Effects of an Oral Growth Hormone Secretagogue in Older Adults

Heidi K. White, Charles D. Petrie, William Landschulz, David MacLean, Ann Taylor, Kenneth Lyles, Jeanne Y. Wei, Andrew R. Hoffman, Roberto Salvatori, Mark P. Ettinger, Miriam C. Morey, Marc R. Blackman, and George R. Merriam, for the Capromorelin Study Group

Duke University School of Medicine and Geriatric Research Education and Clinical Center (GRECC), Durham Veterans Affairs (VA) Medical Center (H.K.W., K.L., M.C.M.), Durham, North Carolina 27710; Pfizer Global Research and Development (C.D.P.), Groton, Connecticut 06340; Endocrine Clinical Research (W.L.), Eli Lilly and Co., Indianapolis, Indiana 46285; Brown University Medical School (D.M.), Providence, Rhode Island 02912; Novartis (A.T.), Cambridge, Massachusetts 02139; GRECC, Central Arkansas Veterans Affairs (VA) Healthcare System, and University of Arkansas for Medical Sciences (J.Y.W.), Little Rock, Arkansas 72205; VA Palo Alto Health Care System and Stanford University (A.R.H.), Palo Alto, California 94304; The Johns Hopkins University School of Medicine (R.S.), Baltimore, Maryland 21205; Radiant Research and the Regional Osteoporosis Center (M.P.E.), Stuart, Florida 34996; Washington DC VA Medical Center (M.R.B.), Washington, D.C. 20422; and VA Puget Sound Health Care System and University of Washington School of Medicine (G.R.M.), Seattle and Tacoma, Washington 98493

Context: GH secretion declines with age, possibly contributing to reduced muscle mass, strength, and function. GH secretagogues (GHS) may increase muscle mass and physical performance.

Objectives/Design: We conducted a randomized, double-masked, placebo-controlled, multicenter study to investigate the hormonal, body composition, and physical performance effects and the safety of the orally active GHS capromorelin in older adults with mild functional limitation.

Intervention/Participants: A total of 395 men and women aged 65–84 yr were randomized for an intended 2 yr of treatment to four dosing groups (10 mg three times/week, 3 mg twice a day, 10 mg each night, and 10 mg twice a day) or placebo. Although the study was terminated early according to predetermined treatment effect criteria, 315 subjects completed 6 months of treatment, and 284 completed 12 months.

Results: A sustained dose-related rise in IGF-I concentrations occurred in all active treatment groups. Each capromorelin dose prompted a rise in peak nocturnal GH, which was greatest with the least frequent dosing. At 6 months, body weight increased 1.4 kg in subjects receiving capromorelin and decreased 0.2 kg in those receiving placebo ($P = 0.006$). Lean body mass increased 1.4 *vs.* 0.3 kg ($P = 0.001$), and tandem walk improved by 0.9 sec ($P = 0.02$) in the pooled treatment *vs.* placebo groups. By 12 months, stair climb also improved ($P = 0.04$). Adverse events included fatigue, insomnia, and small increases in fasting glucose, glycosylated hemoglobin, and indices of insulin resistance.

Conclusions: In healthy older adults at risk for functional decline, administration of the oral GHS capromorelin may improve body composition and physical function. **(*J Clin Endocrinol Metab* 94: 1198–1206, 2009)**

Age-related decline in physical function is associated with disability (1, 2) and is in part due to loss of muscle mass. GH secretion decreases progressively between the ages of 30 and 70 yr (3, 4), as does the serum concentration of IGF-I (5, 6). Both have been implicated in the etiology of muscle mass decline. Administering GHRH and GH secretagogues (GHS) can restore

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Abbreviations: FBM, Fat body mass; GHS, GH secretagogue(s); HbA_{1c}, glycosylated hemoglobin; HOMA, homeostasis model assessment; LBM, lean body mass; MOS-SS, Medical Outcomes Study-Sleep Scale; PAI, Physical Activity Index; QUICKI, quantitative insulin sensitivity check index.

levels of GH and IGF-I to those of young adults (7–9), suggesting that older adults with relative GH deficiency might also benefit from GH replacement or stimulation (10, 11). There is consensus that GH or GHS can increase lean body mass (LBM) in older persons (10, 12), but effects on muscle strength and physical performance have been less consistent (13–15).

Capromorelin is an orally active pyrazolinone-piperidine GHS that stimulates GHS-1α receptors (16, 17), for which the natural ligand is the gastric peptide ghrelin (18). This ligand-receptor system is distinct from GHRH and its receptor and can synergize with GHRH to enhance GH release (19). Ghrelin has marked appetite-stimulating and GH-releasing effects; thus, clinical effects of a ghrelin mimetic may differ from those of GHRH or GH (20). Capromorelin exhibited high intestinal absorption in rats, consistent pharmacokinetics in rats and dogs including a short half-life, and potent stimulation of GH secretion in several animal species (21, 22). The availability of an orally administered GHS that enhances pulsatile release of GH provides a practical opportunity to test the hypothesis that chronic stimulation of GH release can improve physical function in older adults. In this randomized, double-masked, placebo-controlled, multicenter study, we investigated the safety and effects of long-term capromorelin treatment on circulating GH, IGF-I, body composition, and physical performance in older adults with mild functional limitations.

