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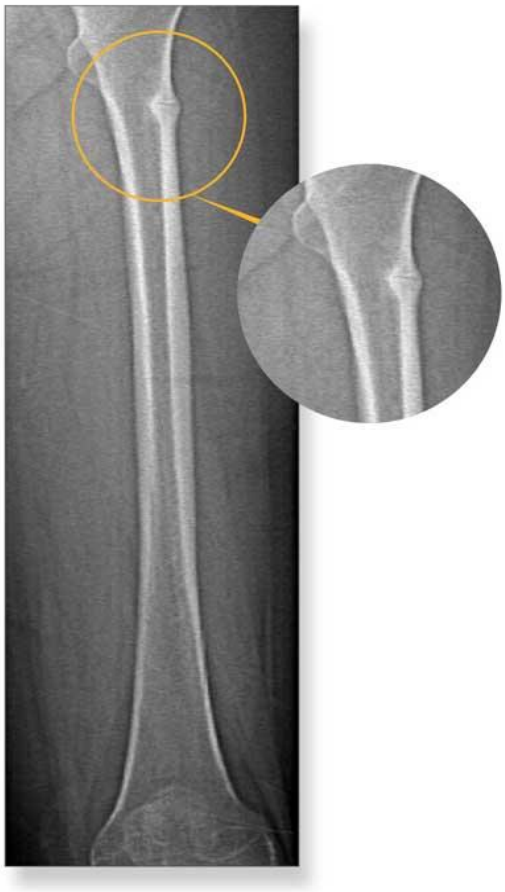

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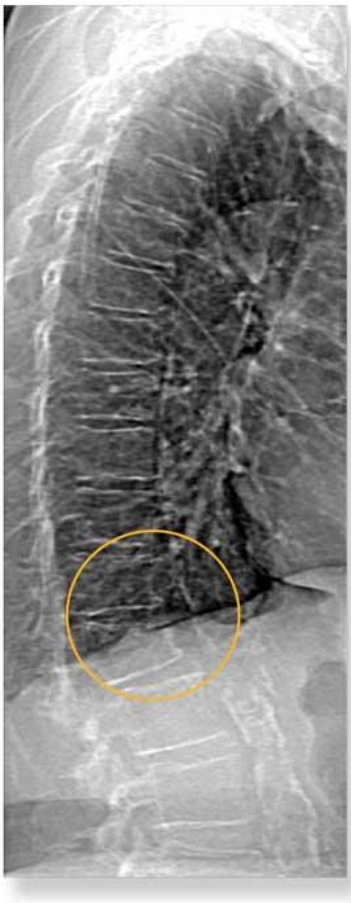

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Oral Administration of the Growth Hormone Secretagogue MK-677 Increases Markers of Bone Turnover in Healthy and Functionally Impaired Elderly Adults*

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ABSTRACT

Growth hormone (GH) stimulates osteoblasts in vitro and increases bone turnover and stimulates osteoblast activity when given to elderly subjects. Probably a major effect of GH on bone is mediated through stimulation of either circulating or locally produced insulin-like growth factor I (IGF-I). We determined the effect of chronic administration of the GH secretagogue, MK-677, on serum IGF-I and markers of bone turnover in 187 elderly adults (65 years or older) enrolled in three randomized, double-blind, placebo-controlled clinical studies lasting 2–9 weeks. Urine was collected for determination of N-telopeptide cross-links (NTXs), a marker of bone resorption, and blood was collected for determination of serum osteocalcin and bone-specific alkaline phosphatase (BSAP), as bone formation markers, and serum IGF-I levels pre- and post-treatment. Dose response data were initially obtained in healthy elderly subjects who received oral doses of 10 mg or 25 mg of MK-677 or placebo for 2 weeks (n = 10–12/group). Treatment with 10 mg and 25 mg of MK-677 for 2 weeks increased mean urine NTXs 10% and 17%, respectively ($p < 0.05$ vs. placebo). Additionally, 50 healthy elderly subjects received either placebo (n = 20) for 4 weeks or 25 mg of MK-677 (n = 30) daily for 2 weeks followed by 50 mg daily for 2 weeks. MK-677 increased mean serum osteocalcin by 8% ($p < 0.05$ vs. placebo). In both studies, MK-677 increased serum IGF-I levels significantly (55–94%). Subsequently, the biological effects of MK-677 were studied in 105 elderly subjects who met objective criteria for functional impairment. Subjects were randomized to receive oral doses of placebo for 9 weeks or either 5, 10, or 25 mg of MK-677 daily for an initial 2 weeks followed by 25 mg of MK-677 daily for the next 7 weeks (n = 63 on MK-677 and n = 28 on placebo completed 9 weeks of therapy). Treatment with MK-677 (all MK-677 groups combined) for 9 weeks increased mean serum osteocalcin by 29.4% and BSAP by 10.4% ($p < 0.001$ vs. placebo) and mean urinary NTX excretion by 22.6% ($p < 0.05$ vs. placebo). The change from baseline serum osteocalcin correlated with the change from baseline serum IGF-I in the MK-677 group (r = 0.37; $p < 0.01$). In conclusion, once daily dosing with MK-677, an orally active GH secretagogue, stimulates bone turnover in elderly subjects based on elevations in biochemical markers of bone resorption and formation. (J Bone Miner Res 1999;14:1182–1188)

