Exercise and Estrogen or Estrogen Alternatives (Phytoestrogens, Bisphosphonates) for Preservation of Bone Mineral in Postmenopausal Women

Philip D. Chilibeck

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Abstract/Résumé
Research in animal models indicates that without estrogen, the effectiveness of exercise for increasing bone mineral in females is reduced. With decreased estrogen levels, there is an increase in the threshold at which strains are detected by bone, in turn reducing the transmission of mechanical to biochemical signals for bone formation. Studies combining estrogen replacement and exercise training in postmenopausal women have yielded mixed results but indicate that the combination of interventions may be more effective than either intervention alone for increasing bone mass. Given the continued debate over the risks and benefits of estrogen replacement, other compounds such as bisphosphonates or phytoestrogens may be preferred in combination with exercise training for optimally increasing bone mass and preventing osteoporotic fracture. Studies on animals show that the combination of bisphosphonate or phytoestrogen supplementation with exercise training is effective, but trials in humans are lacking.

La recherche au moyen de modèles animaux indique que, sans œstrogènes, l’impact de l’exercice physique sur l’augmentation de la densité minérale des os est réduit. Avec la diminution des niveaux d’œstrogènes, le seuil de détection de tension s’élève, ce qui réduit
la transmission du stimulus mécanique en un stimulus biomécanique de formation des os. Les résultats des études combinant l’œstrogénothérapie et l’entraînement physique chez des femmes postménopausées sont divergents, mais leur analyse révèle que la combinaison des deux approches serait plus efficace pour augmenter la masse osseuse que l’une ou l’autre, considérée individuellement. Compte tenu des divergences d’opinions concernant les risques et les bienfaits associés à l’œstrogénothérapie, d’autres composés comme les bisphosphonates ou les phytoestrogènes pourraient constituer une solution de rechange combinée à l’entraînement physique pour augmenter de façon optimale la masse osseuse et prévenir les fractures dues à l’ostéoporose. Les études chez les animaux indiquent que la combinaison des bisphosphonates ou des phytoestrogènes avec l’entraînement physique donne de bons résultats, mais les études chez les êtres humains font défaut.

Introduction

Exercise is often recommended for preserving bone mineral and preventing osteoporotic fracture (Chilibeck et al., 1995). It has become evident, however, that the increase in bone mineral density (BMD) with training is quite small (Kelley et al., 2001; Wolff et al., 1999) and that exercise may have to be combined with other interventions to achieve levels of bone mineral density that could be clinically significant for the prevention of fractures. This article reviews the physiological rationale for combining estrogen replacement and exercise training for preserving bone mineral in postmenopausal women. Because of the Women’s Health Initiative trial, which found adverse affects of estrogen replacement in postmenopausal women (Writing Group for the Women’s Health Initiative Investigators, 2002), this article will also explore the combinations of other interventions, such as bisphosphonates and phytoestrogens, with exercise for the prevention of bone loss.

Incidence of Osteoporosis

One out of every four women over the age of 50 is believed to have osteoporosis (Melton et al., 1992). One out of every three women over the age of 65 will suffer a vertebral fracture sometime in her remaining life, and one out of three women of very old age will suffer a hip fracture due to osteoporosis (Riggs and Melton, 1986). The burden of health care costs in Canada in 1993 attributed to osteoporosis and its related fractures was estimated at $465 million (Goeree et al., 1996); by 1996 the cost associated with hip fracture alone was estimated at $650 million (Wiktorowicz et al., 2001). This cost is increasing rapidly along with the increase in the number of postmenopausal women in Canada. The number of osteoporotic fractures in Canada is expected to proliferate, quadrupling over the next 40 years (Papadimitropoulos et al., 1997; Wiktorowicz et al., 2001).