Subjects and Methods

Participants

Healthy men and women between the ages of 65 and 84 yr were recruited through advertisements. Standardized assessment criteria were used to select subjects at risk for functional decline (2, 23): habitual gait speed of 0.6 to 1.3 m/sec, inclusive, for men, and 0.6 to 1.2 m/sec for women; or dominant hand grip strength of less than 40 kg for men and less than 24 kg for women. In addition, subjects had to have one or more limitations of function based on either a subset of items from the SF-36 Health Survey (24) or Nagi's Instrumental Activities of Daily Living (25) or to have experienced two or more falls within the last 24 months. Given the diabetogenic risk of GH administration in obese patients, a body mass index of 30.0 kg/m^2 or less was required.

Subjects were excluded for diabetes mellitus, use of anticoagulants, seizure disorder, cancer treatment within 5 yr, poorly controlled hypertension, unstable or recent onset angina, myocardial infarction within 6 months, cognitive impairment, depression, significant limitations of lower extremity function (canes were allowed), bradycardia (<50 beats per minute), systolic blood pressure below 100 or above 170 mm Hg, orthostatic hypotension, a positive stool guaiac, and for men a prostate-specific antigen above 4 ng/ml. All laboratory tests had to be within 20% of the normal range: *i.e.* complete blood count with differential and platelet counts, absolute neutrophil count, blood urea nitrogen, creatinine, hemoglobin, hematocrit, glycosylated hemoglobin (HbA_{1c}), serum albumin, total bilirubin, serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, alkaline phosphatase, and urinalysis. Subjects who participated in strength training programs were excluded, and participants were asked not to begin strength training during the protocol. Aerobic exercise was encouraged but not stipulated by the protocol.

Study design

There were four capromorelin dosing regimens (10 mg three times per week, 3 mg twice a day, 10 mg each night, and 10 mg twice a day) and one placebo-treated group. The active regimens were chosen based on phase IIa data demonstrating a direct relation between dosing frequency and IGF-I levels and an inverse relation between dosing frequency and pulsatile GH release. The protocol was Institutional Review Board approved at 12 U.S. sites, and all participants provided written informed consent. The study included a prescreening assessment, screening and baseline visits, and then 11 visits over the planned 24 months. Body composition and physical performance were determined at baseline and at 3, 6, 12, and 24 months. The study design was proposed by the sponsor based upon results of earlier phase IIa studies and finalized with the active participation of investigators at Duke University and the Duke Clinical Research Institute. Hormonal data were analyzed by one of the academic investigators. The remainder of the data analyses were performed by the sponsor based on requests by the first author.

Percentage LBM and percentage fat body mass (FBM) were chosen as primary measures of body composition at the 6-month interim analysis. Three measures of physical performance (stair climb, 6-min walk, and maximum gait velocity) were chosen as primary endpoints at 12 and 24 months (1, 26, 27).

Measurements

Body composition measurements were obtained in the morning in the fasting state using whole-body dual x-ray absorptiometry (Hologic, Bedford, MA). Synarc (Maynard, MA) provided methods, quality assurance, and cross-instrument calibration. Grip strength was obtained using a hand dynamometer, and gait speed using an Ultratimer (DCPB Electronics, Glasgow, Scotland, UK). Six-minute walk distance was recorded using a rolling measuring wheel. Stair climb was determined by measuring the time required to climb 8–12 standard stairs and then calculating power as the weight of the subject multiplied by height climbed per second. Tandem stand was performed by placing one foot directly in front of the other and measuring time in this position to a maximum of 15 sec. Tandem walk was performed by having the subject walk heel to toe a distance of 10 feet, recording the better time of two trials. Five chair rises started with the subject sitting with her/his back against the chair. The measured time ended with full upright posture on the fifth stand from the chair.

Health status measures included the SF-36 Health Survey (28), Mini-Mental Status Exam (29), Geriatric Depression Scale (30), Nagi's Instrumental Activities of Daily Living (22), Medical Outcomes Study-Sleep Scale (MOS-SS) Index II (31), and Physical Activity Index (PAI) (32). Responses on the SF-36 were aggregated to generate Physical Health Component and Mental Health Component scores. The range of scores is from 0 to 100, with higher scores reflecting better functioning. On the MOS-SS Index II, a high score reflects greater sleep disturbance. The PAI assesses subject activity on an average day, and the PAI score provided an estimate of energy expenditure (kilocalories per week) used as a covariate in statistical models for physical performance measures.

Safety and tolerability

Subjects were queried regarding adverse events, and safety laboratory tests were collected. Abnormal test findings that required intervention or evaluation and clinically significant changes in the physical examination were reported. Two insulin sensitivity indexes, quantitative insulin sensitivity check index (QUICKI) [1/log (fasting insulin μU/ml) + log(fasting glucose mg/dl))] and homeostasis model assessment (HOMA) [fasting insulin concentration (μU/ml) $\times$ fasting glucose concentration (mmol/liter)/22.5], were calculated to determine the diabetogenic potential of capromorelin (33, 34).

