Effect of resistance exercise and growth hormone on bone density in older men

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(Received 15 August 1996; returned for revision 29 September 1996; finally revised 4 February 1997; accepted 24 March 1997)

Summary

OBJECTIVE The purpose of this study was to evaluate whether 16 weeks of heavy resistance exercise training combined with daily growth hormone administration (GH) increases bone mineral density in 64–75-year-old men greater than resistance exercise training without GH supplementation.

DESIGN Eighteen healthy, elderly men (67 ± 1 year) followed a 16-week progressive resistance training programme (75–90% maximum strength, 5–10 repetitions/set, 4 sets/day, 4 days/week) after double-blind, random assignment to either a GH (12.5 or 18 μg/kg/day, equivalent to 25 or 36 mU/kg/day, n = 7) or placebo (n = 11) group.

MEASUREMENTS Before and at the end of 16 weeks of resistance exercise with or without GH administration, body composition, whole body and regional bone mineral density (BMD) were determined by dual-energy X-ray absorptiometry. Serum osteocalcin and IGF-I were determined by radioimmunoassay before, during and at the end of treatment.

RESULTS Increments in fat-free mass and training-specific maximum voluntary muscle strength were similar in both groups after training. Serum insulin-like growth factor-I (IGF-I) and osteocalcin levels were increased (P < 0.05) after exercise training plus GH. In comparison to initial measures, bone mineral density (g/cm²) of the proximal femur (Ward’s triangle) was increased (P < 0.05) after 16 weeks of exercise training plus placebo treatment. Sixteen weeks of exercise training plus GH treatment did not increase whole body, spine or hip (femoral neck, trochanter, Ward’s triangle) bone mineral density more than exercise plus placebo treatment.

CONCLUSIONS These findings suggest that in these older men with normal bone mineral density, short-term resistance exercise training increased regional bone mineral density, but the addition of daily GH administration did not enhance whole body or regional bone mineral density despite GH-induced increments in serum IGF-I and osteocalcin. This implies that GH administration during a 16-week resistance exercise training programme may increase bone turnover without increasing bone mineral accumulation.

Advancing age is associated with a decrease in bone mineral density which increases fracture risk in women and men. Ageing is also associated with a decrease in circulating concentrations of growth hormone (GH), insulin-like growth factor-I (IGF-I), gonadal and adrenal steroids and a reduction in physical activity. These changes in endocrine and activity patterns have been postulated to affect bone mineral density because they are known to play a role in the regulation of the rates of bone formation and resorption. However, the precise nature of this regulation and the effects of hormone replacement therapy and progressive exercise training on bone mineral density in older people are unclear.

Growth hormone and IGF-I status appear to be important determinants of bone mass. Bone mineral density has been shown to be lower in men and women with adult onset GH-deficiency than in normal age-matched individuals (Holmes et al., 1994; Beshyah et al., 1995a), and higher in conditions of GH excess (Aloia et al., 1972; Kotzmann et al., 1993). Prolonged administration of GH to adults with adult onset GH-deficiency has been reported to increase bone mineral density in some studies (Vandeweghe et al., 1993; Baum et al., 1994; Rosén et al., 1994), but not others (Stiegler & Leb 1994; Beshyah et al., 1995b; Holmes et al., 1995). In older women, GH administration was effective only in maintaining bone mineral density (Clemmesen et al., 1993; Holloway et al., 1994), whereas in older men treated with GH for 6 months, it resulted in a significant increase in the mineral density of the lumbar spine (Rudman et al., 1990). Biochemical markers of bone metabolism indicate that bone turnover rate is increased in response to GH administration (Holmes et al., 1995; Holloway et al., 1994; Johansen et al., 1990). Thus, whether or not GH
Eighteen sedentary, healthy elderly (64–75 years) men were enrolled in this study (Table 1) which was part of a larger study examining the effects of 16 weeks of resistance exercise and daily GH administration on muscle protein metabolism (Yarasheski et al., 1995), and was approved by the Washington University School of Medicine Human Studies Review Board. After the purpose and procedures were explained, written informed consent was obtained from each volunteer.

Prior to enrollment, volunteers received a physical examination, including a medical history, blood chemistry profile (SMA-12), complete blood count and urinalysis. They were classified as having normal glucose tolerance as assessed with an oral glucose tolerance test (NDDG criteria), had <1 mm ST-segment depression and a normal blood pressure response during a treadmill graded exercise test (Bruce protocol). Volunteers with cardiovascular, metabolic or neuromuscular disease were excluded.

