Resistance Exercise Training Restores Bone Mineral Density in Heart Transplant Recipients

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Objectives. This was a prospective, randomized, controlled study designed to determine the effect of resistance exercise training on bone metabolism in heart transplant recipients.

Background. Osteoporosis frequently complicates heart transplantation. No preventative strategy is generally accepted for glucocorticoid-induced bone loss.

Methods. Sixteen male heart transplant recipients were randomly assigned to a resistance exercise group that trained for 6 months (mean ± SD age 56 ± 6 years) or a control group (mean age 52 ± 10 years) that did not perform resistance exercise. Bone mineral density (BMD) of the total body, femur neck and lumbar spine (L2 to L3) was measured by dual-energy X-ray absorptiometry before and 2 months after transplantation and after 3 and 6 months of resistance exercise or a control period. The exercise regimen consisted of lumbar extension exercises (MedX) performed 1 day/week and variable resistance exercises (Nautilus) performed 2 days/week. Each exercise consisted of one set of 10 to 15 repetitions performed to volitional fatigue.

Results. Pretransplantation baseline values for regional BMD did not differ in the control and training groups. Bone mineral density of the total body, femur neck and lumbar vertebra (L2 to L3) were significantly decreased below baseline at 2 months after transplantation in both the control (−3.3 ± 1.3%, −4.5 ± 2.8%, −12.7 ± 6.2%, respectively) and training groups (−2.9 ± 1.1%, 5.9 ± 3.2%, −14.8 ± 3.1%, respectively). Six months of resistance exercise restored BMD of the whole body, femur neck and lumbar vertebra to within 1%, 1.9% and 3.6% of pretransplantation levels, respectively. Bone mineral density of the control group remained unchanged from the 2-month posttransplantation levels.

Conclusions. Within 2 months after heart transplantation, ~3% of whole-body BMD is lost, mostly due to decreases in trabecular bone (~12% to ~15% of lumbar vertebra). Six months of resistance exercise, consisting of low back exercise that isolates the lumbar spine and a regimen of variable resistance exercises, restores BMD toward pretransplantation levels. Our results suggest that resistance exercise is osteogenic and should be initiated early after heart transplantation.

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also reported that 4 months of resistance exercise in middle-aged and older men was associated with increased BMD and bone remodeling. However, these relations have not been studied in organ transplant recipients receiving long-term glucocorticoids. In the present study, we prospectively determined BMD in heart transplant candidates before transplantation and longitudinally tracked their changes in BMD at intervals after transplantation.

Methods

Subjects. The descriptive characteristics of the heart transplant recipients are presented in Table 1. Sixteen male patients listed with the United Network for Organ Sharing as orthotopic heart transplant candidates were recruited. The patients were randomly and prospectively assigned either to a training group that would participate in a program of resistance exercise after transplantation or to a control group that would not perform specific resistance exercises. All the heart transplant recipients participated in postoperative walking programs that were comparable in intensity and duration, but only the training group performed specific resistance exercises.

All the heart transplant recipients had biatrial anastomosis at the time of transplantation and were receiving standard triple-drug immunosuppressive therapy with cyclosporine, prednisone and azathioprine. Whole-blood cyclosporine trough levels, calculated as an average of four determinations over 8 months after transplantation, were similar in the training (mean ± SD) 249 ± 18 ng/ml) and control (256 ± 26 ng/ml) groups. Three transplant recipients in the training group and three in the control group were receiving supple-

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<th>Abbreviations and Acronyms</th>
<th>BMD = bone mineral density</th>
<th>DXA = dual-energy X-ray absorptiometer</th>
<th>ISHLT = International Society for Heart and Lung Transplantation</th>
<th>PTH = parathyroid hormone</th>
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Table 1. Descriptive Characteristics of Heart Transplant Recipients in Control and Training Groups*

<table>
<thead>
<tr>
<th>Control Group</th>
<th>Training Group</th>
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<tr>
<td>(n = 8)</td>
<td>(n = 8)</td>
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<tr>
<td>(mean ± SD)</td>
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<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)†</th>
<th>Waiting list (wk)</th>
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<tr>
<td>52 ± 10</td>
<td>173 ± 9</td>
<td>85 ± 11</td>
<td>26 ± 17</td>
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<td>56 ± 6</td>
<td>172 ± 5</td>
<td>78 ± 8</td>
<td>21 ± 13</td>
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*There were no significant differences between groups at baseline. †Body weight at pretransplantation bone scan.
or a control peri xd. Thus, the final DXA scan was performed 8 months after cardiac transplantation.