Blood was collected in the morning after an overnight fast for determinations of IGF-I and GH. A subset of participants (n = 11–16 in each group) underwent 12-h overnight blood sampling. After a medication administration at 2200 h on a Monday, Wednesday, or Friday (to ensure that all treatment groups received active medication), blood was drawn every 20 min for GH measured by a two-site chemiluminescent immunometric assay using a solid phase murine monoclonal antibody and an alkaline phosphatase-conjugated murine monoclonal second antibody

(DPC Immulite, Los Angeles, CA). The sensitivity of the assay is 0.05 μg/liter. The assay is linear between 0.05 and 40 μg/liter and has an interassay precision of 10%. IGF-I was measured by nonextraction immunoradiometric assay (Diagnostic Systems Laboratories, Webster, TX). The sensitivity is 8 μg/liter. The assay is linear between 8 and 1000 μg/liter and has an interassay precision of 10%. Measurements were performed through MDS Clinical Laboratories (Toronto, Ontario, Canada).

Statistical methods

A sample size of 265 was required to provide 90% power to detect a 0.6 SD difference in %LBM at 6 months and a 0.6 SD difference in performance measures between treatment groups and placebo at 12 and 24 months. Interim analyses were preplanned for body composition at 6 months and for physical performance at 12 months with preset criteria of no significant difference at the 0.1 level.

Although primary outcome measures were selected in advance, a large number of secondary outcome variables were also included in this phase II exploratory study in which the utility of *a priori* formal adjustment for multiple comparisons is less than in a confirmatory phase III trial. Hence, no formal correction for type I errors was employed.

Linear models including terms for gender, age, enrollment site, PAI at baseline, change in PAI, baseline score, and treatment group were fit to the change scores of primary and secondary body composition and physical performance outcome variables by ordinary least squares using analysis of covariance. Dose finding for subsequent studies was not performed because this study was terminated early. Therefore, data from the four treatment groups were analyzed as a pooled treatment group in comparison to placebo for all body composition and physical performance measures and adverse events. However, outcomes for individual treatment groups in comparison to placebo for selected outcome variables are displayed graphically to highlight potential differences based on dosage and dosing intervals. All available data were analyzed according to the group assignment. Missing data were not imputed. The incidence rates of adverse events and abnormal laboratory test results were tabulated by pooled treatment group and placebo group and compared for significant differences in proportions by χ^2 testing.

Results

Participant characteristics

After prescreening telephone interviews, 675 volunteers were invited for screening evaluation, of whom 395 (162 men, 233 women) met inclusion and exclusion criteria and were randomized (Fig. 1). Fifty-three subjects (16.9%) in the pooled treatment group and 12 subjects (14.8%) in the placebo group withdrew due to adverse events. An additional 27 subjects (8.6%) in the pooled treatment group and eight subjects (9.9%) in the placebo group withdrew for other reasons. The treatment and placebo groups were similar (Table 1). Baseline characteristics of the subjects who did not complete 12 months were similar to those who did, except for reduced grip strength (26.1 *vs.* 28.2 kg; $P = 0.047$), habitual gait speed (1.14 *vs.* 1.22 m/sec; $P = 0.003$), and SF-36 Physical Health Component (46.2 *vs.* 48.7; $P = 0.008$).

As per protocol, an interim analysis was performed after 265 subjects completed 6 months of treatment. Although absolute LBM increased, participants also gained weight, and therefore the increase in %LBM was not significant. Because the predetermined interim efficacy criteria of a trend at the $P = 0.1$ level for %LBM was not met, the protocol was discontinued. At termination, 315 participants had completed 6 months of treatment, and 284 participants completed 12 months. Eleven subjects did not complete the 12-month evaluation due to study termination. Fewer participants completed the 18-month (n = 141) or 21-month (n = 43) evaluations; therefore, these data are not presented.

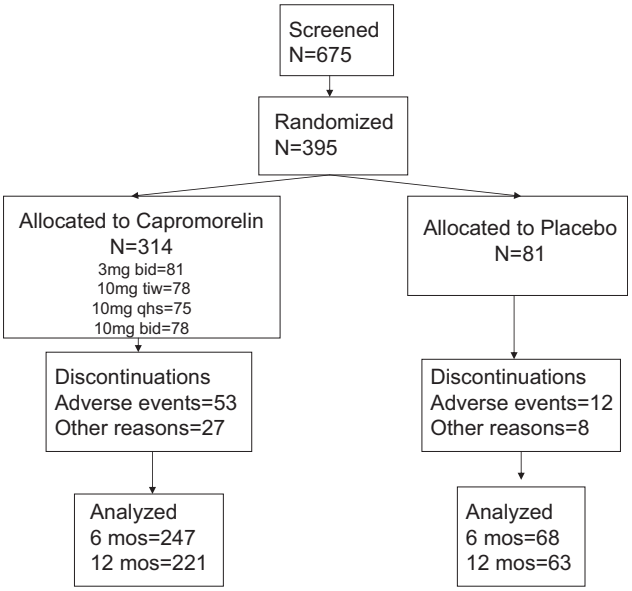

FIG. 1. Study flowchart.