With age comes a gradual loss of bone. However, given the decline in estrogen associated with menopause, the remodeling cycle is accelerated, resulting in a high rate of bone loss (Riggs and Melton, 1992). Because estrogen suppresses bone turnover, decreased estrogen levels result in an increase in bone turnover with a greater increase in bone resorption than bone formation (Eastell et al., 1993). Women begin losing bone around the age of 35, at a rate of 0.5% to 1% per year,
and at an accelerated rate of 3% to 5% per year in the decade after menopause (Osteoporosis Society of Canada, 1996).

The incidence of osteoporotic fractures in Canada is growing faster than can be explained by age alone (Martin et al., 1991). An increasingly sedentary lifestyle may be one factor contributing to this increased incidence of osteoporosis (Martin et al., 1991). Indeed, a less physically active lifestyle has been associated with a decrease in bone mass (Chilibeck et al., 2000; Talmage et al., 1986) and an increase in the incidence of osteoporotic fracture (Cooper et al., 1988). Exercise is therefore recommended for the prevention of osteoporosis.

Combining Exercise Training and Estrogen Replacement

PHYSIOLOGICAL RATIONALE

When bone is stressed (as from exercise), it undergoes a certain amount of strain, which is hypothesized to result in a biochemical signal to initiate the formation of new bone and the removal of damaged bone (Frost, 1992). Once new bone is formed, strain is reduced and no longer induces bone formation. In this manner bone adapts to the loads placed on it by becoming stronger and strain-resistant. Decreased estrogen levels accompanied by menopause may increase the set point for bone to detect loads, causing bone to be less sensitive to mechanical force and eliciting a decrease in bone mass for a constant load (Lanyon, 1996; Schiessl et al., 1998). Low estrogen levels therefore makes loading less effective for increasing bone mass.

The optimal intervention for preserving bone mass in postmenopausal women may therefore be a combination of increased loading and estrogen replacement (in this article, “hormone replacement” will refer to the combination of estrogen and progestin, whereas “estrogen replacement” will refer to unopposed estrogen). A number of animal models have supported this hypothesis. When bone from female rats is exposed to estrogen or placed under strain by external loads, there is an increase in osteoblast activity and recruitment which increases the amount of bone that osteoblasts produce (Cheng et al., 1996; 1997). When loading and estrogen treatment are combined, the effects are greater than the addition of both loading and estrogen alone. The effects of loading are blocked by inhibiting the biochemical mediators thought to be responsible for the transduction of strain into a stimulus for bone formation (Cheng et al., 1997).

The same inhibitor does not affect the actions of estrogen. This suggests that loading (exercise) and estrogen act via different mechanisms to induce bone formation. This supports the contention that an optimal therapy should involve a combination of these treatments. These findings have been replicated in a menopausal animal model (ovariectomized rats) in which the effects of exercise training and estrogen replacement on bone were shown to be independent and additive (Yeh et al., 1993; 1994). On the other hand, others have recently suggested a synergistic effect between the two interventions (Li, Jee, et al., 2003).

The possible mechanisms by which estrogen and exercise result in an increase in bone mineral are summarized in Figures 1 and 2, respectively. Estrogen passes through osteoblast (or osteoblast precursor) cell and nuclear membranes to
Figure 1. Mechanisms by which estrogen affects bone cells. Solid arrows indicate stimulation or activation; dashed arrows indicate inhibition. See text for details.

Figure 2. Mechanisms by which exercise affects bone cells. Adapted from Ajubi et al. (1999) and Chen et al. (2000). See text for details.
bind to a DNA-bound receptor (Oursler et al., 1993). Once bound, it increases the transcription of genes coding for proteins that regulate factors involved in proliferation and differentiation of osteoblasts (i.e., nitric oxide, growth factors, cytokines, bone morphometric protein), or factors (i.e., inhibitory cytokines, osteoprotegerin) that, when released by osteoblasts, cause inhibition of osteoclasts and inhibition of bone resorption (Bord et al., 2001; Liao et al., 2002; Lindberg et al., 2002; O’Shaughnessy et al., 2000; Zhou et al., 2003). Alternatively, binding of estrogen to its nuclear receptor may decrease the transcription of factors produced by osteoblasts (i.e., stimulatory cytokines) that, when released, stimulate osteoclastic activity (Liao et al., 2001).