Resistance exercise training. The training group began supervised resistance exercise at 2 months after transplantation and continued to exercise for a 6-month period. The training regimen consisted of two components: 1) lumbar extensor training 1 day/week on a MedX lumbar extension machine; and 2) upper and lower body resistance training 2 days/week using Nautilus and MedX variable resistance machines. All training sessions involved one transplant recipient supervised by at least two exercise specialists. Before resistance exercise sessions, seated blood pressure and pulse rate measurements were recorded and were followed by 5 min of low intensity walking on a treadmill. A single set consisting of 10 to 15 repetitions was completed for each exercise. The initial training resistance represented 50% of one repetition maximum. The subjects were not permitted to exceed 15 repetitions. Rather, when 15 repetitions were successfully achieved, the resistance was increased by 5% to 10% at the next training session. Thus, the exercise prescription strived to have subjects use the greatest resistance possible to complete 15 repetitions. The following exercises were performed in order: lumbar extension, duo-decline chest press, knee extension, pullover, knee flexion, triceps extension, biceps flexion, shoulder press and abdominals. Special precautions were taken to ensure adequate maintenance of blood pressure in preload-dependent cardiac denervated heart transplant recipients. Upper body exercises were alternated with lower body exercises in an attempt to prevent blood pooling. Symptomatic subjects walked 2 min between exercises or performed standing calf raises. All subjects concluded each training session with a 5 min cool-down walk at low intensity on the treadmill.

The frequency of lumbar training for this study was based on previous research (12) that demonstrated that MedX lumbar training once a week is as effective as training two or three times a week for increasing lumbar extension strength. Lumbar extension training required subjects to sit in the lumbar extension machine with their knees positioned so that the femurs were parallel to the seat. The subjects were secured in place by femur, pelvic and thigh restraints that stabilized the pelvis. A head rest was adjusted to the level of the occipital bone for comfort and support. This stabilization procedure has been previously described (12).

Statistical analysis. Descriptive characteristics were compared between groups using analysis of variance. Analysis of covariance with repeated measures was used to analyze the temporal pattern of BMD, body mineral content and total bone calcium before and after transplantation. When a significant group by time interaction was observed, within-group comparisons between time points and between-group comparisons at each time point were done using analysis of covariance with contrast analysis for obtaining appropriate post hoc custom hypothesis tests. All statistical analyses were performed using the SAS statistical program (SAS Institute Inc.). An alpha level of p ≤ 0.05 was required for statistical significance.

Results

Allograft rejection. Table 2 details the incidence of acute rejection episodes during the study and the glucocorticoid treatment regimens. Acute allograft rejection was determined by endomyocardial biopsy and graded using the International Society for Heart and Lung Transplantation (ISHLT) system. We enhanced immunosuppression only for ISHLT grade 3A or 3B rejection (Table 2). No patient failed to respond to corticosteroid therapy, and none had evidence of “humoral rejection,” or hemodynamic compromise. There were 11 episodes of acute rejection in the control group and 9 in the training group (p ≥ 0.05).

Bone mineral density. Absolute values for regional BMD in the control and training groups are presented in Table 3. Results of the BMD scans are expressed as grams hydroxyapatite divided by the projected area in square centimeters (g/cm²). Pretransplantation values for total body BMD, femur neck BMD, lumbar vertebral body BMD (L2 to L3) and lumbar vertebra middle BMD (L2 to L3) were not significantly different (p ≥ 0.05) between the control and training groups.

