Combining physical exercise with drug therapies for osteoporosis has been attempted with the aim to maximize osteogenic stimulus. Potential synergetic effects may prevent post-menopausal bone loss, or maximise gains during peak bone mass acquisition. However, research studies yielded mixed results, impeding the emergence of a consensus on the effects of exercise and drug therapies for osteoporosis on bone tissue. Independent, additive or synergetic effects of exercise and drug therapies have been reported, but while animal studies offer promising results, human studies are less clear.

The aim of this work was to critically review existing data on the subject in an attempt to clarify existing knowledge and to encourage further investigations with a 2 x 2 factorial design, as elucidation of these questions will benefit osteoporosis prevention.

Introduction

Osteoporosis may be defined conceptually as a condition of general skeletal fragility evidenced by low BMD and microarchitectural alterations such that fractures occur with minimal trauma, often no more than is applied by routine daily activity. Osteoporosis is unarguably a major public health problem, and osteoporotic fractures are expected to grow with increasing life expectancy of the population (1). Interventions based on preventive or curative treatments have proven efficient in preventing bone loss, increasing bone mass, and eventually reducing fracture risk (2). It should not be overlooked however, that osteoporosis aetiology is multifactorial and bone fragility is not only dependent on bone mass. At any age, intervention strategies other than medication should not be underestimated (3). Accordingly, nutritional, hormonal, and exercise interventions have been applied, with varying outcomes (4). Regular physical exercise seems to be effective in maintaining and even increasing bone mass and strength in pre and post-menopausal women (5, 6). Although peak bone mass is mainly dependent on genetic factors, environmental influences such as calcium intake (7) and physical activity make a significant contribution (8, 9). Many studies have proven the ability of physical exercise to increase peak bone mass, especially if activity is initiated before puberty (10). Thus, achievement of peak bone mass and postmenopausal bone loss, are two critical phases during which exercise interventions are of particular clinical interest.

Hence, it appears relevant to question whether therapies aimed at increasing bone mass increase their potency when associated with physical exercise, as outcomes may greatly influence osteoporosis prevention strategies.

In order to look upon the synergetic effect of two therapeutic modalities, one needs to implement a clinical trial with a 2 x 2 factorial design (11). This kind of intervention not only allows testing the efficiency of each therapeutic modality separately, but also enables to appraise their interaction. Designing studies, which adequately measure the interaction between therapy and physical activity, is extremely difficult and requires a great number of patients, hence data are scarce. Other investigators pointed out that these aspects contribute to the poor methodology affecting clinical trials with exercise interventions (12).

Bisphosphonates and physical exercise

Numerous studies confirmed the ability of bisphosphate treatment to inhibit
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Bone loss during menopause (13). A logical strategy for tackling osteoporosis is to associate the osteogenic effects of exercise with the anti-resorptive action of bisphosphonates. Additionally, part of post-menopausal bone loss has been associated with decreased muscle strength resulting from a reduction in physical activity (14).

The effects of physical exercise (PE), running on a treadmill initiated after a two-week Etidronate (Eti) treatment have been studied in ovariotomized rats (15). In this study, rats were split into five groups: 1) sham; 2) ovariotomy (ox); 3) ox + Et; 4) ox + Eti; 5) ox + Et + Eti. Using histomorphometry, the results show an interaction between Etidronate treatment and subsequent physical exercise, as evidenced by increased trabecular bone area of the proximal tibia. Additionally, a gain in BMD was seen at the proximal femur, but mid- and distal regions however, remained unchanged. At a cellular level, etidronate reportedly reduced the osteoclast number while exercise in-creased the osteoblast number, without altering the osteoclast number, without altering the osteoclast number (15).

Chilibeck et al. set up a randomized trial to study the combined effects of etidronate and exercise in post-menopausal women (16). Forty-eight women, with a mean age of fifty-seven years, were divided into four groups: 1) Eti + PE; 2) Eti only; 3) PE only and 4) placebo without PE. Etidronate was taken over 12 months, at a dose of 400mg/day during fourteen days, every nineteen days. Resistance training was carried out three times a week, for forty-five minutes. When pooling the data of all the Eti groups, bone density gains at the lumbar spine and whole body significantly outreached those of the placebo group. However, no interaction between PE and Eti emerged. Alendronate, another potent amino-bisphosphonate, has been tested in association with physical exercise in women (17) and rats (18). Uusi et al. (17), in a clinical trial using a 2 x 2 factorial design, studied the association of physical exercise with a daily intake of 5mg of alendronate in 164 postmenopausal women (age: 54 ± 2 years). Daily exercise protocol comprised 20 minutes of jumping activities, 15 minutes of stretching and other non-impact exercises. It appeared that the alendronate treatment increased BMD at the lumbar spine and femoral neck, but that exercise alone had no effect. Besides, no interaction between alendronate and PE could be evidenced. Nevertheless, some structural indices, such as the section modulus and the ratio cortical surface over total bone surface at the tibia, were significantly increased in the exercise groups, while remaining unchanged in the sedentary groups. In contrast, it seems that in ovariet-o-mized rats, alendronate associated with PE (treadmill running) induces a synergistic effect, as evidenced by increases in bone masses and failure loads at the femur and L4 vertebral body (18).