Hormonal responses

Serum IGF-I concentrations increased in all treatment groups compared with placebo and with pretreatment measures ($P < 0.001$), and the increase was directly related to the total weekly capromorelin dose (Fig. 2A). IGF-I responses were sustained during the treatment period and returned to baseline after treatment was discontinued (Fig. 2B). In subjects in whom GH levels were collected from 2000 h to 0800 h after an evening dose of drug, peak GH responses reflected the interval between doses more than the size of each dose, with higher responses in the least frequent dosing schedules (Fig. 3). The frequency of overnight GH peaks, by Pulsar analysis (35), did not vary significantly among dosing and placebo groups (data not shown).

Body composition

There were no significant changes in the primary body composition endpoint, %LBM, or %FBM at 6 or 12 months (Table 2), whereas LBM and total weight increased significantly at 6 months in the treatment group and LBM remained significantly increased with capromorelin at 12 months. Members of the four active treatment groups experienced similar increases in LBM (Fig. 4). Men and women experienced similar improvements in LBM without a statistically significant change in the %LBM.

Physical performance

At 6 months, change in tandem walk speed, a secondary measure, increased significantly in the treatment *vs.* placebo group (Table 2). At 12 months, one of the three primary performance

TABLE 1. Baseline characteristics of treatment groups

	Pooled treatment (n = 314)	Placebo (n = 81)
Demographics		
Gender (male)	41%	41%
Age (yr)	72.7 ± 4.8	73.4 ± 4.9
Health status measures		
Weight (kg)		
Men	80.7 ± 9.8	80.4 ± 9.0
Women	65.5 ± 9.0	63.5 ± 7.9
Height (cm)		
Men	176 ± 6	176 ± 7
Women	160 ± 7	159 ± 6
Body mass index (kg/m^2)		
Men	26.1 ± 2.6	25.9 ± 2.0
Women	25.4 ± 2.9	25.1 ± 2.5
SF-36 Physical Health Component	47.9 ± 7.6	47.7 ± 7.3
SF-36 Mental Health Component	57.2 ± 5.3	57.4 ± 5.9
Mini-Mental Status Exam	29.29 ± 1.0	29.11 ± 1.5
Geriatric Depression Screen	3.0 ± 3.2	3.6 ± 3.7
MOS-SS index II	20.00 ± 12.11	19.45 ± 11.5
PAI (kcal/wk)	92,963 ± 111,061	80,068 ± 102,832
Fasting glucose	91.1 ± 10.8	89.2 ± 12.3
HbA_{1c}	5.8 ± 0.4	5.8 ± 0.4
Fasting insulin (μU/ml)	8.7 ± 7.8	7.9 ± 4.9
QUICKI	0.360 ± 0.034	0.364 ± 0.037
HOMA	0.202 ± 0.012	0.201 ± 0.012
Grip strength (kg)		
Men	35.5 ± 7.2	34.6 ± 8.0
Women	22.0 ± 4.1	21.1 ± 4.5
Body composition measures		
% LBM		
Men	70.2 ± 4.7	70.3 ± 5.3
Women	57.8 ± 6.5	58.3 ± 5.3
% Fat mass		
Men	26.5 ± 4.9	26.4 ± 5.4
Women	39.3 ± 6.6	38.7 ± 5.5
LBM (g)		
Men	56,982 ± 6,447.8	57,465 ± 4,373.3
Women	38,212 ± 4,631.8	37,596 ± 4,655.9
Fat mass (g)		
Men	21,791 ± 5,640.6	22,106 ± 6,701
Women	26,519 ± 6,870	25,224 ± 5,540.5
Physical performance measures		
Maximum gait speed		
Men	1.81 ± 0.32	1.76 ± 0.29
Women	1.67 ± 0.30	1.61 ± 0.27
Power stair climb		
Men	364.7 ± 124.9	349.4 ± 108.6
Women	241.4 ± 64.6	227.2 ± 60.7
6-min walk		
Men	1,837 ± 329.6	1,805 ± 298.3
Women	1,668.7 ± 277.2	1,672 ± 224.5
5 chair rises		
Men	12.6 ± 3.4	12.9 ± 3.1
Women	12.8 ± 3.0	13.2 ± 3.5
Habitual gait speed (m/sec)		
Men	1.22 ± 0.19	1.17 ± 0.19
Women	1.18 ± 0.20	1.15 ± 0.17
Tandem stand		
Men	12.1 ± 4.6	12.7 ± 4.2
Women	11.5 ± 5.1	9.8 ± 5.4
Tandem walk		
Men	9.7 ± 3.4	10.0 ± 3.3
Women	10.9 ± 4.2	13.1 ± 4.9

Data are expressed as mean ± SD, unless indicated otherwise.

