.m. during admissions). All research staff and volunteers remained blinded throughout the study and during data verification. We monitored adherence by pill counts.

Outcome Measures

We measured serum growth hormone and IGF-I levels in duplicate in the GCRC Core Laboratory. We assessed 24-hour mean growth hormone and endogenous growth hormone secretory dynamics by using the cluster method (11) and an automated multiple-parameter deconvolution method (9, 12). The **Appendix** (available at www.annals.org) provides details of all assay methods.

We evaluated fat-free mass and total body fat by using a 4-compartment model (13) and dual x-ray absorptiometry (DXA) on a Hologic QDR-2000 (Hologic, Bedford, Massachusetts) in pencil-beam mode (14). Dual x-ray absorptiometry measurements included appendicular lean

soft tissue of the arms and legs as an estimate of total appendicular skeletal muscle mass (TASM) (15); appendicular fat; and bone mineral density of the femoral neck, spine (L2–L4), and total hip.

We divided the DXA TASM estimates by height in square meters (TASM [kg]/m²) (15). We used this index of relative limb muscle mass to compute a T-score for each individual, relating the TASM/m² to that of sex-concordant young adults (16). We defined sarcopenia as values more than 2 SD below values in young, sex-specific reference populations (17, 18).

We used cross-sectional computed tomographic images to measure the areas of abdominal visceral and subcutaneous fat and mid thigh skeletal muscle at predefined anatomical locations (19); we excluded data if the subsequent scan location differed or we had technical difficulties (4 placebo group recipients and 3 MK-677 recipients). One blinded observer analyzed the dual x-ray absorptiometry and computed tomographic scans.

We measured total body water by using the deuterium oxide dilution technique (20) and extracellular water by using bromide dilution (21). We assessed intracellular water as the difference between total body water and extracellular water. To determine the relative relationships among total, extracellular, and intracellular water, we expressed each component in terms of kilograms of fat-free mass at each point. We chose the scale of measure for the analysis a priori. We also report the raw data in typical units for comparison.

We determined concentric force during flexion and extension of the knee and shoulder every 6 months by using a Cybex II isokinetic dynamometer (CSM, Boston, Massachusetts). Participants performed 6 repetitions of maximal effort over 90 degrees at 60 degrees/s, and the mean of the last 5 repetitions was computed by using proprietary software (22). We calculated total work by multiplying the mean per repetition by 5.

Function tests performed every 6 months included walking 30 meters as quickly as possible (best of 2 trials), walking as far as possible in 6 minutes on an indoor track, descending and ascending 4 flights of stairs, and rising and sitting 5 times from an armless chair with an 18-inch seat height.

To compensate for differences in muscle mass between men and women, we analyzed all strength and function measurements in terms of kilograms of baseline appendicular skeletal muscle (lean) from DXA. We used arm lean and leg lean for shoulder and knee strength, respectively, and baseline TASM (sum of arms and legs) for the function tests. We chose the scale of measure used in this analysis a priori; the raw data are also reported.

Participants completed 4 questionnaires every 6 months to assess quality of life and general well-being: the 20-item Short Form Health Survey, the Beck Depression Inventory, the Pittsburgh Sleep Quality Index, and the Body Cathexis Scale. The **Appendix** provides additional

details of quality of life, muscle strength, and function assessments.

We measured cholesterol, cortisol, and insulin sensitivity (estimated by the Quicki Index method [23] from fasting insulin and glucose) every 6 months.

To determine whether the effects of MK-677 treatment were sustained for 2 years or reversed when changed to placebo, we analyzed several end points in a subgroup of participants who completed 24 months in each of the 3 treatment groups (**Figure 1**).