Exercise programme

All subjects followed a 16-week supervised progressive resistance exercise training programme consisting of moderate-to-high-intensity (75–90% maximum strength) low-repetition (5–10) exercise, completing 4 sets of each exercise per session and 4 sessions/week. The weight training exercises involved all major muscle groups, alternated daily between lower (leg press, knee flexion, knee extension) and upper body exercises (biceps curl, shoulder press, deltoid lifts, bench press, latissimus pullover, arm cross), and were done on Nautilus exercise equipment.

Eleven subjects were randomly assigned to the resistance exercise training plus placebo injection group (Genentech excipient in sterile water) and 12 subjects were randomly assigned to a group that exercise-trained in the same manner but received a daily injection of recombinant human GH (rhGH; Genentech, Inc., USA). The subcutaneous injections were given in the afternoon (1500–1800 h, after exercise sessions) 7 days/week, and administration was rotated daily among 4 injection sites (2 arms and 2 thighs). Five subjects assigned to the GH group did not complete the study because of fluid retention and symptoms of arthralgia and carpal tunnel compression that have been described previously (Yarasheski & Zachwieja, 1993; Yarasheski et al., 1995). These subjects were not included in the data analysis. Therefore, the GH dose was reduced and of the 7 subjects who completed the study, 3 subjects received 18 g rhGH/kg/day and 4 subjects received 12.5 g/kg/day for the entire 16-week treatment period: 1 μg GH is approximately 2 mU.

Bone mineral density and body composition

Bone mineral density of the lumbar spine, proximal femur (neck and Ward’s triangle), and total body was measured by dual-energy X-ray absorptiometry (QDR-1000/W, Hologic, Waltham, MA, USA) before and at the end of the exercise programme. In 60–70-year-old women, the coefficient of
variation (CV) for bone mineral density measures was ≤1.8% at all sites except Ward’s triangle, which had a CV of 3.0%. Body fat and fat-free mass were also determined by DXA (enhanced whole body software, v5.64), and for comparison purposes, by hydrostatic weighing as described previously (Kohrt et al., 1992).

**Serum biochemistry**

Serum IGF-I and osteocalcin concentrations were determined by radioimmunoassay (Gundberg et al., 1985; Davenport et al., 1988) before and at 8 and 16 weeks of treatment. Blood samples were obtained in the morning after an overnight fast, ~16 hours after the previous GH/placebo injection.

**Dietary intake**

Before and at 4-week intervals during the treatment period, a research dietitian interviewed the participants to assess their habitual intake of calcium and phosphorous. The dietary intake survey for each participant was analysed for mineral composition using the Nutritionist III software package (N2 Computing; Salem, OR, USA).

**Statistical analyses**

Differences between the groups in baseline measures and in treatment-induced changes in the bone mineral density measures were assessed with independent t-tests. Paired t-tests were used to compare initial and final measures within a group. Changes in serum IGF-I and osteocalcin were assessed with a 2×3 ANOVA (2 groups, 3 time points). Statistical significance was accepted as \( P \leq 0.05 \). All data are expressed as mean ± SE.

**Results**

As reported previously (Yarasheski et al., 1995), these older men had reduced maximum voluntary upper and lower body muscle strength in comparison to young men \( (P<0.01) \). Strength training increased \( (P=0.01) \) maximum voluntary muscle strength on 7 exercises similarly in both groups \( (60 \pm 8\% \text{ placebo vs } 57 \pm 7\% \text{ GH recipients}) \).

On average, both groups had lower than normal \( (124–450 \mu g/l) \) baseline serum IGF-I concentrations (Table 1, Fig. 1). Four months of strength training exercise did not increase circulating IGF-I concentrations significantly in the placebo group. In the exercise group treated with GH, serum IGF-I concentrations were increased \( (P<0.05 \text{ vs initial, and } P<0.05 \text{ vs placebo}) \). The highest serum IGF-I concentration was 424 \( \mu g/l \), and occurred in one subject receiving 18 \( \mu g \) GH/kg/day.