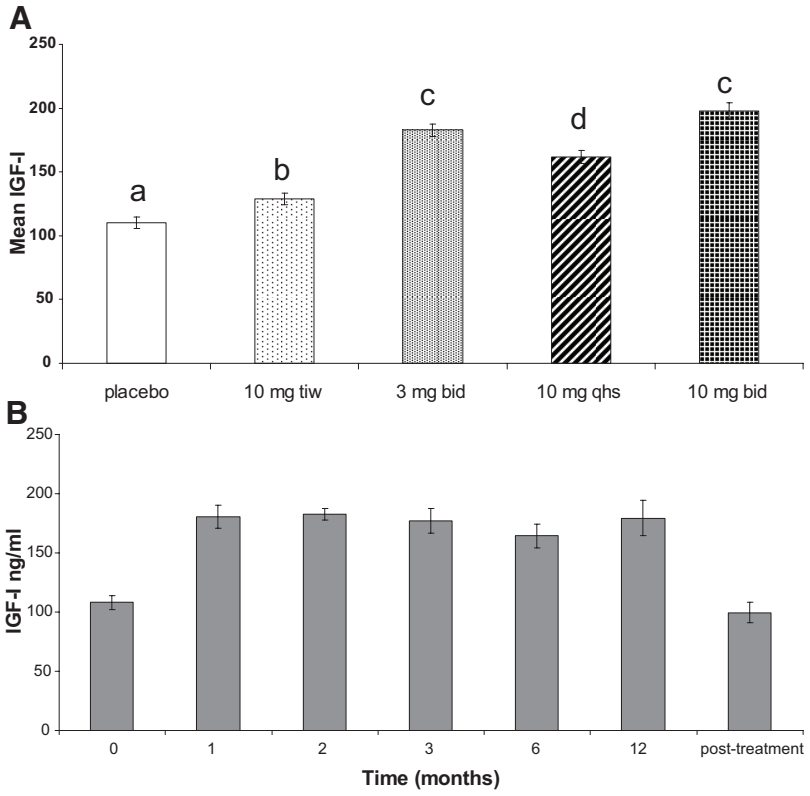

FIG. 2. A, Mean levels of IGF-I, as measured after 2 months of treatment, in the placebo and four active dosing groups. Different letters (a-d) indicate significant differences among groups, $P < 0.01$. B, Sustainability and consistency of IGF-I responses at baseline (0), during capromorelin treatment, and after treatment in the 3 mg twice daily dosing group (42 mg/wk).

measures, power stair climb, also improved significantly, and improvements in tandem walk remained highly significant. Changes in the 6-min walk and five chair stands approached significance. Separate analyses of male and female [1]participants indicated that most of the improvement in power stair climb occurred in female participants. Both male and female participants experienced significant improvement in the tandem walk. Figure 5 illustrates the changes observed over time in the four capromorelin dosage groups and placebo for the physical performance measures of power stair climb, 6-min walk, five chair rises, and tandem walk. At 12 months the percentage change from baseline in the stair climb was 7.0 ± 20.2 *vs.* 0.9 ± 17.8% for the treatment *vs.* placebo groups ($P = 0.02$), and the percentage change for the tandem walk was a decrease in time of 7.7 ± 27.7 *vs.* 0.4 ± 28.1% for the treatment *vs.* placebo groups ($P = 0.04$).

Safety and tolerability

Capromorelin-treated subjects exhibited greater increases in appetite (14 *vs.* 4.9%) and insomnia (30.3 *vs.* 17.3%) as well as higher fasting glucose concentrations at 6 and 12 months (Table 3). Similarly, glycosylated hemoglobin (HbA_{1c}) values rose slightly but significantly at 6 months and remained higher at 12 months (Table 3), but there was no significant difference in the frequency of hyperglycemia as an adverse event. Quantitative insulin sensitivity indexes QUICKI and HOMA showed significantly increased insulin resistance (Table 3) in the active treatment group. In subanalysis of the four dosages of capromorelin, these changes in QUICKI and HOMA were dose-related according to the cumulative dose. Among the treated participants, seven (2%) were found to have glucose in their urine specimens compared with zero placebo recipients, and triglyceride levels 30% above the upper limit of normal were more common among treated participants [n = 66 (22%)] than among placebo-treated participants [n = 13 (17%)], but these differences were not statistically significant. There was a significant increase in sleep disturbance as measured by the MOS-SS Index II in the capromorelin group at 6 months, but not at 12 months (Table 3).

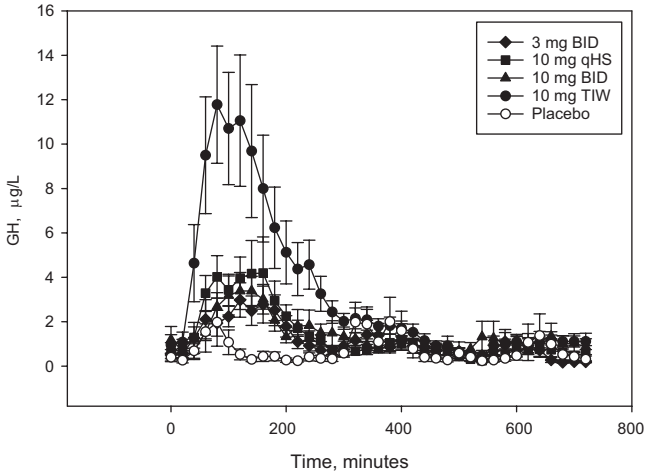

FIG. 3. Time course of GH responses to the different oral doses of capromorelin or to placebo. Values are the means ± SEM of levels at each time point. Responses returned to baseline levels by 6 h after dosing.