It is controversial as to whether there is a direct stimulation of osteoblast proliferation and differentiation by estrogen, and it has been argued that this depends on the in-vitro cell model system studied (see Oursler et al., 1993, for review). Bone resorption and formation are coupled processes; therefore, it is most likely that estrogen decreases resorption by affecting the release of factors by the bone-forming cells (osteoblasts). As outlined above, this may involve an increase in factors that inhibit osteoclast activity, or a decrease in factors that stimulate osteoclast activity (Oursler et al., 1993). Finally, estrogen may directly affect osteoclasts by inhibiting the differentiation of osteoclast precursors into mature osteoclasts (Srivastava et al., 2001) or decreasing the synthesis of osteoclastic lysosomal enzymes which play a role in bone resorption (Oursler et al., 1992).

The exact mechanisms by which exercise affects bone are also controversial (Figure 2). In response to exercise-induced strain, pulsatile fluid flow is increased through an interstitial network connecting osteocytes, osteoblasts, and bone lining cells (Ajubi et al., 1999; Chen et al., 2000; Forwood, 2001). Osteocytes, osteoblasts, and bone lining cells are connected to the collagen matrix of bone by integrins, a form of glycoprotein (Forwood, 2001). These integrins span the membrane of the cell and connect to the cell’s actin cytoskeleton, which is connected to the cell’s nucleus.

The integrin-cytoskeleton complex may regulate the production of anabolic paracrine factors (i.e., prostaglandins, nitric oxide, or insulin-like growth factor) that, when released, stimulate osteoprogenitor cells to divide and produce osteoblasts, which in turn produce new bone matrix (Duncan and Turner, 1995; Forwood, 2001). Fluid flowing past the osteocyte, osteoblast, or bone lining cells applies force to the integrins, causing a rearrangement of the actin cytoskeleton within the cells, which mediates the opening of ion channels and allows calcium entry into the cell or calcium release from intracellular stores. Calcium modulates key enzymes involved in prostaglandin production which, when released, stimulates osteoblast differentiation and proliferation (Ajubi et al., 1999).

Alternatively, it has been suggested that intracellular calcium is first released in response to perturbations of the cell membrane by shear stress, causing the rearrangement of the actin cytoskeleton into “stress fibres” which anchor to the integrins (Chen et al., 2000; Pavalko et al., 1998). The re-organized actin interacts with myosin to increase the internal tension in the cell, transmitting signals from the outside of the cell (via the force of fluid flow against the integrins) to the nucleus to regulate gene expression. This leads to an increase in key transcription factors and expression of key enzymes involved in prostaglandin production.
Although from Figures 1 and 2 it appears that estrogen and exercise may act on bone cells via different mechanisms, recent in-vitro studies suggest a link between the two, as strain-related osteoblast proliferation is blocked by estrogen receptor modulators (Damien et al., 1998; 2000). This suggests that the strain response is mediated through the estrogen receptor.

EFFECTS ON POSTMENOPAUSAL WOMEN

The evidence from animals—that a low estrogen level in females may decrease the sensitivity of bone for detecting mechanical loads—is supported by a review of exercise studies in postmenopausal women. Without estrogen replacement, the effect of exercise training is small, resulting in an increase (over control groups) of BMD of approximately 1% per year for the lumbar spine and proximal femur (Wolff et al., 1999). While this is statistically significant, an increase of about 5% is needed to show a clinically significant reduction in fracture (Guyatt et al., 2002). Estrogen replacement may therefore be necessary for bone to adequately respond to mechanical loads produced during exercise.