Monitoring for Adverse Effects

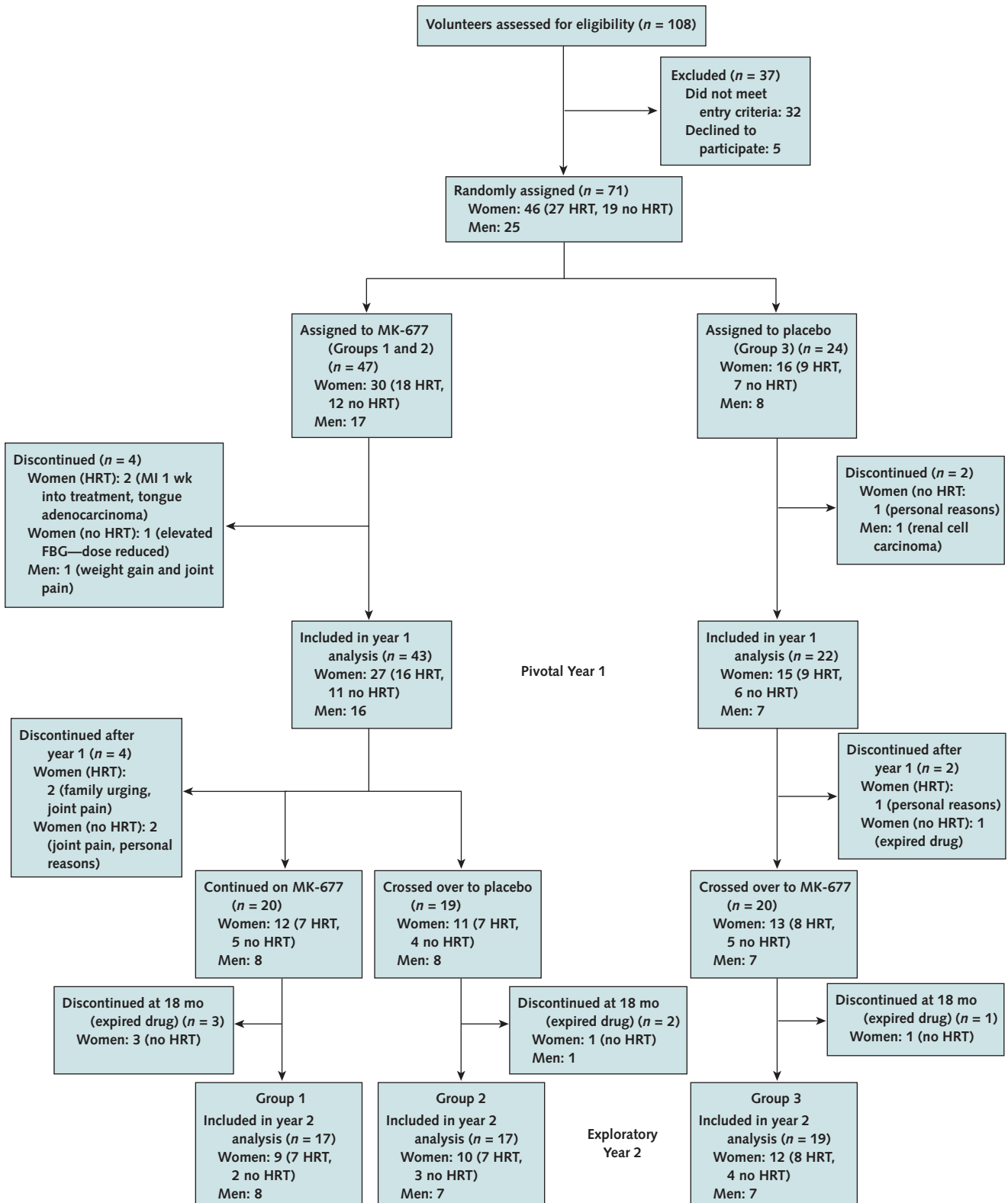
Each year, volunteers were seen monthly for the first 3 months and every 3 months thereafter for a physical examination, documentation of medications and vital signs, and questioning about side effects and overall well-being. We performed a complete blood count and chemistry panel and monitored levels of hemoglobin A_{1c} (HbA_{1c}) and fasting blood glucose in all participants and prostate-specific antigen and testosterone in men. Women received annual Papanicolaou smears and mammography.

Statistical Analysis

The 2 primary end points were fat-free mass and abdominal visceral fat. The study was powered for the pivotal first 12 months; the **Appendix** describes the power analysis in detail. We did not know whether men, women receiving hormone replacement therapy, and women not receiving hormone replacement therapy would respond differently. Consequently, we conducted the random assignments a priori so that equal numbers of these 3 populations would be assigned to MK-677 and placebo. We therefore focused the power analyses on the pivotal 12-month change comparison between the 2 treatment groups as a whole and not on specific subgroup comparisons, such as sex or hormone replacement therapy.

We conducted all statistical analyses under the guidelines of the intention-to-treat principle and did not impute missing data points. We performed the analyses on the baseline and the 6- and 12-month primary and secondary outcomes and decided the data analysis plan a priori. We used repeated-measures analysis of covariance to analyze the primary outcome data for the 6- and 12-month changes in fat-free mass, abdominal visceral fat, and IGF-I and growth hormone levels. For each analysis of covariance, we considered treatment (MK-677 or placebo), time (6 or 12 months), and treatment-by-time interaction to be potential sources of variability. We used the participants' baseline measurements as the analysis of covariance covariate. We analyzed the fat-free mass and abdominal visceral fat data in the same scale on which we measured them and report them as a difference between arithmetic means. We transformed the growth hormone and IGF-I data to the natural logarithmic scale before conducting the statistical analyses so that the variance and normality assumptions of the linear model were not violated and report the results as a ratio of geometric means (fold change).

Figure 1. Study flow diagram.



FBG = fasting blood glucose; HRT = hormone replacement therapy; MI = myocardial infarction.

We constructed linear contrasts to estimate the mean intraparticipant change in response at 6 and at 12 months and to estimate the baseline-adjusted difference in change in response at 6 and 12 months between the MK-677 and placebo groups. For the pivotal 12-month comparison (MK-677 versus placebo), we rejected the null hypothesis of equality of means if the *P* value of the *F* statistic was less than 0.05. For the 6-month between-group comparison, we rejected the null hypothesis if the *P* value of the *F* statistic was less than 0.05 after implementing the Bonferroni post hoc test correction. For the 12-month comparison, we constructed the 95% CI on the basis of the *t* test distribution quantile values at the 2.5 and 97.5 percentiles, whereas the 6-month comparison was based on the 1.25 and 98.75 percentiles of the distribution. With the exception of the quality-of-life data, we analyzed all secondary outcome data by using repeated-measure analysis of covariance and report them exactly as the primary outcome data. For the quality-of-life data, we performed a factor analysis (24) of the different scales of the questionnaires to create an overall well-being factor; the **Appendix** describes this in detail.