Discussion

This study confirms previous studies with GH injections (12) and with another oral GHS, MK-677 (36, 37), which produced significant increases in total body weight and LBM, as we observed with capromorelin. More importantly, capromorelin produced statistically significant improvements in some measures of physical performance compared with placebo. Tandem walk improved at 6 months and persisted at 12 months, and power stair climb improved at 12 months of treatment. There were trends toward improvement in the 6-min walk and five chair rises tests. While this report was under review, Nass *et al.* (37) published results of a similar study MK-677 in a group of healthy seniors. The increases of LBM and total body weight at 6 and 12 months were similar to those reported here. Of note, in contrast to our results, they did not observe improvement in physical functional performance measures. Although the exact reasons for this difference are not clear, this may reflect our choice of "pre-frail"

TABLE 2. Change scores for measures of body composition and physical performance

	6 months			12 months		
	Capromorelin	Placebo	*P* value	Capromorelin	Placebo	*P* value
Body composition						
% LBM	0.79 ± 1.97	0.53 ± 1.75	0.32	1.25 ± 2.06	0.97 ± 1.86	0.33
% Fat mass	−0.73 ± 1.95	−0.52 ± 1.74	0.42	−1.18 ± 2.10	−0.93 ± 1.89	0.40
LBM (g)	1446.5 ± 2717.1	338.7 ± 1576.9	0.001	1607.3 ± 3286.9	587.5 ± 1371.0	0.02
FBM (g)	−14.3 ± 2548.4	−461.2 ± 1606.76	0.18	−425.8 ± 2591.8	−673.6 ± 1949.2	0.49
Total body weight (g)	1376.6 ± 4564.6	−188.6 ± 1928.9	0.006	1166.3 ± 5183.9	−113.2 ± 2218.6	0.06
Performance measures						
Primary outcomes						
Maximum gait speed (m/sec)	0.03 ± 0.22	0.02 ± 0.19	0.64	0.01 ± 0.22	0.01 ± 0.19	0.97
Stair climb (kg∗cm/sec)	22.12 ± 61.16	11.94 ± 61.21	0.19	15.88 ± 59.77	0.29 ± 50.16	0.04
6-min walk (feet)	47.26 ± 162.97	28.94 ± 148.31	0.37	57.64 ± 172.28	15.05 ± 164.06	0.06
Secondary outcomes						
5 chair rises (sec)	−0.88 ± 2.42	−0.54 ± 2.44	0.26	−1.02 ± 2.40	−0.43 ± 2.89	0.07
Habitual gait speed (m/sec)	0.04 ± 0.16	0.01 ± 0.17	0.25	0.01 ± 0.17	0.00 ± 0.16	0.79
Tandem stand (sec)	0.48 ± 4.83	0.13 ± 5.59	0.52	0.47 ± 5.41	−0.22 ± 5.66	0.24
Tandem walk (sec)	−1.40 ± 3.45	−0.52 ± 3.58	0.02	−1.34 ± 3.47	−0.10 ± 3.47	0.002

Data are expressed as mean ± SD, adjusted for age, sex, center, baseline score, baseline PAI, and change from baseline PAI. Performance measures are also adjusted for baseline maximum gait speed.

subjects with evidence of mild to moderate physical impairment, in contrast to the subjects in their study who were characterized as healthy without any requirement of impairment. To our knowledge, our study is the first report of improvement in measures of physical performance compared with placebo in older adults after use of an oral GHS (38, 39), and it supports the hypothesis that stimulation of GH release may result in improvements not only in body composition but also in physical function. Aging is associated with a relatively greater decline in type 2 (fast twitch) *vs.* type 1 muscle fibers (40). Muscle power effect is mediated more by fast twitch type 2 fibers, whereas type 1 slow twitch fibers may be more important for muscle endurance. Limited evidence suggests that type 2 fiber expression may be relatively increased in response to GH and/or IGF-I (38). The study of Nass and colleagues had only one active dosing group and placebo, while the design of our study allowed examination of whether the pattern of dosing as well as the total weekly dose affected the results. IGF-I responses seemed in general to reflect total dose, whereas acute GH responses were affected by dosing interval as well as the total dose. Functional improvements did not significantly differ among the different active doses and dosing intervals.