Studies combining estrogen or hormone replacement with exercise training in postmenopausal women are summarized in Table 1. Several studies have shown that a combination of exercise and estrogen or hormone replacement results in gains in BMD above that of either intervention alone (Kohrt et al., 1995; 1998; Notelovitz et al., 1991). Limitations of these studies include non-random designs (Kohrt et al., 1995; 1998), a lack of statistical power because of small group size (Notelovitz et al., 1991), and studying women who were already on hormone replacement before the trial (Notelovitz et al.). The effect of estrogen replacement alone for this study may therefore have occurred mostly before the trial. Studies of exercise training that use non-random designs generally result in larger increases in BMD compared to studies using randomized designs (Wolff et al., 1999), indicating that non-randomized studies may be susceptible to bias.

Three other studies (summarized in Table 1) combining hormone replacement and exercise training did not show an additive effect of the two interventions on BMD (Cheng et al., 2002; Heikkinen et al., 1997; Prince et al., 1991). In the study by Prince et al. (1991), the effects of exercise training may have been minimal because the site where the bone measurements were taken, the forearm, was only stressed once a week during the exercise program. Heikkinen et al. (1997) and Cheng et al. (2002) conducted the only fully randomized studies with exercise, estrogen replacement, and placebo groups. Heikkinen et al. did not provide a detailed description of the exercise training, thus it is difficult to determine whether it was adequate. A limitation of the study by Cheng et al. is that the exercise + hormone replacement group participated in more exercise sessions than the exercise-only group. Large randomized studies with sufficient exercise protocols are needed to confirm whether exercise training and estrogen or hormone replacement have an additive effect for improving BMD. Recent studies highlighting the risks of hormone replacement, summarized below, may make such trials difficult.

Risk of Hormone Replacement. The Women’s Health Initiative, which randomly assigned 16,608 women to receive hormone replacement or placebo, then followed them for 5.2 years, showed that hormone replacement (0.625 mg/d con-
### Table 1  Studies Combining Exercise Training and Hormone Replacement in Postmenopausal Women

<table>
<thead>
<tr>
<th>Study &amp; Design</th>
<th>Yrs post-menopause</th>
<th>Previous HRT</th>
<th>Main Results</th>
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<tbody>
<tr>
<td><strong>Notelovitz et al. (1991)</strong></td>
<td>4.2 (estrogen + exerc group)</td>
<td>19/20 Ss on HRT &gt;6 mo prior to study</td>
<td>Spine BMD: Exerc + estrogen (↑8.3%) = Estrogen only (↑1.5%); Total body BMD: Exerc + estrogen (↑2.1%) = Estrogen only (↑0.6%); Radial BMD: Exerc + estrogen (↑4.1%) &gt; Estrogen only (↓0.3%)</td>
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<td>20 surgically menopause women (45y) given 0.625 mg conjugated estrogen/d, randomized to: Resistance, 5 exerc, 15–20 min, 3 d/wk; or No training; for 12 months</td>
<td>6.5 (estrogen-only group)</td>
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<td><strong>Prince et al. (1991)</strong></td>
<td>5.6 yrs for 3 randomized groups; 4.5 for Controls (signif. diff. from other groups)</td>
<td>Not reported</td>
<td>Forearm BMD: Exerc + HRT (↑2.7%) &gt; Exerc + calcium (↓0.5%); Exerc (↓2.6%); Controls (↓2.7%)</td>
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<tr>
<td>N = 120 (56y) w/low forearm BMD, randomized (double blind, placebo control) to: Exerc (1 hr low-impact aerobics 1 d/wk + 30 min walking 2d/wk); Exerc + calcium (1g/d); or Exerc + HRT (0.625 mg/d) estropipate for 1 mo, then 1.25 mg/d for 23 mo + 2.5 mg medroxyprogesterone acetate). Vs. 42 Controls (55y) w/normal BMD over 2 yrs</td>
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<td><strong>Heikkinen et al. (1997)</strong></td>
<td>0.5 to 3 yrs</td>
<td>None</td>
<td>Femoral neck BMD: increase in pooled exerc groups &gt; non-exerc groups (% change not reported); pooled HRT groups (↑1%) &gt; non-HRT groups (↓3%); Spine BMD: pooled HRT groups (↑5%) &gt; non-HRT groups (↓1.5%); Trochanter BMD: pooled HRT groups (↑4%) &lt; non-HRT groups (↓1)</td>
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<td>N = 78 (49–55y) randomized to 3 groups: (a) Sequential monthly treatmt 2mg estradiol valerate (EV) (11d), followed by 2mg EV + 10mg medroxyprogesterone (MPA) (10d), followed by placebo (7d); (b) 3 monthly sequential 2mg EV (70d), followed by 2mg EV + 20mg MPA (14d), followed by placebo</td>
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(continued)
Table 1  (Cont.)