We designated the effects of year-2 treatment as exploratory. We performed a separate post hoc analysis of end points based on responses in year 1 to determine whether the effects were maintained or reversed in participants who had complete data at baseline, 12, and 24 months. We analyzed only the change from baseline to 24 months, in the same way as the year 1 data, and implemented a post hoc correction for the 3 treatment groups. We used SAS, version 9.1 (SAS Institute, Cary, North Carolina), to conduct the statistical analyses.

Additional methods, baseline data, and all results are presented in the supplementary appendix materials (available at www.annals.org). Data are presented as means (95% CIs). All statistical comparisons at 6 and 12 months are between MK-677 and placebo.

Role of the Funding Source

This investigator-initiated GCRC study was funded by the National Institutes of Health and conducted and analyzed at the University of Virginia. All decisions regarding the design, conduct, analysis, and submission of the manuscript were made independently by the authors.

RESULTS

Figure 1 shows the flow of study participants, and the **Table** shows baseline demographic characteristics.

Treatment occurred between September 1998 and November 2003. Because the study drug expired in November 2003, 6 participants received treatment for only 18 months (2 placebo recipients and 4 MK-677 recipients) and 1 for only 12 months (placebo recipient). Seventy-one volunteers were randomly assigned; 65 participants (drop-

out rate, 8.5%) completed year 1: 23 men, 25 women receiving hormone replacement therapy, and 17 women not receiving hormone replacement therapy. The treatment groups were well matched at baseline, with no significant differences between groups. Fifty-nine participants completed 18 months and 53 completed 24 months of treatment (**Figure 1**).

In 4 participants, we blindly back-titrated the dose of study drug to 10 mg/d because of increased fasting glucose level after crossover from placebo to MK-677 in year 2 (an 81-year-old man who completed 2 years); increased fasting glucose level in 1 woman receiving MK-677 (withdrawn after 3 months); and increased joint pain in 2 women receiving MK-677 (withdrew after 12 months).

Growth Hormone and IGF-I Levels

Figure 2 shows the effects of treatment in the pivotal year 1. After 12 months of MK-677 treatment, 24-hour mean growth hormone levels increased 1.8-fold (CI, 1.56- to 2.0-fold) from baseline (*P* < 0.001). This was accounted for by enhanced pulsatile growth hormone secretion (**Appendix Table 1**, available at www.annals.org), as shown in a representative participant (**Figure 2, C**). Serum IGF-I levels also increased by 1.5-fold (CI, 1.4- to 1.6-fold; *P* < 0.001). In 22 of 43 participants, IGF-I levels were sustained in the normal range for young adults; **Appendix Figure 2** (available at www.annals.org) shows individual IGF-I results.

Body Composition

Fat-Free Mass, TASM, and Thigh Muscle Area

Fat-free mass measured by DXA decreased in the placebo group and increased in the MK-677 group (change, -0.5 kg [CI, -1.10 to 0.2 kg] vs. 1.1 kg [CI, 0.7 to 1.5 kg], respectively; *P* < 0.001) (**Figure 3, A**). This increase was observed with both DXA and the 4-compartment model (*R*² = 0.98). Total appendicular skeletal muscle mass (limb lean) decreased in the placebo group and increased in the MK-677 group (change, -0.3 kg [CI, -0.6