Human studies combining bisphosphonates and physical exercise meeting the 2x2 factorial design criteria are summarized in Table I.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Mean age</th>
<th>Intervention</th>
<th>Duration of exercise program</th>
<th>Measurement site</th>
<th>Main BMD outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chilibeck et al. (16)</td>
<td>57</td>
<td>Strength training</td>
<td>3 days/week over 12 months</td>
<td>Total body</td>
<td>Lumbar spine</td>
</tr>
<tr>
<td>Uusi-Rasti et al. (26)</td>
<td>54</td>
<td>Alternate aerobic/jump or step program</td>
<td>3 days/week over 12 months</td>
<td>Lumbar spine</td>
<td>Proximal femur</td>
</tr>
</tbody>
</table>

Calcium and physical exercise
One of the most important questions unanswered in the field of lifestyle-related bone health research is whether there is an interaction between calcium intake and physical activity. As aforementioned, this requires a clinical trial with a 2 (calcium/no calcium) x 2 (exercise/no exercise) factorial design. It was already suggested more than ten years ago, that calcium supplementation has the potential to modify the bone response to increased training loads (20). However, published data on this issue are still scarce. Specker (21) looked upon intervention studies reporting the effects of daily calcium intake and physical activity on bone mass. This review identified 16 intervention studies, with peri- or post-menopausal cohorts ranging from 5 to 130 subjects. This meta-analysis yields indirect evidence that physical activity has a positive effect on bone mass, but only for calcium intake above 1000 mg/day. Similarly, high calcium intake triggered BMD changes only if associated with physical exercise.

Another meta-analysis (22) came to the same conclusion: it appears that a certain threshold is required for calcium to have an effect. Indeed, BMD changes in response to aerobic exercise were greater in the groups consuming more than 1000 mg calcium per day than in those taking less than 1000 mg/day. Also, animal studies suggest that low calcium intake or reduced calcium

Table I. Summary of the studies with a 2x2 factorial design combining bisphosphonates and physical exercise in post-menopausal women.

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bioavailability limit the bone response to exercise (23).

A recent intervention study on 239 children, aged between three and five years old, (178 of whom completed the study) associated calcium supplementation with an exercise program (24). The children were randomized into two groups, one being assigned to gross motor activities and the other to fine motor activities. In both groups, children were then supplemented at random with either 1000 mg/day calcium or placebo. Bone measurements were made at the distal tibia. A significant interaction between exercise and calcium supplementation emerged, evidenced by an increase in cortical thickness and cross-sectional area. Gross motor activities induced greater tibial periosteal and endosteal circumferences than did fine motor activities. Calcium intake did not affect periosteal or endosteal circumferences. Conversely, in the calcium-supplemented group, the greatest increase in cortical thickness and cortical area at the tibia occurred in the subjects assigned to fine motor activities. Eventually, physical activities had no positive effects on bone mass unless calcium intake exceeded 1100 mg/day.

A research team led by Iulano-Burns followed during 8.5 months 66 girls (mean age 8.8 years) divided into four different groups (25). The girls were randomly assigned to either moderate impact exercise with or without calcium supplementation, or low impact exercise with or without calcium supplementation. Exercise sessions lasted 20 minutes and were performed three times a week. Food was enriched with 434 ± 19 mg of calcium/day. Analysis of covariance was used to test main effects and interaction of calcium and exercise on bone mass. In order to account for changes inherent to growth, bone parameters were adjusted for initial bone length and BMC. As a result, an interaction between calcium and exercise was seen at the femur, but not at the tibia, despite a 3% increase in BMC at the tibia and fibula. At non-weight bearing sites, such as the humerus, radius and ulna, an additional 2 to 4 % increase in BMC was seen in the calcium-supplemented groups, compared to the non-supplemented groups. The authors concluded that the greatest bone gains at weight bearing sites were achieved when short exercise bouts of moderate intensity were associated with increased calcium intake. Exercise has been shown to induce specific local adaptations whereas calcium is thought to have more systemic effect (25).

Bearing in mind that physical exercise increases bone mass at weight-bearing bone sites, the assumption that calcium may have effects even on non-weight-bearing bone sites has been comforted in a recent study involving 218 premenopausal women (26). Using QCT, the investigators found that high calcium intake was associated with greater cortical cross-sectional area and bone strength index at the radius. In contrast, physical exercise exerted positive effects on the bone mass of weight-bearing sites such as the tibia.