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<tr>
<td>(7d); (c) Placebo. Each group further randomized to exerc (guided 1 hr/wk loading of spine and hip + 2hr/wk home-based exerc). Intervention for 2 yrs</td>
<td>16.5 yrs</td>
<td>Not on HRT</td>
<td>Total body BMD: Exerc + HRT (↑2.7%) &gt; HRT (↑1.2%), Exerc (↑1.5%) &gt; Control (↓0.5%); Lumbar spine BMD: Exerc + HRT (↑6.1%) &gt; Exerc (↑1.7%), Control (0%); Trochanter BMD: Exerc + HRT (↑3.1%) &gt; Exerc (↑0.8%), Control (↑0.2%)</td>
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<td>Kohrt et al. (1998)</td>
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<td>for 2 yrs</td>
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<td>N = 54 (66y) non-randomly assigned to: Control; Exerc (walk, jog, 45 min/d; 3d/wk); HRT (0.625/d) conjugated estrogens + 5 mg/d medroxyprogesterone acetate 13d every 3 mo); or Exerc + HRT for 12 months</td>
<td></td>
<td>prior to the study</td>
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<td>Cheng et al. (2002)</td>
<td>0.5–5 yrs</td>
<td>On HRT &lt; 6 mo at least 2 yrs prior to the study</td>
<td>Proximal femur vBMD: Exerc + HRT (↑4.5%), HRT (↑4.8%) &gt; Control (↓1.3%); Tibial shaft vBMD: Exerc + HRT (↑2.2%) &gt; Control (↓0.9%); Proximal femur PMI: Exerc + HRT (↓0.2%) &gt; Control (↓7%); Femoral shaft PMI: Exerc + HRT (↑1.5%), HRT (↑2%) &gt; Control (↓1%), Exerc (↓1%); Proximal tibia PMI: Exercise + HRT (↑1%), HRT (↑1%), Exerc (0%) &gt; Control (↓3.5%)</td>
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<tr>
<td>N = 80 (50–57y) randomized (double blind, placebo control) to: HRT (2 mg/d estradiol + 1 mg/d noretisterone acetate); Exerc (jumping 6d/wk); Exerc + HRT; or Control, for 12 months</td>
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Note: HRT = hormone replacement therapy; BMD = areal bone mineral density (g/cm²); vBMD = volumetric bone mineral density (g/cm³); PMI = polar moment of inertia (avg distribution of bone mineral around its bending axis, a reflection of whole bone strength).
jugated equine estrogens + 2.5 mg/d medroxyprogesterone acetate) increased the risk of breast cancer, endometrial cancer, coronary heart disease, stroke, and pulmonary embolism. The absolute risk increase was small (e.g., 7 more coronary heart disease cases, 8 more strokes, 8 more pulmonary embolisms, and 8 more invasive breast cancers per 10,000 person-years) but exceeded the benefit of 6 fewer colorectal cancers and 5 fewer hip fractures (Writing Group, 2002). It has been known for years that hormone replacement slightly increases the risk of breast cancer (Risch and Howe, 1994; Steinberg et al., 1991), but the Women’s Health Initiative is the first large-scale trial that showed the risks outweigh the benefits. Subsequent data from the Women’s Health Initiative indicate that combined estrogen and progestin also results in a slight worsening of cognitive function and increased risk for dementia (Rapp et al., 2003; Shumaker et al., 2003). For these reasons, many women are hesitant to start hormone replacement.