INTRODUCTION

SEVERAL LINES OF EVIDENCE suggest that growth hormone (GH) could be useful in the treatment of osteoporosis due to its anabolic properties. GH stimulates osteoblast proliferation and differentiation in vitro.[1] Depending on the species and cell lines, GH also increases osteoblast production of insulin-like growth factors I and II (IGF-I and IGF-II)[1] both of which are mitogenic, increase human osteoblast differentiation, and are likely important local regulators of bone remodeling. Furthermore, GH stimulates bone formation and increases the strength of cortical bone in aged rats.[2]

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Table 1. Subject Characteristics

Study	n	*Men/Women [n (%)]*	*Mean age (range)*	*Body weight (lb) (mean ± SD)*	*Body height (in) (mean ± SD)*
I	32	men—17 (53%)	74.5 (65–81)	165 ± 31	68.4 ± 3.7
		women—15 (47%)	73.0 (65–79)	149 ± 38	62.3 ± 3.3
II	50	men—32 (64%)	72.5 (65–85)	173 ± 22	68.0 ± 4.3
		women—18 (36%)	71.5 (65–83)	134 ± 29	62.8 ± 3.7
III	105	men—69 (66%)	77.5 (65–94)	166 ± 30	67.7 ± 3.1
		women—36 (34%)	78.0 (65–92)	144 ± 38	61.8 ± 3.5

Human aging is associated with declining serum concentrations of GH and IGF-I.[3–5] This reduction may contribute to the decrease in bone mass that accompanies aging.[6] Recombinant human growth hormone (rhGH) increases markers of bone turnover, suggesting an overall increase in bone remodeling, in healthy and osteoporotic elderly women and GH-deficient adults.[7–11] rhGH (3 mg subcutaneously three times/week) given to postmenopausal women increased osteocalcin, a marker of bone formation, by ~40% from baseline by 3 months of treatment.[12] In men older than 60 years of age, GH given for 6 months slightly increased lumbar spine bone mass (1.6%).[13] Recently, stimulated bone turnover has been shown in GH-deficient adults treated with rhGH based on histomorphometric changes.[14] While stimulation of the skeleton did not result in increased trabecular bone volume, cortical thickness increased significantly. Whereas GH alone decreased bone mineral density (BMD) in GH-deficient adults after 1 year of treatment,[15] longer term studies of rhGH in GH-deficient adults did show increases in BMD by 18 months.[16] Initial decreases in bone mass after GH administration may be a result of the hormone's effect to accelerate both sides of the bone balance equation, formation and resorption. Whether this increase in bone turnover would result in a clinically significant gain in bone mass after long-term administration in elderly subjects is unknown.

MK-677 is an orally active nonpeptide spiropiperidine previously demonstrated to be functionally indistinguishable in vitro and in vivo[17] from GH-releasing peptide 6, a relatively selective GH secretagogue.[18–20] MK-677 enhances pulsatile release of GH, resulting in sustained elevations in IGF-I, and is well tolerated after oral administration in animals, healthy young men, and older men and women.[17,21–23]

The studies reported herein provide dose-response data for MK-677 on bone turnover using well established biochemical indices in healthy elderly adults as well as in functionally impaired adults.