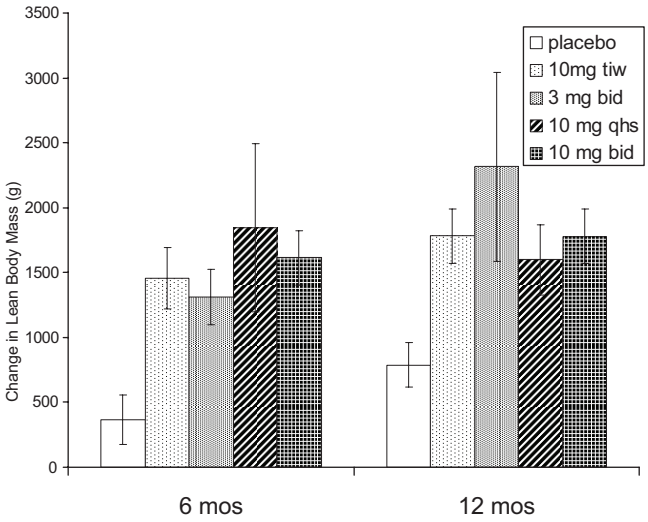

FIG. 4. Changes in lean body mass for the four active treatment groups and the placebo group at 6 and 12 months.

The magnitude and clinical importance of our findings can be compared with the results of exercise intervention studies. A home-based exercise program in a slightly older but similarly impaired group showed significant improvements only in balance tests including tandem walk (41), similar to our study. Stair climb is a sensitive measure of lower extremity power. In one exercise trial in frail nursing home residents, stair climb improved by 23–34% after 10 wk of high-intensity resistance training (42). The 7% improvement in stair climb seen in our study (more prominent in women than men) is noteworthy in our modestly impaired participants for whom no exercise was prescribed.

Although our results support the hypothesis that GH stimulation may benefit physical performance and delay functional decline in older adults, the magnitude of improvement we observed was modest. Several factors may have limited our ability to observe the physical performance effects. First, we selected healthy older adults on the basis of mild impairment in physical performance, so potential ceiling effects on performance measures may have underestimated the drug effect; indeed the baseline habitual gait speed observed was nearly at the limit of our exclusion criteria. Subjects who did not complete 12 months of treatment scored somewhat worse on baseline physical performance characteristics compared with subjects who did complete 12 months. This potentially biased the results further toward a group with a higher level of function than the overall group recruited. Secondly, the duration of this intervention may have been too short to detect all measurable changes in physical performance. Thirdly, we did not select study participants to have pretreatment age-related reductions in serum concentrations of IGF-I, which might have led to greater responses to the GHS.