In comparison to estrogen + progestin, unopposed estrogen is associated with a smaller risk of breast cancer (Li, Malone, et al., 2003) but an increased risk of endometrial cancer (Gambacciani et al., 2003; Weiderpass et al., 1999). Unopposed estrogen is therefore only recommended for women who have had a hysterectomy. The risk of breast cancer also decreases for women taking cyclic compared to continuous progestins in combination with estrogen (Porch et al., 2002). There is some evidence that a low-estrogen regimen may be of some benefit for preventing bone loss (i.e., 0.025 mg/d estradiol delivered transdermally, or 0.3 mg/d conjugated equine estrogens + 2.5 mg/d medroxyprogesterone), and this may be an option for women who want to reduce their risks (Gambacciani et al., 2001; Rubinacci et al., 2003).

The remainder of this article reviews recent studies that have combined exercise training with interventions that have biological effects similar to estrogen on BMD, specifically bisphosphonates and phytoestrogens. These may be preferred for women who want to minimize risks.

**Exercise Combined With Bisphosphonates.** Bisphosphonates are compounds characterized by two carbon-phosphate bonds and were originally used as anti-scaling agents (Fleisch, 1997). They bind strongly to calcium phosphate, prevent bone resorption, and have been used often as a therapy for preventing bone mineral loss. Tamaki et al. (1998) evaluated the effect of combining exercise training with bisphosphonate (etidronate) in ovariectomized rats. Rats were assigned to exercise training (treadmill running), etidronate supplementation, combined exercise and etidronate, or controls. Exercise training and etidronate were found to have an interaction for increasing BMD of the proximal femur. At the cellular level, etidronate decreased the osteoclast number (decreased bone resorption) while exercise training increased the osteoblast number (increased bone formation). This suggests that exercise training and bisphosphonate therapy may be additive for increasing BMD.

Two studies combining exercise and bisphosphonates in postmenopausal women are summarized in Table 2. In contrast to the findings on animals, BMD was increased only by bisphosphonate administration; it was unaffected by either strength training (Chilibeck et al., 2002) or jump training (Uusi-Rasi et al., 2003). Exercise training had a positive effect on geometric properties of bone in the one study in which this was assessed (Uusi-Rasi et al., 2003). This would increase
bone strength despite the lack of change in BMD. Recent studies have emphasized that exercise may have a greater impact on architectural and geometric properties of bone, rather than on BMD (Adami et al., 1999; Heinonen, 2001; Jarvinen et al., 1998), and thus the small changes in BMD observed in exercise studies (Wolff et al., 1999) may underestimate the positive effects of exercise on bone (Jarviven et al., 1999).

Exercise Combined With Phytoestrogens. Phytoestrogens are found in various plant products including soybeans, as isoflavones, and flaxseed, as lignans (Umland et al., 2000). Most research on phytoestrogens has involved the specific class of phytoestrogens found in soybeans, the isoflavones. Isoflavones are structurally similar to estradiol and have been shown to compete with estradiol for estrogen receptor sites (Shutt and Cox, 1972; Verdeal et al., 1980). They act as estrogen antagonists in some cases and estrogen agonists in others (Umland et al., 2000). With bone cells they seem to act as agonists.

A number of studies in animals (Arjmandi et al., 1998; Picherit et al., 2001; Toda et al., 1999) and a few small preliminary studies in perimenopausal and post-
menopausal women (Alekel et al., 2000; Clifton-Bligh et al., 2001; Dalais et al., 1998; Morabito et al., 2002; Potter et al., 1998) have demonstrated a positive effect of isoflavones on bone. At the cellular level, isoflavones have a positive effect on osteoblasts obtained from healthy human donors (Viereck et al., 2002). In contrast to estrogen, isoflavones do not increase breast cancer rates. Case-control and epidemiological studies indicate that isoflavone intake is associated with a decreased risk of breast cancer (Ingram et al., 1997; Murkies et al., 2000; Torres-Sanchez et al., 2000). Isoflavones therefore may serve as natural selective estrogen receptor modulators by acting as agonists for estrogen receptors on bone and anta-gonists for estrogen receptors on breast tissue (Li et al., 1999; Zava and Duwe, 1997).