The temporal pattern of relative changes in total body BMD and femur neck BMD (percent change from pretransplant baseline) is shown in Figure 1. Total body BMD decreased significantly below pretransplantation values at 2 months after transplantation in both the control (−3.3 ± 1.3%) and training groups (−2.9 ± 1.1%). Six months of resistance exercise training restored total body BMD to within 1% of pretransplantation levels in the training group; the control group continued to lose total body BMD at 3 (−5.8 ± 2.5%) and 6 months (−6.9 ± 3.7%). Femur neck BMD was significantly diminished below baseline at 2 months after transplantation in both the control (−4.5 ± 2.8%) and training groups (−5.9 ± 3.2%). However, femur neck BMD was restored to within 1.9% of pretransplantation levels after 6 months of resistance exercise in the training group. In contrast, BMD diminished further at 3 (−6.3 ± 2.5% below baseline) and 6 months (−7.2 ± 3.7%) in the control group.

The evolution of relative changes in BMD for the lumbar vertebral body and lumbar vertebral middle are shown in Figure 2. At 2 months after transplantation, lumbar BMD (L2 and L3) was markedly decreased in the vertebral body and the
vertebral middle in both the control (−12.2 ± 5.5% and
−12.7 ± 6.2%) and training groups (−14.9 ± 4.4% and
−14.8 ± 3.1%). The control group had further significant (p ≤ 0.05) reductions in lumbar vertebral BMD at 3 months and demonstrated little remineralization at the conclusion of the study. Indeed, lumbar BMD levels at 3 and 6 months of the control period were not significantly different in the control group and appeared to plateau at levels that were 16% below pretransplantation baseline levels. In contrast, specific lumbar extension exercise 1 day/week for 6 months was singularly effective in promoting remineralization of the lumbar vertebrae in the training group. The BMD of the lumbar vertebral body and the lumbar vertebral middle were restored to within 2.0% and 3.6%, respectively, of pretransplantation levels.

**Bone mineral content and total bone calcium.** Absolute values for body mineral content (g) and total bone calcium (g) in the control and training groups are presented in Table 3. Pretransplantation values for body mineral content and total bone calcium were not significantly different (p = 0.05) between the control and training groups.

The relative changes in body mineral content and total bone calcium after transplantation (percent change from pretransplant baseline) are presented in Figure 3. Similar decreases in body mineral content were recorded at 2 months after transplantation in the control (−5.1 ± 1.2% from baseline) and training groups (−5.4 ± 2.4% from baseline). Body mineral content levels remained suppressed in the control group (−6.9 ± 3.3%) but returned to within 2.4% of baseline levels in the training group after 6 months of resistance exercise. Total bone calcium also decreased dramatically in the early postoperative period in both the control (−5.9 ± 1.1% from baseline) and training groups (−5.8 ± 1.9% from baseline), but improvement in total bone calcium was observed only in the group that trained. Body mineral content and total bone calcium in the control group were not significantly different between 3 and 6 months of the control period.

**Discussion**

**Principal findings.** To our knowledge, this prospective, controlled study is the first to provide quantitative data on the efficacy of resistance exercise training as a therapy for defective bone metabolism in heart transplant recipients. The evolution of axial and appendicular bone mass was determined from DXA scans performed before transplantation, 2 months after transplantation and after 3 and 6 months of a resistance exercise program or a control period. Our results demonstrate that regional bone demineralization occurs within 2 months of heart transplantation and is characterized by a rapid early phase and a plateau phase after ~5 months. Our results also indicate that BMD losses from compartments with trabecular bone, such as the clinically important lumbar spine, are proportionately greater than BMD losses from regions with cortical bone. The BMD of the lumbar vertebral body was diminished by 12.2% and 14.9% in the control and training groups, respectively, at only 2 months after transplantation.

The main finding of this study is that a 6-month program of monitored resistance exercise, consisting of a specific low back exercise that isolates the lumbar spine and a regimen of variable resistance exercises for the total body, restores regional BMD toward pretransplantation levels in heart transplant recipients despite continued immunosuppression with glucocorticoids. In contrast, regional BMD in the control group did not indicate any statistically significant recovery toward preoperative levels by 8 months after transplantation.