MATERIALS AND METHODS

Subjects

Table 1 provides data on the characteristics of all subjects in each of the three studies. In the first two studies, 82 healthy elderly male or female volunteers (age 65–85 years) were selected for participation. All subjects were in general good health on the basis of medical history, physical exam, electrocardiogram, urinalysis, blood counts, and routine serum chemistry analysis. The only medications allowed were stable doses of thyroid hormone replacement, <1000 mg of acetaminophen daily, and up to one aspirin tablet daily. In the third study, 105 elderly men and women (age 65–94 years) who were ambulatory, had a serum IGF-I level <165 ng/ml (50th percentile for age), a strength deficit at extensor or flexor muscles of the knee and met objective criteria for musculoskeletal impairment based on a National Institute of Aging performance-based measure score of 4–11 were recruited from the community at 10 sites throughout the United States.[24] The performance characteristics of these patients are described in more detail in a separate report.[25] Ethical Review Committee approval was obtained at each participating site, and written informed consent was obtained from each subject.

Study design

Dose-ranging study in healthy elderly subjects: In a randomized, double-blind, placebo-controlled, parallel-group study to preliminarily evaluate the tolerability and activation of bone resorption by MK-677,[23] healthy elderly subjects received 10 mg or 25 mg of MK-677 daily or placebo for 14 days (n = 10–12/group). Urine was collected for determination of N-telopeptide cross-links (NTXs) and creatinine pretreatment and on day 14. Clinical and laboratory safety data and serum IGF-I concentrations were determined pretreatment and on day 14 of treatment.

Four-week safety and tolerability study in healthy elderly: In this double-blind, randomized, parallel-group study, 50 healthy elderly subjects were randomized to receive MK-677 (n = 30) or placebo (n = 20). Subjects received either placebo for 4 weeks or 25 mg of MK-677 daily for the initial 2 weeks followed by 50 mg of MK-677 daily for the final 2 weeks. Blood was collected at ~9:00 a.m., at pretreatment, and after 28 days for determination of serum IGF-I and serum osteocalcin. Clinical and laboratory safety data were determined pre- and post-treatment.

Nine-week study in elderly patients with functional impairment: In this double-blind, multicenter, parallel group, pilot study, ambulatory elderly men and women who met objective criteria for musculoskeletal impairment as detailed above were treated with MK-677 or placebo. Patients were randomized to receive placebo for 9 weeks or 5, 10, or 25

Table 2. Effects of Two Weeks Treatment with MK-677 on Biochemical Markers of Bone Turnover in Healthy Elderly Subjects

Parameter	*MK-677 dose*	n	*Mean ± SE pretreatment*	*Mean % change ± SE posttreatment week 2*
Urine NTX/Cr	placebo	10	26 ± 3	−17 ± 8
(nmol of BCE/mmol of Cr)	10 mg	12	24 ± 3	10 ± 8*
	25 mg	10	29 ± 7	17 ± 12*
Serum BSAP†	placebo	9	8 ± 1	2 ± 3
(U/l)	10 mg	11	13 ± 1	1 ± 4
	25 mg	9	11 ± 2	3 ± 7

* MK-677 dose versus placebo ($p < 0.05$, between-group test).

† One subject from each treatment group was missing paired (pre- and post-treatment) BSAP values.

mg of MK-677 daily for 2 weeks, followed by 25 mg of MK-677 daily for the subsequent 7 weeks. This design was selected to reassess the dose-response relationship as regards safety and serum IGF-I concentrations in frail elderly subjects prior to longer term exposure at the maximum dose.[24] Blood was collected at ~9:00 a.m. for serum osteocalcin and serum bone-specific alkaline phosphatase (BSAP) assay pretreatment and at the end of week 9. Urine was collected for determination of NTXs and creatinine. Serum and urine samples were frozen until subsequent assay. Clinical and laboratory safety data including serum creatinine were determined pretreatment and at the end of week 9.

Serum IGF-I assay: Serum IGF-I was measured by a competitive binding radioimmunoassay after acid-ethanol extraction (Endocrine Sciences, Callabasas Hills, CA, U.S.A.). At a mean serum concentration of ~280–310 ng/ml, the within- and between-assay coefficients of variation (CVs) were 5.9% and 8.2%, respectively.

Assays for biochemical markers of bone turnover: Serum osteocalcin was measured using an immunoradiometric assay (CIS International, Pacific Biometrics, Seattle, WA, U.S.A.) with interassay CVs of 4.3% and 5.5% at serum concentrations of 8.9 ng/ml and 19.7 ng/ml, respectively. Urinary NTXs were measured using the Osteomark assay from Ostex (Seattle, WA, U.S.A.) with an interassay CV of 4.0%. Urinary NTX data were normalized by urinary creatinine (NTX/Cr) in the 2-week study and volume of glomerular filtrate in the 9-week study. Serum BSAP was measured using an immunoradiometric assay (Tandem-R Ostase; Hybritech, Inc., San Diego, CA, U.S.A.) with an interassay CV of 7.4%. Each subject's pre- and post-treatment samples were assayed using the same kit.