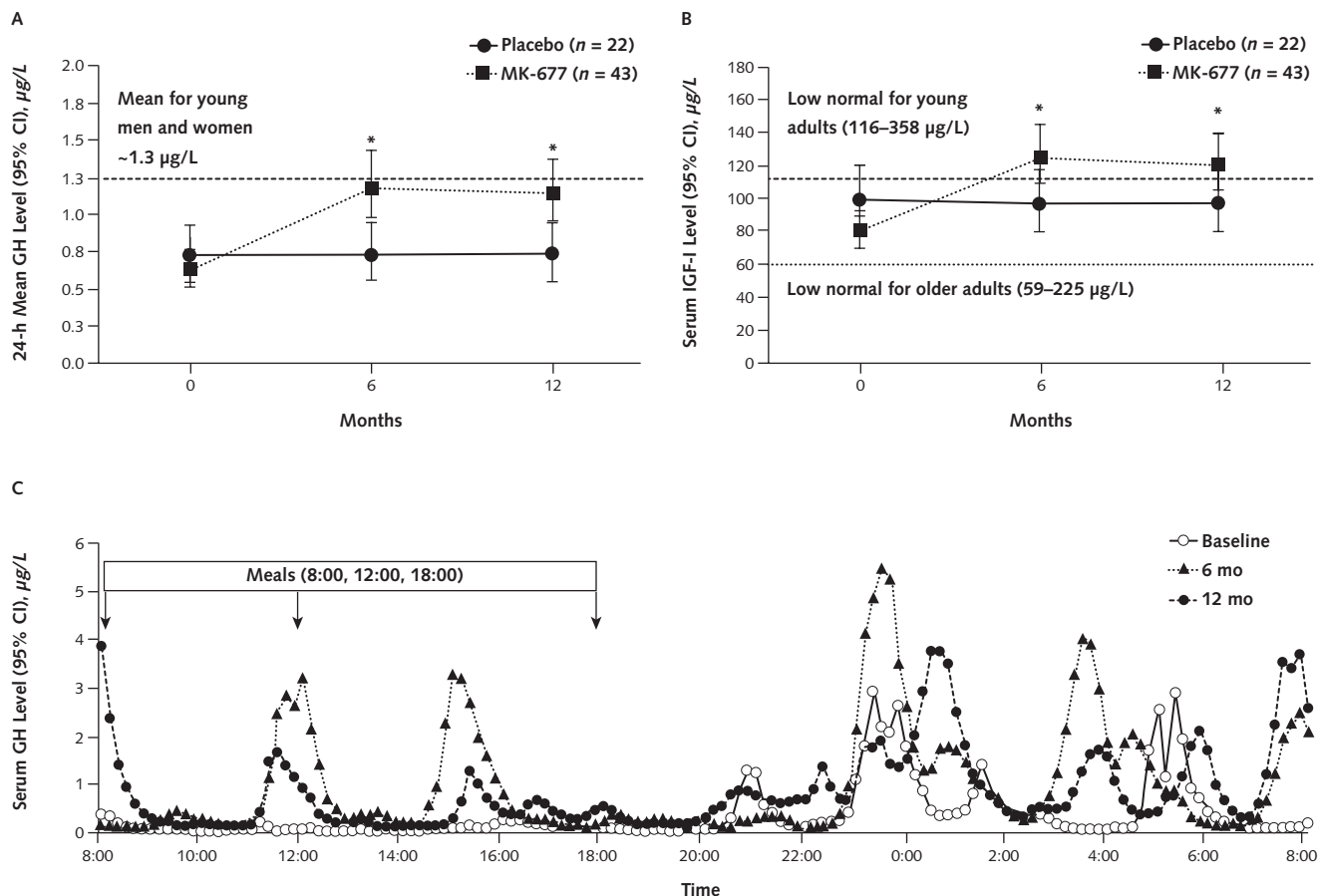
Table. Demographic Characteristics*

Characteristic	Placebo Group (n = 22)	MK-677 Group (n = 43)
Men, n	7	16
Women receiving HRT, n	9	16
Women not receiving HRT, n	6	11
Age, y		
Mean (SD)	66.5 (5.5)	67.9 (5.4)
Range	60.7–80.7	60.2–80.4
Body mass index, kg/m ²		
Mean (SD)	26.2 (3.9)	26.1 (3)
Range	19.0–34.5	20.8–33.8

HRT = hormone replacement therapy.

* The placebo and MK-677 groups did not significantly differ at baseline.

Figure 2. Growth hormone (GH) and insulin-like growth factor I (IGF-I) levels at baseline and at 6 and 12 months, and a representative GH profile.



Growth hormone and IGF-I data were not normally distributed and were analyzed on the natural logarithmic scale. Line graphs show geometric means and 95% CIs. Results of growth hormone deconvolution analysis are included in **Appendix Table 1** (available at www.annals.org). **A.** Mean 24-hour GH levels. The dashed line indicates 24-hour mean GH level for young men and women combined ($\sim 1.3 \mu\text{g/L}$). $*P < 0.001$ for MK-677 versus placebo. **B.** Serum IGF-I levels. The lower dotted line indicates the lower limit of the IGF-I normal range for older adults (59 to 225 $\mu\text{g/L}$), and the upper dashed line indicates the lower limit in adults age 21 to 25 years (116 to 358 $\mu\text{g/L}$). **C.** Representative 24-hour GH profile in a 70-year-old man with a body mass index of 23.2 kg/m^2 who received MK-677 for 1 year. His 24-hour mean GH levels were 0.37, 1.0, and 0.86 $\mu\text{g/L}$ at baseline, 6 months, and 12 months, respectively. The pulsatile pattern of GH secretion at baseline is maintained and enhanced at 6 and 12 months, primarily because of increased secretion per peak rather than peak frequency.

to 0.1 kg] vs. 0.5 kg [CI, 0.3 to 0.8 kg], respectively; $P < 0.001$).

Thigh muscle area by computed tomography changed by -0.5 cm^2 (CI, -3.2 to 2.2 cm^2) in the placebo group and 1.5 cm^2 (CI, -0.5 to 3.5 cm^2 ; $P = 0.20$) in the MK-677 group (**Appendix Table 2**, available at www.annals.org).

Total Body Water and Cell Mass

When each body water compartment was expressed per fat-free mass at each point, treatment groups did not differ significantly (**Appendix Table 3**, available at www.annals.org).