Two studies to date have evaluated interventions combining exercise training with phytoestrogen supplementation, one with ovariectomized rats (Nakajima et al., 2001) and one with ovariectomized mice (Wu et al., 2001). The ovariectomized rats were either given isoflavones, subjected to resistance exercise (graded treadmill running with weights strapped to their backs), a combination of exercise and isoflavone, or assigned to controls. The groups receiving isoflavone or exercise training had higher BMD of the femur compared to the control group, and the group receiving the combination of interventions had the greatest benefit. Most important, the combination group was the only group to have significantly higher bone strength than the control group (Nakajima et al., 2001).

The study of ovariectomized mice used a similar design, with mice assigned to receive isoflavone, exercise training (treadmill running on an incline), a combination of isoflavone and exercise training, or controls (Wu et al., 2001). These were compared to a group of ovariectomized mice given estrogen replacement. Again, the group receiving the combination of interventions had the greatest femoral BMD; this was slightly higher than for the group receiving estrogen replacement. Geometric properties such as bone cross-sectional area and periosteum perimeter were highest in the exercise and combination therapy groups and unaffected by estrogen replacement.

These changes in geometric properties, along with the increases in BMD, would increase bone strength most favourably in the group receiving the combination of interventions. Histological analyses showed that trabecular bone volume and trabecular thickness were highest, and trabecular separation lowest, in the groups receiving the combination of interventions or estrogen replacement. Again, this architectural change would result in favourable bone strength. Regarding side-effects, uterine weight was significantly higher in the estrogen replacement group and unaffected by isoflavone or exercise training. Needed are studies in humans to confirm whether phytoestrogens in combination with exercise can increase BMD to clinically significant levels, while also monitoring potential health side-effects.

SUMMARY AND FUTURE STUDIES

Studies of animal models have demonstrated that the effectiveness of exercise for increasing bone mass in females is reduced if estrogen levels are reduced (Lanyon, 1996; Schiessl et al., 1998). This is supported by the relatively small effect of exercise training in postmenopausal women not given hormone replacement (Wolff et al., 1999). Studies combining exercise training and hormone replacement in postmenopausal women are promising but show mixed results (Cheng et al., 2002;
Heikkinen et al., 1997; Kohrt et al., 1998; Notelovitz et al., 1991; Prince et al., 1991) and may be limited by small sample size (Kohrt et al., 1998; Notelovitz et al., 1991), non-random designs (Kohrt et al., 1998), and perhaps inappropriate exercise programs (Prince et al., 1991).

Because the risk-to-benefit ratio of hormone replacement continues to be debated (Writing Group, 2002), other interventions such as bisphosphonates and phytoestrogens may be preferred for combining with exercise training. Research on ovariectomized rats has shown that combining bisphosphonates or phytoestrogens with exercise training can be beneficial for increasing BMD to a greater extent than either intervention alone (Nakajima et al., 2001; Tamaki et al., 1998; Wu et al., 2001). However, studies combining bisphosphonates and exercise training in humans have yielded mixed results (Chilibeck et al., 2002; Uusi-Rasi et al., 2003).

The greatest benefits of exercise on bone may not be through increasing BMD, but through changing the architectural and geometric characteristics of bone (Adami et al., 1999; Heinonen, 2001; Jarvinen et al., 1998; Wu et al., 2001). A combination of interventions may therefore be optimal for increasing bone strength through an increase in BMD by estrogen, bisphosphonates, or phytoestrogens and a favourable change in geometric and architecture properties through exercise training (Nakajima et al., 2001; Uusi-Rasi et al., 2003; Wu et al., 2001). Additional pharmacological interventions that have not been explored in combination with exercise include the third-generation bisphosphonates (i.e., Risedronate) and selective estrogen receptor modulators (i.e., Raloxifene) (Guyatt et al., 2002).

References


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