Statistical methods

In the studies in healthy subjects, unpaired *t*-tests were used to assess between-group differences. In the functionally impaired elderly study, analysis of variance with factors for treatment and study center was used to assess between-group differences. Within-group differences were analyzed with paired *t*-tests. Where appropriate, a logarithmic transformation was performed before statistical analysis. Differences in baseline were accounted for by analyzing percentage change from baseline or log-transformed fold change for all variables, as appropriate. The results are presented as the mean and SEM or geometric mean and SEM for log-transformed data. Correlations were calculated using Spearman's correlation coefficient. A two-tailed probability of ≤ 0.05 was considered significant.

RESULTS

Dose-ranging study in healthy elderly subjects

Baseline mean (SE) serum IGF-I concentrations in the placebo, 10 mg, and 25 mg MK-677 groups were 145,[10] 121,[12] and 139[15] ng/ml, respectively. Following 2 weeks of treatment with 10 mg and 25 mg of MK-677 daily in healthy elderly subjects, the geometric mean percentage change (SE) from baseline serum IGF-I was ~33%[10] and 55%,[10] respectively, which were both significantly greater than the response after placebo of –14%[7] ($p < 0.05$ vs. placebo). Mean increases of 10% and 17% in urine NTXs were observed after treatment with 10 mg and 25 mg of MK-677, respectively ($p < 0.05$ for both dose levels vs. placebo) (Table 2). MK-677 was not associated with a significant change in serum BSAP after this short interval of treatment.

Four-week safety and tolerability study in healthy elderly

Mean baseline serum IGF-I concentrations in the placebo and MK-677 groups were 104 ng/ml[8] and 125 ng/ml,[8] respectively. Treatment with MK-677 (25 mg/day for 2 weeks followed by 50 mg/day for 2 weeks) increased serum IGF-I levels 85%[10] at week 2 and 94%[10] at week 4, which was significantly greater than the placebo response of 3%[4] and 1%[5] at weeks 2 and 4, respectively ($p < 0.001$ vs. placebo at both timepoints). In 26 subjects (men and women combined), MK-677 increased serum osteocalcin on average by 8%[4] at week 4 compared with a 26%[3] decrease in the 19 subjects in the placebo group ($p < 0.05$ vs. placebo) (Table 3). The decrease in the placebo group was associated with the male subjects. When women were ana-

TABLE 3. EFFECT OF FOUR WEEKS TREATMENT WITH MK-677 ON SERUM OSTEOCALCIN

			Serum osteocalcin	
	MK-677 dose*	n	Pretreatment (ng/ml)	Geometric mean ± SE % change
All subjects	placebo	19	8.2 ± 5.5	–25.5 ± 10.4
	25/50 mg	26	7.6 ± 4.5	7.6 ± 8.9†
Women	placebo	9	5.7 ± 1.9	–21.1 ± 11.7
	25/50 mg	9	4.8 ± 1.5	42.3 ± 14.5†
Men	placebo	10	10.6 ± 8.8	–28.8 ± 12.9
	25/50 mg	17	9.1 ± 6.1	–11.9 ± 9.6†‡

*Twenty-five milligrams for 2 weeks followed by 50 mg for 2 weeks versus placebo for 4 weeks.

† MK-677 versus placebo ($p < 0.05$, between-group test).

‡ Percent change versus baseline ($p < 0.05$ within-group test).

lyzed separately, there was no significant decrease from baseline in serum osteocalcin in the placebo group. In the women, MK-677 had increased serum osteocalcin by 42% at week 4 ($p < 0.05$ vs. baseline; $p < 0.05$ vs. placebo).

Nine-week study in elderly patients with functional impairment

Mean baseline serum IGF-I concentrations in the placebo and MK-677 groups were 100 ng/mml[8] and 95 ng/ml,[9] respectively. Treatment with MK-677 for 9 weeks (at 25 mg/day for the last 7 weeks) increased serum IGF-I by ~68%[7] compared with –4%[7] after placebo treatment ($p < 0.05$ vs. placebo). Data on biochemical markers of bone turnover are shown in Table 4. Treatment with MK-677 for 9 weeks increased serum osteocalcin by 29.4% ($p < 0.001$ vs. placebo) and serum BSAP by 10.4% ($p = 0.001$ vs. placebo) in these elderly patients with functional impairment. The increases in serum osteocalcin and serum BSAP were similar in men and women (data not shown). After 9 weeks of treatment, MK-677 also increased urine NTXs by 22.6% ($p < 0.05$ vs. placebo). The increase in urine N-telopeptide was similar in men and women and whether normalized by volume of glomerular filtrate or urinary creatinine (data not shown). Additionally, the change from baseline serum osteocalcin was correlated with the change from baseline serum IGF-I ($r = 0.37$; $p < 0.01$). No other correlations were statistically significant.