Total body water increased by 0.1 kg (CI, -0.7 to 0.9 kg) in the placebo group and 1.7 kg (1.2 to 2.3 kg) in the MK-677 group ($P = 0.001$). Both groups had similar in-

creases in extracellular water (placebo, 1.0 kg [CI, 0.02 to 2.1 kg]; MK-677, 1.0 kg [CI, 0.2 to 1.7 kg]). Intracellular water decreased in the placebo group but increased in the MK-677 group (change, -1.0 kg [CI, -2.1 to 0.2 kg] vs. 0.8 kg [CI, -0.1 to 1.6 kg], respectively; $P = 0.021$) (**Figure 3, B**). The loss of intracellular water or cell mass in the placebo group is reflected in a loss of total fat-free mass (**Figure 3, A**), specifically TASM. Conversely, the increase in cell mass in the MK-677 group is reflected in the significant increase in total fat-free mass and TASM (**Figure 3, A**).

Abdominal Visceral and Abdominal Subcutaneous Fat

Abdominal visceral fat increased 4.2 cm^2 (CI, -6.2 to 14.5 cm^2) in the placebo group and 8.4 cm^2 (CI, 1.6 to 15.3 cm^2) in the MK-677 group ($P = 0.68$) (**Figure 3, C**).

Abdominal subcutaneous fat increased 1.3 cm² (CI, -12.5 to 15.0 cm²) in the placebo group and 18.0 cm² (CI, 8.7 to 27.2 cm²) in the MK-677 group ($P = 0.054$).

Body Weight and Total Body Fat

Body weight increased 0.8 kg (CI, -0.3 to 1.8 kg) in the placebo group and 2.7 kg (CI, 2.0 to 3.5 kg) in the MK-677 group ($P = 0.003$) (Figure 3, D). Total body fat by DXA increased 1.1 kg (CI, 0.2 to 1.9 kg) in the placebo group and 1.8 kg (CI, 1.2 to 2.5 kg) in the MK-677 group ($P = 0.130$).

Limb Lean (TASM) and Limb Fat

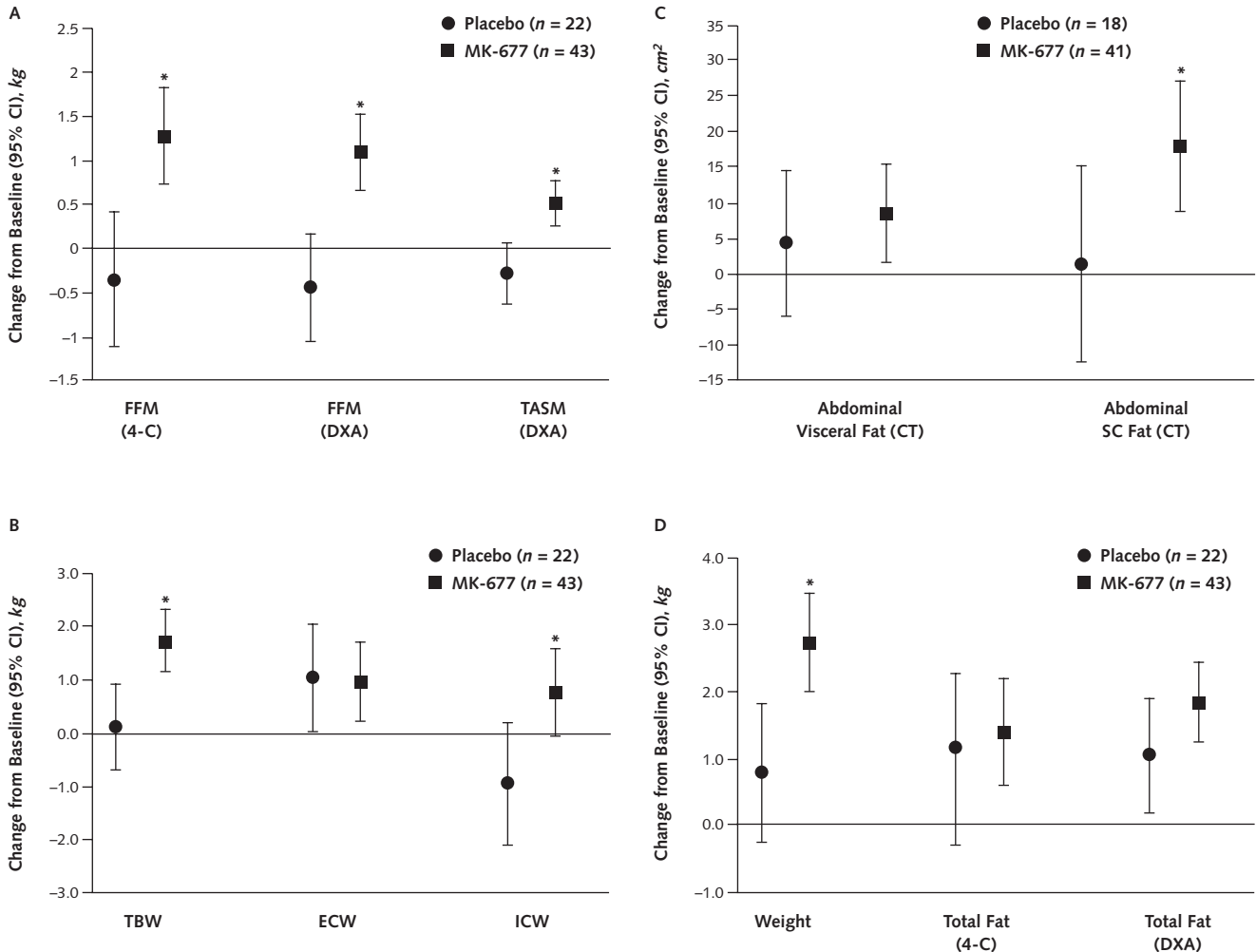
Figure 4 compares the mean changes in limb lean and limb fat as they relate to the mean changes in fat-free mass