Initially, serum osteocalcin concentrations were similar in vs placebo group) into the normal range at 8 weeks \( (238 \pm 35 \mu g/l) \) and 16 weeks \( (252 \pm 33 \mu g/l) \). The highest serum IGF-I concentration was 424 \( \mu g/l \), and occurred in one subject receiving 18 \( \mu g \) GH/kg/day.
both groups (Table 1, Fig. 2). In the placebo-treated group, osteocalcin concentration was not changed after 8 or 16 weeks of exercise training. In the GH-treated group, osteocalcin concentration was increased after 8 and 16 weeks, and both these increments were greater than in the placebo group ($P < 0.008$).

Strength training without GH supplementation reduced body fat by $1.7 \pm 0.7$ kg ($P < 0.04$) and increased fat-free mass by $2.1 \pm 0.6$ kg ($P < 0.007$) when measured by hydrostatic weighing (Fig. 3). In the GH-treated group, body fat was decreased by $2.0 \pm 0.6$ kg ($P < 0.02$) and fat-free mass was increased by $3.3 \pm 0.8$ kg ($P < 0.01$). As reported previously (Yarasheski et al., 1995), GH administration was associated with an increase in total body water that accounts for a large portion (75%) of the increase in fat-free mass observed in the GH-treated group. When corrected for fluid accumulation, the changes in body composition were not different between the 2 groups. In addition, the changes in body composition measured by hydrostatic weighing were not different from the changes measured by DXA.

Bone mineral density of the whole body, lumbar spine (L2–L4), femoral neck and Ward’s triangle was normal in all men and similar in both groups before treatment (Table 1, Fig. 4). In the exercise plus placebo group, bone mineral density at the weakest region of the femoral neck (Ward’s triangle) was increased ($P < 0.05$) in comparison to initial measures, while bone mineral density at all other measured sites was unchanged in response to 16 weeks of resistance exercise training. There were no differences ($P > 0.05$) in the magnitude of change in bone mineral density between the exercise plus GH group and the exercise plus placebo group. More specifically, the increase in bone mineral density at Ward’s triangle in the placebo treated group was not significantly greater than the small changes in bone mineral density at Ward’s triangle in the exercise plus GH group. In fact, in the exercise plus GH group, bone mineral density in the whole body and at the femoral neck sites tended to decrease ($P < 0.05$) in comparison to initial measures.

Both groups consumed calcium and phosphorus in amounts above the recommended daily amount (800 mg) when evaluated before and during the treatment period (Table 1). Dietary intake of these minerals was not different between the 2 groups.

Discussion

We found that healthy 64–75-year-old men, who had normal regional and whole body bone mineral density, low serum IGF-I concentrations and muscle weakness prior to resistance exercise training, experienced significant increases in fat-free mass and muscle strength in response to 16 weeks of strength training exercise. In the placebo-treated group short-term resistance exercise training was accompanied by an increase in bone mineral density at Ward’s triangle in the femoral neck. Conversely, short-term resistance exercise training supplemented with daily injections of recombinant human growth hormone (12.5 or 18 μg rhGH/kg/day), did not increase bone mineral density in the whole body, spine or hip regions when compared with the changes observed in the exercise plus placebo group.

The ability of short-term resistance exercise training to increase bone mineral density in older men, primarily in the femoral neck region, has been reported by Menkes and colleagues (1993). They reported a 3.8% increase ($P<0.05$) in femoral neck bone mineral density after 16 weeks of pneumatic variable resistance exercise training (3 days/week) in previously sedentary 59 ± 2-year-old men. They concluded, and our findings support the contention, that 16 weeks of high intensity resistance exercise training provides a mechanical loading to bone that can increase regional bone mineral density.

In an avian model, the osteotrophic response to mechanical loading was positively related to the magnitude of strain applied to the bone, and very few loading cycles per day were necessary to bring about an optimal response (Rubin & Lanyon 1984, 1985). This suggests that resistance exercise training at relatively high intensities would be the type of physical activity most likely to stimulate bone mineral accretion. Prospective studies of the effects of strength training on bone mass have yielded equivocal results, showing that bone mineral density was increased significantly (Snow-Harter et al., 1992; Menkes et al., 1993; Ryan et al., 1994), maintained relative to the decreases in non-exercising controls (Gleeson et al., 1990; Nelson et al., 1994) or decreased (Rockwell et al., 1990). Possible reasons for these discrepant findings include the subjects’ initial bone mineral density and the duration and intensity of the exercise programme.