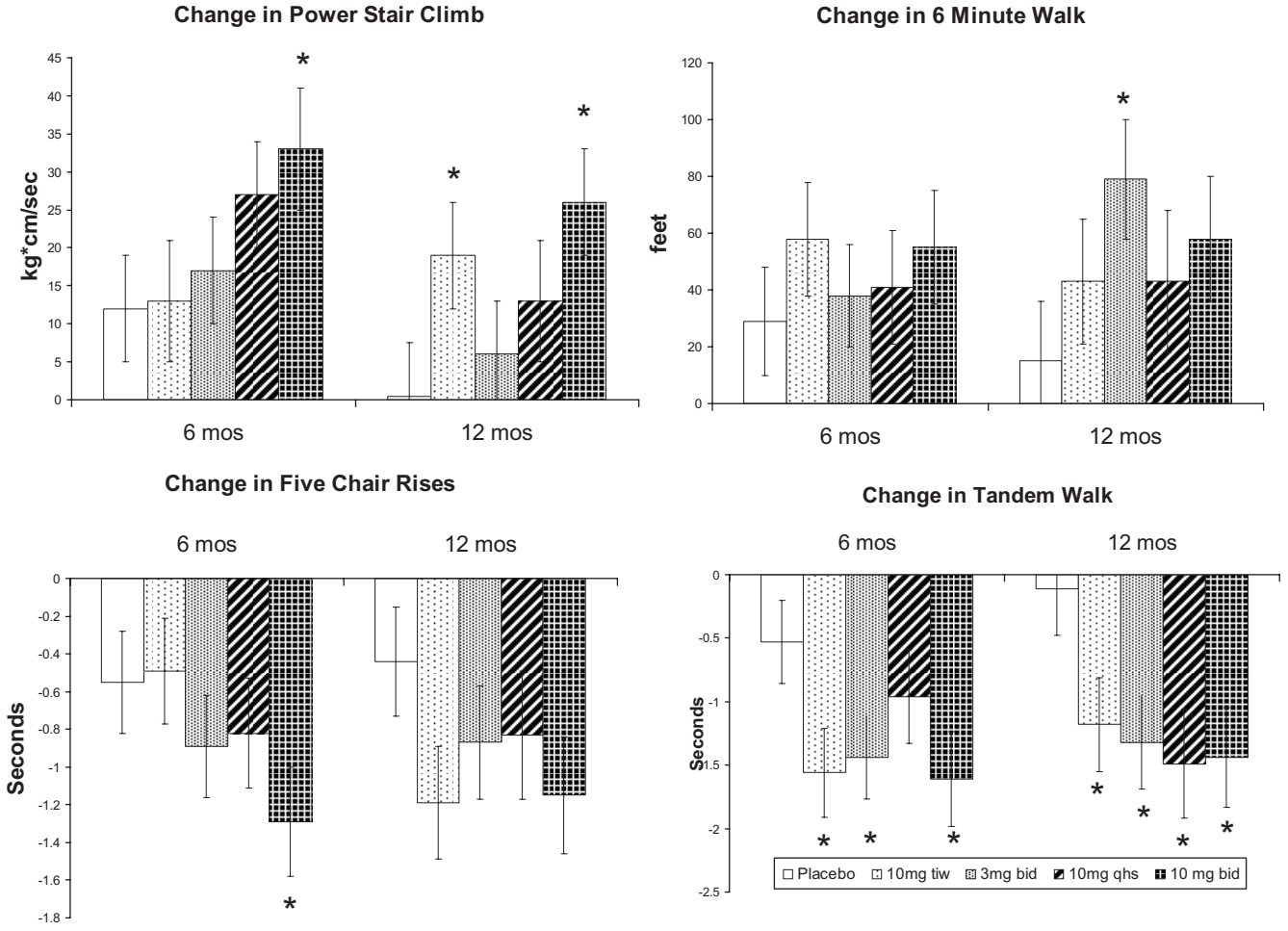

FIG. 5. Change in scores for all four treatment groups and placebo group at 6 and 12 months for selected performance measures. *, $P < 0.05$ in comparison with placebo group.

Although increases in IGF-I concentrations followed a dose-response relationship, the acute rises in GH were less consistently related to the magnitude of each dose, but were directly correlated with the interdose interval, consistent with findings in previous studies using other ghrelin mimetics (43). There are several possible explanations for this phenomenon. As shown in *in vitro* studies of perifused rat pituicytes, the GH response to frequent or continuous stimulation with another ghrelin mimetic decreases over time, but a full GH response can still be evoked by administering GHRH instead, suggesting partial GHS receptor-specific desensitization (44). In addition, elevations in IGF-I, which were highest in the 10 mg twice a day group, may have suppressed acute GH responses to each dose. Total integrated GH, as reflected in the IGF-I increases, may still be greatest in the highest dosing groups. We measured GH levels only for 12 h after a dose, whereas measurement over the full interdose period would have been needed to measure integrated GH concentrations.

Ghrelin and its mimetics may also act by non-GH mechanisms, such as by affecting appetite and caloric balance, or the thymus and proinflammatory cytokine pathways (45). In our study, capromorelin increased appetite, which likely contributed to the observed increase in weight, almost entirely attributable to increased LBM. Given the potential roles of reduced IGF-I and

TABLE 3. Change scores for selected measures

	6 months			12 months		
	Pooled treatment	**Placebo**	***P* value**	**Pooled treatment**	**Placebo**	***P* value**
Glucose (mg/dl)	4.18 ± 11.03	−1.11 ± 7.96	0.0001	5.39 ± 11.61	0.85 ± 9.88	0.005
HbA_{1c} (%)	0.19 ± 0.33	0.00 ± 0.22	0.0001	0.07 ± 0.45	−0.14 ± 0.29	0.0008
Fasting insulin (μU/ml)	0.74 ± 6.21	−0.32 ± 4.98	0.002	0.85 ± 4.98	−0.12 ± 4.86	0.003
QUICKI	−0.0063 ± 0.0232	0.0016 ± 0.0227	0.0001	−0.0054 ± 0.0232	0.0018 ± 0.0221	0.0001
HOMA	0.0024 ± 0.0079	−0.0006 ± 0.0075	<0.0001	0.0021 ± 0.0079	−0.0006 ± 0.0073	0.0001
MOS-SS Index II	2.76 ± 11.51	−1.56 ± 8.68	0.004	1.80 ± 11.17	0.64 ± 10.01	0.47

Data are expressed as mean ± SD and are adjusted for age, sex, center, baseline score, baseline PAI, change from baseline PAI, and baseline maximum gait speed.

augmented proinflammatory cytokines in the development of disability (46), there is heightened interest in the potential of GHS to suppress proinflammatory pathways, and thereby attenuate the decline in physical performance and function leading to such age-associated disorders as heart failure (47).

Capromorelin was well tolerated. Although insomnia and increased appetite were frequent side effects of capromorelin, they did not result in excessive withdrawal of participants. The changes in fasting glucose and HbA_{1c} were of minimal clinical consequence. There was a small but statistically significant change in two calculated measures that indicate greater insulin resistance, as also reported in the study of Nass *et al.* (37). Impaired glucose tolerance has been reported with other GHS compounds (37, 43) and ghrelin has similar properties (48). Impaired fasting glucose and new diabetes have been reported with GH (13, 14). We observed no differences in other common GH-related adverse events including edema, arthralgias, or carpal tunnel syndrome (14).

In summary, this study suggests that administration of the orally active GHS capromorelin for 1 yr can improve physical performance in generally healthy older adults with mild functional decline. Further research appears warranted to appraise the risk-benefit profile of these compounds and determine their potential utility for maintaining and improving physical function and reducing disability in selected populations of older adults.

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Address all correspondence and requests for reprints to: Heidi K. White, M.D., M.H.S., Duke University School of Medicine, Box 3003, Durham, North Carolina 27710. E-mail: White031@mc.duke.edu.

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