and total fat mass in both groups. Placebo recipients lost limb lean, whereas about 50% of the increase in fat-free mass in MK-677 recipients was in the limbs. The average increase in limb fat in the MK-677 group was greater than that in the placebo group (1.1 kg vs. 0.24 kg; $P = 0.001$).

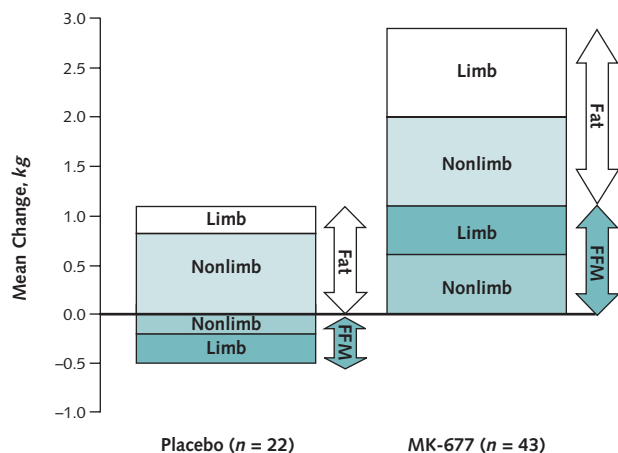
T-Score for TASM/m²

Appendix Figure 3 (available at www.annals.org) shows individual T-scores for TASM/m² at baseline and 12 months. After 1 year, the T-score improved in 27 of 43 (63%) MK-677 recipients (mean, 0.29 [CI, 0.16 to 0.42]), whereas 18 of 22 (82%) placebo recipients experienced no change or a decrease in T-score (mean, -0.13 [-0.32 to 0.06]; $P < 0.001$).

Figure 3. Changes in body composition at 12 months.



Graphs show arithmetic differences (95% CI). Asterisks indicates a significant difference (MK-677 vs. placebo) at 12 months. 4-C = 4-compartment model; CT = computed tomography; DXA = dual energy x-ray absorptiometry; ECW = extracellular water; FFM = fat-free mass; ICW = intracellular water; SC = subcutaneous; TASM = total appendicular skeletal mass; TBW = total body water. **A.** Changes in FFM (by 4-C model and by DXA) and TASM (by DXA). **B.** Changes in TBW, EBW, and ICW. The increase in TBW and ICW with MK-677 are consistent with the anabolic effects of the drug. **C.** Changes in abdominal visceral and abdominal SC fat cross-sectional areas by computed tomography. **D.** Changes in body weight and total fat by 4-C model and DXA.

Figure 4. Mean changes in fat and fat-free mass (FFM) at 12 months.

Limb = appendicular lean soft tissue and appendicular fat; nonlimb = total minus limb.

Bone Mineral Density

After 12 months, femoral neck bone mineral density increased in the placebo group and decreased in the MK-677 group (change, 0.012 g/cm² [CI, 0.002 to 0.022 g/cm² vs. -0.005 g/cm² [CI, -0.012 to 0.002 g/cm²], respectively). The difference between the MK-677 and placebo groups was small but significant (-0.018 g/cm²; $P = 0.004$). Spine and total hip bone mineral density did not significantly differ. We observed the same pattern after excluding 5 participants receiving alendronate (3 MK-677 recipients and 2 placebo recipients).

Appendix Tables 2, 3, and 4 (available at www.annals.org) show the detailed effects on other body composition end points and bone mineral density.

Muscle Strength

Shoulder flexion total work decreased in the placebo group but not in the MK-677 group. When we corrected for baseline arm appendicular skeletal muscle mass, shoulder flexion total work decreased more in the placebo group than the MK-677 group (change, -5.7 N·m/kg [CI, -10.1 to -1.4 N·m/kg] vs. -1.0 N·m/kg [CI, -4.1 to 2.1 N·m/kg]; $P = 0.073$). Total work in knee extension or flexion or in shoulder extension did not significantly differ between groups (Appendix Table 5, available at www.annals.org).

Function and Quality of Life

No measure of function (Appendix Table 6, available at www.annals.org) or quality of life (Appendix) significantly changed when the 2 groups were compared.