Because the life-cycle of a bone remodelling unit is several months (Parfitt, 1987), it is possible that a longer exercise training programme with or without GH administration may have resulted in greater increments in bone mineral density in these healthy older men. In this regard, studies in rats have shown that there is an early, transient increase in bone resorption in response to exercise that is not immediately coupled with an increase in the rate of bone formation (Yeh & Aloia, 1990; Yeh et al., 1993). This may have limited the magnitude of the effect of resistance exercise on bone mineral in this 16-week study. Also, prolonged GH administration (12 months) has been reported to increase bone mineral density in GH-deficient adults (O’Halloran et al., 1993; Vandeweghe et al., 1993; Degerblad et al., 1995).

In spite of the increase in bone mineral density at Ward’s triangle observed in the exercise plus placebo group serum osteocalcin concentration was not significantly increased in this group, suggesting that whole body bone turnover rate was not markedly affected by the exercise programme. However, hip bone turnover may have been enhanced by exercise, but since serum osteocalcin concentration reflects whole body bone turnover activity, it may not be sensitive enough to detect the effect of exercise on bone turnover in a small localized region of bone.

In comparison with the exercise plus placebo group, we observed no greater increments in whole body, lumbar spine and femoral neck bone mineral density in the exercise plus GH group. Instead, in comparison to initial values, whole body and femoral neck bone mineral density were reduced in the exercise plus GH group. Also, 16 weeks of resistance exercise plus GH increased serum osteocalcin concentrations, an indication that bone turnover rate was increased. These observations imply that bone remodelling processes were activated by short-term resistance exercise plus GH, and suggest that the rate of bone resorption exceeded the rate of formation, and a small reduction in net bone mineral density in the whole body and femoral neck measures occurred during this short period of treatment. A decrease in bone mineral density during short-term (6 months) GH administration to GH-deficient adults has been reported previously (Binnerts et al., 1992; Thorén et al., 1993), and it has been suggested that longer periods of GH treatment might be required to overcome the initial imbalance in bone formation and resorption rates, so that net bone mineral accumulation may occur (O’Halloran et al., 1993; Vandeweghe et al., 1993; Degerblad et al., 1995; Holmes et al., 1995).

Our findings suggest that circulating GH and IGF-I play a minor role in modulating the effect of short-term resistance exercise on bone mineral density. This is consistent with the reports of Yeh et al. (1993, 1994c) that GH potentiated the exercise-induced increase in bone formation in mature rats, but bone mass was not enhanced by GH administration. Similarly, our findings are analogous to reports of increased regional bone mineral density in elderly men after 16 weeks of resistance exercise that did not result in an increase in serum GH or IGF-I levels in the training group (Ryan et al., 1994). These observations imply that the improvements in bone mineral density that accompany short-term resistance exercise training do not require an increase in serum GH or IGF-I. However, bone tissue measures of IGF-I were not made in these studies. The possibility remains that bone IGF-I levels may be increased
by resistance exercise, as it appears to be with treadmill exercise in the femur and tibia of rats (Yeh et al., 1994a), and this might explain the increase in bone mineral density that accompanies resistance training.

The failure of the short-term resistance exercise training programme plus GH injections to stimulate bone mineral accretion further could not be attributed to insufficient dietary calcium or phosphorous or insufficient serum IGF-I concentrations, because serum IGF-I levels were increased into the normal range by daily GH administration. It is possible that a higher GH dose would be more effective at improving bone density (Rudman et al., 1990) but, on the basis of the prevalence of side-effects observed at these doses, a higher dose would not be recommended. Instead, a paradigm of GH replacement more analogous to physiological release patterns (short, pulsatile, episodic) might minimize side-effects, and when combined with a longer resistance exercise training programme (>16 weeks), may optimize beneficial effects and should, therefore, be examined.

In conclusion, these observations suggest that 16 weeks of resistance exercise training combined with daily GH administration (12.5 or 18 μg rhGH/kg/day) increased bone turnover rate, but did not increase bone mineral density in excess of that observed during 16 weeks of resistance exercise training without GH supplementation.

Acknowledgements

Supported by AG05562, RR00036, AM20579 and Genentech, Inc. K. Yarasheski was supported by AG00444 and W. Kohrt was supported by NIH Research Career Development Award AG00663. Mary Wallace-Lammert, Kevin Kincaid and Karen Korchina provided technical assistance.

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