Our team investigated the combined effects of physical exercise and calcium intake on bone accrual during puberty (27). A cohort of young girls were divided into four groups: 1) exercise (7.2h/week) + 800 mg calcium phosphate/day; 2) exercise (7.2h/week) + placebo; 3) moderate activity (1.2h/week) + 800 mg calcium phosphate/day; 4) moderate activity (1.2h/week) + placebo. BMD gains after one year were significantly greater in the 'exercise+calcium' group, while no difference emerged between the three other groups. Thus, it seems that exercise requires high calcium intake to induce significant BMD gains. Studies in children combining calcium and physical exercise with a 2 x 2 factorial design are presented in Table II.

To conclude, the mechanisms that underpin bone gains remain a matter of debate, as it is still not fully understood why the combined effects of calcium and exercise are more efficient than either one alone.

Physical exercise and estrogens

Oestrogen therapy at menopause provided efficient in lowering post-menopausal bone loss and has long been considered the backbone of osteoporosis prevention (28). The menopause-related decrease in oestrogen levels is thought to enhance sensitivity of the bone to mechanical strain, thus rendering physical exercise less efficient in increasing bone mass (29). Recent data indicate that the early response of bone

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Table II. Summary of the studies with a 2 x 2 factorial design combining calcium and physical exercise in children.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Mean age</th>
<th>Intervention</th>
<th>Duration of exercise program</th>
<th>Measurement site</th>
<th>Main BMD outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specker et al. (24)</td>
<td>4</td>
<td>Fine Motor Group (FMG): activities designed to keep children seated</td>
<td>30 min/day over 12 months</td>
<td>Total body</td>
<td>The difference in BMC gain at the leg between FMG and GMG was more marked in the children taking calcium than in the placebo-fed group.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gross Motor Group (GMG): jumping, hopping, skipping</td>
<td></td>
<td>Arm and Leg</td>
<td></td>
</tr>
<tr>
<td>Iulano-Burns et al. (25)</td>
<td>9</td>
<td>Low impact group; low impact dance routines and stretching</td>
<td>20 min. 3 times/week over 8.5 months</td>
<td>Total body</td>
<td>Bone gains at the femur were greater in the calcium+ exercise group than in the calcium-only group.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate impact group: hopping, jumping and skipping</td>
<td></td>
<td>Lumbar spine</td>
<td>Physical exercise but not calcium increased bone mass at loaded sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Arm and Leg</td>
<td>Calcium but not physical exercise increased bone mass at non-loaded sites</td>
</tr>
</tbody>
</table>
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...cells to mechanical strain and estrogens might share a common path involving the oestrogen-receptor ER-β (30-33). Besides, Lee and co-workers reported that the adaptive response of bone to mechanical strain required a functional oestrogen receptor -α (34). Additionally, evidence showed that the oestrogen-receptor ER-α modulates the bone density response to physical exercise in young pubertal and pre-pubertal girls (35). The literature reflects the absence of a consensus. Some studies indicate that the effects of oestrogen and mechanical strain on bone mass density are independent, while others claim effects are additional or synergistic depending on the bone site considered (36-39). Furthermore, some investigators reported that adding physical exercise to hormonal replacement therapy (HRT) was no more effective on BMD than HRT alone (40-43). However, the main limitations of these studies were lack of randomization (37), insufficient statistical power due to small group size (38), inclusion of women already taking HRT before entering the study (38, 43), insufficient loading of bone (40), poor description of exercise prescription (45), and discrepancies in training volume in-between study groups (42).

To our knowledge, only one study bears the title “synergistic effect of physical exercise and oestrogen”. This work analyzed histomorphometric parameters at the femur and lumbar vertebral bone mass density and trabecular bone mass density in ovariectomized rats (39). However, it seems that the results do not quite echo the title, as none of the nine parameters tested at the lumbar spine evolved, and only three out of the 13 femoral parameters revealed the announced interaction between treatment and exercise.

**Conclusion**

Studies combining physical exercise with drug therapies for osteoporosis in an attempt to either prevent postmenopausal bone loss, or maximize gains during peak bone mass acquisition, yielded mixed results. If animal studies showed that bisphosphonate combined to exercise are more effective in increasing BMD than each factor taken separately, results in humans are less promising. Further investigations with a 2 x 2 factorial design are required to shed more light on the interaction between exercise and therapy. Eventually, beyond the effects of exercise on bone mass, bone quality, as well as structural changes in bone micro and macro architecture, need to be described. Indeed, elucidation of such mechanism may lead to a novel therapeutic approach to osteoporosis.

**References**

27. COURTEIX D, JAFFRE C, LESPELLERENCES E, BENHAMOU CL. Cumulative effects of calcium supplemenation and physical activity on bone accretion in premenarchal children: a
Exercise and Drug Interventions: A review / E. Lespessailles & S. Prouteau

32. DAMIEN E, PRICE JS, LANYON LE: Mechanical strain stimulates osteoblast proliferation through the estrogen receptor in male as well as females. J Bone Miner Res 2000; 15: 2169-77.