Clinical Outcomes

Lipids

At 12 months, low-density lipoprotein cholesterol levels changed by 0.12 mmol/L (CI, -0.07 to 0.3 mmol/L; 4.6 mg/dL [CI, -2.7 to 11.6 mg/dL]) in the placebo group but -0.14 mmol/L (CI, -0.27 to -0.01 mmol/L; -5.4 mg/dL [CI, -10.4 to -0.4 mg/dL]; $P = 0.026$) in the MK-677 group. Total and high-density lipoprotein cholesterol levels did not differ between groups (Appendix Table 7, available at www.annals.org).

Cortisol

Twenty-four-hour mean cortisol concentrations decreased in the placebo group (change, -18 nmol/L [CI, -55 to 19 nmol/L]; -0.1 μg/dL [CI, -1.4 to 1.2 μg/dL]) but increased in the MK-677 group (change, 47 nmol/L [CI, 28 to 71 nmol/L; 2.0 μg/dL [CI, 1.0 to 2.9 μg/dL]; $P = 0.020$) (Appendix Table 7).

Safety Data

Total testosterone levels in men did not change (Appendix Table 7). Prostate-specific antigen levels remained in the normal range or decreased with MK-677 treatment, except for a transient increase in 1 man. Results of mammography, Papanicolaou smears, and routine laboratory tests did not change over 2 years.

Insulin Sensitivity

Appendix Figure 4 (available at www.annals.org) shows individual glucose and HbA_{1c} responses. Mean fasting blood glucose levels did not change in the placebo group (0.0 mmol/L [CI, -0.3 to 0.2 mmol/L]; 1.0 mg/dL [CI, -5.0 to 3.0 mg/dL]) and increased 0.3 mmol/L (CI, 0.1 to 0.4 mmol/L; 5.0 mg/dL [CI, 2.0 to 7.0 mg/dL]; $P = 0.015$) in the MK-677 group. In 2 placebo recipients and 16 MK-677 recipients, fasting glucose increased from less than 5.6 mmol/L to 5.6 to 6.1 mmol/L [101 to 110 mg/dL]. In 3 MK-677 recipients with baseline fasting glucose concentrations less than 5.6 mmol/L [100 mg/dL] and 3 with concentrations greater than 5.6 mmol/L, glucose levels increased to 6.1 to 6.7 mmol/L (110 to 120 mg/dL) in 4 participants and to 6.9 mmol/L (125 and 126 mg/dL) in 2 participants. Mean HbA_{1c} level decreased in the placebo group and increased in the MK-677 group (change, -0.1% [CI, -0.2% to 1.0%] vs. 0.2% [CI, 0.1% to 0.3%], respectively; $P = 0.002$); at 12 months, 8 participants had an HbA_{1c} level greater than 6% (6.1% in 4, 6.3% in 3, and 6.4% in 1). Insulin sensitivity, as estimated by the Quicki Index, was also reduced after 12 months of treatment ($P < 0.001$) (Appendix Table 8, available at www.annals.org). One 81-year-old man had an increase in fasting blood glucose and HbA_{1c} levels after crossing over from placebo to MK-677; after dose reduction and institution of a low-carbohydrate diet, the values returned to normal.

Adverse Effects

Eight of 22 (36%) placebo recipients reported an increase in appetite, compared with 29 of 43 (67%) MK-677 recipients ($P = 0.033$); appetite returned to normal in 3 months in 50% of MK-677 recipients and more gradually in others. Participants in both groups reported mild, transient edema (6 of 22 [27%] placebo recipients vs. 19 of 43 [44%] MK-677 recipients; $P = 0.30$); transient muscle pain (2 of 22 [9%] placebo recipients vs. 14 of 43 [33%] MK-677 recipients; $P = 0.076$); and joint pain (17 of 22 [77%] placebo recipients vs. 25 of 43 [58%] MK-677 recipients; $P = 0.20$).

In year 1, adenocarcinoma of the tongue was diagnosed at 12 months in an 82-year-old woman receiving MK-677, and a 68-year-old woman had a myocardial infarction 7 days after starting MK-677. Renal cell carcinoma was diagnosed at 6 months in 1 man receiving placebo. All were withdrawn from the study. At the end of year 2, colon cancer was diagnosed in an 83-year-old woman who received MK-677 in year 1 and placebo in year 2.

Two-Year Exploratory Results

Two-year exploratory analyses of changes from baseline to 24 months in a subgroup of 53 participants (Appendix Table 9, available at www.annals.org) confirmed that the significant changes observed in the pivotal first year were sustained for growth hormone and IGF-I levels (Appendix Figure 5, available at www.annals.org), fat-free mass (by DXA only), and T-score for TASM/m² (Appendix Figure 6, available at www.annals.org). Appendix Figure 7 (available at www.annals.org) shows changes in body weight, total fat mass, fasting blood glucose levels, and abdominal visceral fat. In the group treated for 2 years with MK-677, fasting blood glucose level was not significantly increased ($P = 0.093$ vs. baseline).