Safety and tolerability

Treatment with MK-677 was generally well tolerated in elderly subjects based on review of clinical and laboratory adverse experiences.[23,24] No patient receiving MK-677 had a drug-related serious adverse experience. In the three trials described in this report, only two subjects receiving MK-677 discontinued treatment due to a clinical adverse event felt to be drug-related by the investigator (one due to light headedness/tiredness and shortness of breath and one due to warm sensation). Potentially GH-mediated clinical adverse effects, such as musculoskeletal pain and fluid retention, were limited to mild to moderate intensity and did not result in study discontinuation. Musculoskeletal complaints were reported by 14% and 11% of the subjects receiving MK-677 and placebo, respectively. Fluid retention was reported by 4% and 5% of the subjects receiving MK-677 and placebo, respectively. There was one report of carpal tunnel syndrome in a subject receiving MK-677 and no complaints of breast tenderness or gynecomastia.

From the laboratory perspective, hyperglycemia was the most common adverse effect after MK-677 treatment. In the 9-week study, five patients (6%) had their dose reduced from 25 mg to 10 mg of MK-677 due to hyperglycemia (fasting glucose >140 mg/dl). Three of these subjects (3.6%) with persistently elevated glucose despite dose reduction were subsequently discontinued due to hyperglycemia. In the 2- and 4-week studies, increased values for serum glucose ranging from 126 mg/dl to 162 mg/dl were noted in 23% and 20% of the subjects, respectively, but no subject was discontinued due to hyperglycemia in these studies. The mean increase from baseline glucose in patients treated with MK-677 ranged from 5% to 10% in these studies. Elevations in hepatic serum transaminase activity were occasionally noted. In the 4-week study, 7% of subjects ($n = 2$) receiving MK-677 had reversible (1.5–2.5 greater than the upper limit of normal) increases in serum transaminase values. Transaminase elevations were not noted in the 2- or 9-week studies in any subject receiving MK-677. Finally, in the 9-week study, a mean increase from baseline serum prolactin of 27% was observed, but post-treatment values remained within the physiologic range.

DISCUSSION

In two studies in healthy elderly men and women, the oral administration of MK-677 increased serum IGF-I and a biochemical marker of bone turnover when administered over a 2- to 4-week treatment period over a dose range of 10–50 mg once a day. In a subsequent trial in functionally impaired elderly men and women, the oral administration of up to 25 mg once a day of MK-677 increased indices of both bone resorption and bone formation when administered over a 9-week treatment period. This is the first demonstration that bone metabolism can be stimulated in elderly subjects by chronic administration of an oral GH secretagogue.

In the first two studies reported herein, the response to MK-677 as regards safety and effect on bone turnover was studied in healthy elderly adults prior to proceeding to a study of the biologic effects and safety of MK-677 in elderly subjects with a predefined level of functional impairment.[25] After 2 weeks of treatment with 10 mg and 25 mg of MK-677 in healthy elderly subjects, there was a mean increase of 10% and 17%, respectively, in urine NTXs. Failure to observe an increase in serum BSAP probably reflects the very short duration of the trial and perhaps a slower response since rhGH has had a variable influence on serum BSAP in clinical studies.[7,11] After 2 weeks of treatment with 25 mg followed by 2 weeks of treatment with 50 mg of

TABLE 4. EFFECT OF NINE WEEKS TREATMENT WITH MK-677 ON BIOCHEMICAL MARKERS OF BONE TURNOVER IN FUNCTIONALLY IMPAIRED ELDERLY SUBJECTS

	*Treatment**	n	*Pretreatment (mean ± SE)*	n	*% change† (mean ± SE)*
Serum osteocalcin (ng/ml)	MK-677	62	26.7 ± 1.5	62	29.4 ± 6.5‡
	placebo	28	26.0 ± 1.9	28	0.9 ± 2.1
Serum BSAP (μg/l)	MK-677	63	12.9 ± 1.5	63	10.4 ± 2.8‡
	placebo	27	12.6 ± 1.5	27	–6.9 ± 3.1
Urine NTX (pmol of BCE)/ ml of glomerular filtrate	MK-677	61	4.04 ± 0.3	61	22.6 ± 3.3‡
	placebo	26	3.64 ± 0.4	26	–3.5 ± 7.3

* MK-677 refers to the combined groups of patients who received 5, 10, or 25 mg of MK-677 for 2 weeks followed by 25 mg of MK-677 for the final 7 weeks.