**Bone mineral density in heart transplant candidates.** Other studies have reported diminished BMD in heart transplant recipients, but it was unclear whether postoperative osteoporosis was a consequence of heart transplantation and immunosuppressive agents or simply a continuation of preexisting osteopenia engendered by chronic heart failure (4,5). Our results suggest that regional BMD is reasonably well preserved in heart transplant candidates before heart transpl-
Whole-body BMD levels recorded before transplantation compared favorably with age-matched norms in both the control (97.3% of norm) and training groups (98.5% of norm), indicating that a relatively small amount of bone mineral loss had occurred before heart transplantation. Femur neck BMD assessed before transplantation also compared favorably with age-matched norms in both the control (96% of norm) and training groups (97% of norm). Unfortunately, age-matched norms for BMD in the lateral view of the lumbar spine were not available from the manufacturer of our DXA machine, and comparisons were not possible.

In contrast, significant bone mineral loss reportedly occurs in kidney transplant candidates before kidney transplantation (13). However, these data should not be generalized to other solid-organ transplant groups because preoperative bone loss in kidney transplant candidates is most likely related to the increases in parathyroid hormone and reductions in serum 1,25-dihydroxyvitamin D known to occur with renal failure. Although cyclosporine does cause a variable decline in renal function in most heart transplant recipients after transplantation, the relatively modest renal compromise seen in these patients does not usually lead to dramatic loss of trabecular bone.

**Glucocorticoid effects.** The administration of glucocorticoids (methylprednisolone, prednisone) is almost certainly the major factor in the rapid loss of BMD. Both indirect and direct indexes of skeletal metabolism implicate long-term glucocorticoid therapy in bone demineralization. Osteocalcin, an index of bone formation/bone turnover, has been shown (14–17) to be decreased by as much as 50% in patients receiving long-term glucocorticoid therapy. Direct histologic evidence of diminished bone formation is also demonstrated in glucocorticoid-treated patients (18).

Glucocorticoids alter vitamin D metabolism and decrease net intestinal calcium absorption while increasing urinary excretion of calcium, resulting in a negative calcium balance (19). This negative balance leads to secondary hyperparathyroidism, as evidenced by elevated parathyroid hormone (PTH) levels in heart transplant recipients receiving glucocorticoids (4). However, it seems unlikely that glucocorticoid-induced osteoporosis in heart transplant recipients is due solely to secondary hyperparathyroidism. Excess PTH usually elicits increased compensatory new bone formation coupled with the increased bone resorption. In contrast, histomorphometric and calcium kinetic studies indicate that new bone forma-
tation is decreased, whereas bone resorption is enhanced in glucocorticoid-induced osteoporosis (20). Thus, glucocorticoid-induced osteoporosis is characterized by both accelerated bone loss and inhibition of new bone formation. Additionally, excess PTH usually does not cause disproportionate losses of trabecular bone (20). However, as our data clearly demonstrate, trabecular bone loss is indeed a prominent characteristic of bone demineralization after heart transplantation, suggesting that abnormal skeletal metabolism in heart transplant recipients is mediated by glucocorticoid therapy.

Strategies to prevent osteoporosis. Dietary calcium supplements fail to prevent further loss of BMD (2,3). Intramuscular synthetic salmon calcitonin (50 to 100 IU/24 h) and testosterone (100 mg every 10 days) or estrogens (2 mg of beta-estradiol/24 h or estroderm 0.10 mg twice/week) have also been recommended for heart transplant recipients, but they failed to prevent bone mineral loss after transplantation, with further bone mineral losses ranging from 4% to 10% (2,3). BMD levels remain significantly below age-matched norms and do not indicate any recovery toward preoperative levels in patients up to 36 months after transplantation (2,3). Our results suggest that resistance exercise therapy, as part of a strategy to prevent trabecular bone loss rather than to treat established osteoporosis, should be initiated promptly after heart transplantation. This intervention was safe and not associated with any increase in rejection.

Summary. Within 2 months of successful heart transplantation, ~3% of whole-body BMD is lost, mostly due to losses in the trabecular bone compartment (12% to 15% of lumbar vertebral BMD). A 6-month program of monitored resistance exercise, consisting of a specific low back exercise that isolates the lumbar spine and a regimen of variable resistance exercises that work all major muscle groups safely, restored regional BMD toward pretransplantation levels in heart transplant recipients receiving long-term glucocorticoid therapy. However, regional BMD in the control group did not indicate any recovery toward preoperative levels. Our results suggest that resistance exercise therapy, as part of a strategy to prevent trabecular bone loss, is osteogenic and should be initiated early after heart transplantation.

References