We observed similar changes in participants who received MK-677 in year 2 after placebo in year 1 (group 3), whereas the changes were reversed in those who received MK-677 in year 1 and placebo in year 2 (group 2). One month after crossover and at 3 and 6 months after study completion, IGF-I concentrations returned to pretreatment levels.

DISCUSSION

Healthy elderly persons who received the ghrelin mimetic MK-677 experienced a sustained increase in the amplitude of pulsatile growth hormone secretion and IGF-I levels to those seen in young adults. The likely mechanism was activation of the ghrelin receptor by MK-677, with feedback by IGF-I preventing excess growth hormone production. MK-677 increased fat-free mass by 1.6 kg relative to placebo. To provide perspective, an adult's average lifetime loss of fat-free mass is about 5.5 kg (3). The concomitant increase in intracellular water, which reflects body cell

mass (25), was probably the mechanism for the increase in fat-free mass.

Ghrelin stimulates growth hormone secretion, but it also has effects that are not attributable to increased growth hormone levels. A ghrelin mimetic transiently increases appetite, a novel effect that might counteract physiologic anorexia, a cause of weight loss in elderly persons (26, 27). Unlike growth hormone, which is lipolytic, ghrelin increases fat stores. We found that body weight increased more in MK-677 recipients than in placebo recipients. Although total fat mass increased in both groups, limb fat and limb lean mass increased more in participants receiving MK-677 than in those receiving placebo. Surprisingly, thigh muscle cross-sectional area did not increase, although our study was not powered to detect small but potentially important differences because the single-slice computed tomography method that we used was insufficiently precise. Growth hormone reduces abdominal visceral fat in growth hormone-deficient adults (28) and abdominally obese, postmenopausal women (29) but not in normal elderly participants (30). Although MK-677 increased growth hormone levels, it did not affect abdominal visceral fat, possibly because its combined orexigenic and adipogenic effects counteracted the lipolytic effects of enhanced growth hormone. Finally, although MK-677 did not reduce abdominal visceral fat, it did reduce low-density lipoprotein cholesterol levels at 12 months, an effect not seen with growth hormone in normal elderly participants (8).

Strength, function, and quality of life did not improve after administration of MK-677 in our small, healthy cohort—a result we should possibly have expected. Although strength improved in elderly patients with hypopituitarism after daily injections of growth hormone for 2 to 3 years (31), growth hormone alone does not increase strength in healthy elderly persons (8, 32, 33). Strength improved only in healthy older men receiving growth hormone plus testosterone for 26 weeks (33). Finally, the relationship between strength and physical performance is nonlinear (34); we speculate that increased physical capacity might substantially improve performance in frail adults but not healthy adults.

Sarcopenia is a hallmark of frailty (35, 36) and is associated with increased mortality in elderly persons (37–40). In our healthy sample, MK-677 counteracted 3 important factors that contribute to sarcopenia: reduced secretion of growth hormone, loss of fat-free mass, and inadequate food intake. We did not study patients with sarcopenia, and their response to a ghrelin mimetic is not known.

Of note, our participants tolerated daily administration of MK-677 for the 2-year study period. The most frequent side effects were mild, transient, lower-extremity edema; transient muscle pain; and increased appetite, which subsided in a few months. These effects of physiologically stimulated growth hormone secretion contrast with those of growth hormone administered by injection:

edema, arthralgia, carpal tunnel syndrome, gynecomastia, and new-onset impaired fasting glucose and diabetes mellitus in some persons (8).

Both growth hormone and MK-677 increase insulin resistance and blood glucose in elderly persons (22, 33, 41, 42). We found statistically significant but small increases in fasting blood glucose and HbA_{1c} levels at 12 months. Considering the results of short-term studies with MK-677 (9, 43), which found no statistically significant increase in serum cortisol, the small increase in serum cortisol that we found is unlikely to underlie the increase in fasting glucose level. In patients treated with growth hormone, bone mineral density initially decreases (44); at least 18 months of treatment is needed to demonstrate an increase in bone mineral density (45). Femoral neck bone mineral density decreased at 12 months in MK-677 recipients, which is consistent with the increased bone remodeling that occurs with growth hormone (44). Fracture risk is the best measure of the effects of MK-677 on bone; however, this outcome would require studies of large samples over many years.

Our study has limitations. Its duration was relatively short, and the sample was small. Combining the results for men and women may have missed important sex effects. As a small, randomized study in healthy older adults, ours was a “proof-of-concept” study. It showed, apparently for the first time, that a drug can maintain the IGF-I levels and physiologic pattern of growth hormone secretion seen in young adults for at least 1 year and partially reverse age-related body composition changes.

Frailty is one of the scourges of elderly persons, and as researchers are beginning to learn about its causes, they are asking whether growth hormone deficiency is one of them. A systematic review (8) concluded that the risks of exogenous growth hormone outweigh the benefits and that it is not the long-sought solution to frailty. The promise of MK-677 is that it seems to restore endogenous growth hormone levels in a physiologic secretory pattern, unlike the single high-amplitude pulse observed after exogenous growth hormone administration. We believe that our study sets the stage for an adequately powered clinical trial of sufficient duration in a population vulnerable to frailty.

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