† $p < 0.05$ versus pretreatment for all analyses with MK-677 treatment.

‡ $p < 0.05$ versus placebo.

MK-677, there was an 8% mean increase in serum osteocalcin in healthy elderly subjects. In this study, a 25% decrease in serum osteocalcin was seen in the placebo group. This unexpected decrease did not appear due to technical issues (i.e., pre- and post-treatment samples were assayed in the same batch). The unexplained decrease may be due to the relatively small number of subjects studied and the known variability in bone turnover markers.[7] Of note, the increase in serum osteocalcin was more evident in the elderly women in the trial (42%), which might reflect the generally greater skeletal turnover rates in elderly women.[26] Thus, over the short term, a greater influence of MK-677 in women is not surprising, although no differential effect was observed in the first trial in terms of the urinary NTX response. Furthermore, a gender difference was not observed in the longer term study (see below) in either the markers of bone formation or bone resorption. Neither of the studies provide definitive dose-response data for biochemical markers because of the study design and/or short duration. Nonetheless, they provided the initial evidence that MK-677 treatment did influence skeletal dynamics and that the drug could safely be administered to elderly subjects.

The third study afforded the opportunity to examine the longer term influence of MK-677 on the biochemical markers of bone turnover in the frail elderly. Although the study design precluded a definitive evaluation of dose dependency, the study was of sufficient duration with large enough numbers of participants to permit definition of the response in biochemical indices of bone resorption and formation. In elderly subjects with functional impairment, treatment with MK-677 for 9 weeks increased serum osteocalcin by 29.4%, BSAP by 10.4%, and urine NTXs excretion by 25.3% (effect of MK-677 for all parameters $p < 0.05$ vs. placebo). There was no difference in the response between men and women in this 9-week trial. Increases in both urine NTXs and serum osteocalcin (mean response for both genders) were greater in the elderly subjects with functional impairment compared with the healthy elderly, probably due to the longer treatment duration in these subjects. It is possible that a still longer trial would be necessary to establish the maximum effect on the markers.

Injection of rhGH has been shown to increase markers of bone turnover in healthy and osteoporotic elderly women and GH-deficient adults.[7–12] The mean increase in serum osteocalcin of 29% after 9 weeks of treatment with MK-677 is close to the 40% increase in bone formation markers after 12 weeks of treatment with hGH (8 U subcutaneously three times/week) in women with osteoporosis reported by Clemmensen.[12] Use of GH in elderly patients may be limited, however, due to the frequent occurrence of adverse effects, such as carbohydrate intolerance or fluid retention,[8,13] or the need for dose reduction due to musculoskeletal side effects.[9] MK-677 might reduce the incidence of these adverse effects by producing a more physiologic pattern of GH release which might be better tolerated in terms of glucose tolerance and fluid retention. The studies reported here did not reveal substantial toxicity related to MK-677 as regards fluid retention and musculoskeletal side effects, although treatment was associated with increases in fasting blood glucose which required dose reduction or discontinuation in 6% and 3.6%, respectively, of patients receiving MK-677 for 9 weeks.

In contrast to the agents currently available to treat osteoporosis, which are largely antiresorptive and suppress remodeling, GH and MK-677 have a stimulatory effect on bone remodeling. Previous combination studies of GH and bisphosphonate or calcitonin treatment[27–29] suggested perhaps a more "beneficial" balance on turnover, without evidence of an improved response on BMD. However, whether calcitonin was an adequate resorption inhibitor and the somewhat paradoxical responses to the pamidronate plus GH combination indicate the need for additional studies of such combinations. Whether such treatment would result in greater increases in bone mass compared with the antiresorptive agent alone will require evaluation in long-term clinical studies.

In summary, we have observed that oral administration of MK-677 increases indices of bone turnover when administered over a 2- to 9-week treatment period in either healthy or functionally impaired elderly men and women. Future studies should attempt to determine whether the MK-677–related activation of bone turnover, alone or in combination with a bone resorption inhibitor, will result in increased bone mass and reduced risk of fractures in elderly osteoporotic patients.

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