Review

Is there a synergy between physical exercise and drug therapies for osteoporosis?

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ABSTRACT

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 micro architectural 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 bisphosphonate treatment to inhibit

bone loss during menopause (13). A logical strategy for tackling osteoporosis is to associate the osteogenic effects of exercise to 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 ovariectomized rats (15). In this study, rats were split into five groups: 1) sham; 2) ovariectomy (ovx); 3) ovx + EP; 4) ovx+Eti; 5) ovx + EP + 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 increased the osteoblast number, without altering the osteoclasts 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 ovariectomized 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.

SERM and physical exercise

To our knowledge, the combined effects of SERM and physical activity have barely been studied. One study examined the combined effects of a 40-week raloxifene treatment associated with impact loading activities (19) in three women. Unfortunately, this interesting project would have required a greater number of subjects and a control group to yield conclusive results.

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 exercise 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.

Authors	Mean age	Intervention	Duration of exercise program	Measurement site	Main BMD outcomes
Chilibeck *et al*. (16)	57	Strength training	3 days/week over 12 months	Total body Lumbar spine Proximal femur	No interaction between physical exercise and Etidronate Pooled Etidronate groups: ↑ 2.5 % *vs*. ↓ 0.3% for the placebo group at the lumbar spine
Uusi-Rasi *et al*. (26)	54	Alternate aerobic jump or step program	3 days/week over 12 months	Lumbar spine Proximal femur Distal radius	Neither additive nor interactive effects of Alendronate and physical exercise Exercise only had no effects on bone mass at any site Alendronate had positive effects on the lumbar spine and proximal femur

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 carried out 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 perimenopausal 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 proved 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

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

Authors	Mean age	Intervention	Duration of exercise program	Measurement site	Main BMD outcomes
Specker *et al.* (24)	4	Fine Motor Group (FMG): activities designed to keep children seated Gross Motor Group (GMG): jumping, hopping, skipping	30 min/day over 12 months	Total body Arm Leg	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.
Iulano-Burns *et al.* (25)	9	Low impact group: low impact dance routines and stretching Moderate impact group: hopping, jumping and skipping	20 min, 3 times/week over 8.5 months	Total body Lumbar spine Arm Leg	Bone gains at the femur were greater in the calcium+ exercise group than in the calcium-only group Physical exercise but not calcium increased bone mass at loaded sites Calcium but not physical exercise increased bone mass at non-loaded sites

cells to mechanical strain and estrogens might share a common path involving the oestrogen-receptor ER-α (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 vertebrae in response to exercise 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 maximise 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

1. KANNUS P, VIERNI S, PARKKARI J, PALVANEN M, VUORI I, JARVINEN M: Hip fractures in Finland between 1977 and 1997 and predictions for the future. *Lancet* 1999; 353: 802-5.
2. DELMAS PD: Treatment of postmenopausal osteoporosis. *Lancet* 2002; 359: 2018-26.
3. DEPREZ X, FARDELLONE P: Non-pharmacological prevention of osteoporotic fractures. *Joint Bone Spine* 2003; 70: 818-28.
4. PFEIFER M, SINAKI M, GEUSENS P, BOONEN S, PREISINGER E, MINNE HW: For the ASBMR working group on musculosketal rehabilitation in osteoporosis: a review. *J Bone Miner Res* 2004; 19: 1208-14.
5. WALLACE BA, CUMMINGS RG: Systematic review of randomized trials of the effect of exercice on bone mass in pre and postmenopausal women. *Calcif Tissue Int* 2000; 67: 10-8.
6. BONAIUTI D, SHEA BIOVINE R, NEGRINI S *et al*.: Exercise for preventing and treating osteoporosis in post-menopausal women. Cochrane Data. *Base Syst Rev* 2002; 3: CD000333 Review.
7. BONJOUR JP, CARRIE AL, FERRARI S *et al*.: Calcium-enriched foods and bone mass growth in prepubertal girls : a randomized, double-blind, placebo-controlled trial. *J Clin Invest* 1997; 99: 1287-94.
8. COURTEIX D, LESPESSAILLES E, PERES SL, OBERT P, GERMAIN P, BENHAMOU CL : Effect of physical training on bone mineral density in prepubertal girls: a comparative study between impact loading and non-impact loading sports. *Osteoporos Int* 1998; 8: 152-8.
9. BAILEY DA, MC KAY HA, MINWALD RL, CROCKER PR, FAULKNER RA: A six-year longitudinal study of the relationship of physical activity to bone mineral accrual in growing children: the University of Saskatchewan bone mineral accrual study. *J Bone Miner Res* 1999; 14: 1672-9.
10. BARR SI, MCKAY HA: Nutrition, exercice and bone status in youth. *Int J Sport Nutr* 1998; 8: 124-42.
11. FISHER LD, DIXON DO, HERSON J, FRANKOWSKI RK, HEARRON MS, PEACE KE: Intention-to-treat in clinical trials. *In*: PEACE KE, Eds. *Statistical Issues in Drug Research and Development*. New York, Marcel Dekker 1990: 31-350.
12. BLOCK JE: Interpreting studies of exercice and osteoporosis: a call for rigor. *Controlled clinical trials* 1997; 18: 54-7.
13. *Bisphosphonates in bone diseases*. 4th edition Academic press, Herbert Fleish, 2000.
14. LIPS P, HESP R, REEVE J, WOOTTON R, GREEN JR , KLENERMAN L: High indices of remodelling in iliac trabecular bone predict reduced forearm cortical bone mass indices in patients with proximal femoral fractures. *Bone Miner* 1990; 11: 93 -100.
15. TAMAKI H, AKAMINE T, GOSHI N, KURATA H, SAKOU T: Effects of exercice training and etidronate treatment on bone mineral density and trabecular bone in ovariectomized rats. *Bone* 1998; 23: 147-53.
16. CHILIBECK PD, DAVISON KS, WHITING SJ, SUZUKI Y, JANZEN CL, PELOSO P: Effect of strength training combined with bisphosphonate (etidronate) therapy on bone mineral, lean tissue and and fast mass in postmenopausal women. *Can J Physiol Pharmacol* 2002; 80: 941-50.
17. UUSI RASI K, KANNUS P, CHENG S *et al*.: Effect of alendronate and exercice on bone and physical performance of postmenopausal women: a randomised controlled trial. *Bone* 2003; 33: 132-43.
18. FUCHS RK, SHEA M, WIDRICK J, STARK S, HANSEN B, SNOW CM: Synergistic effects of exercice plus alendronate on bone mass and structural properties in ovariectomized rats. *J Bone Miner Res* 2002; 17: (Suppl. 1) S 192 (*abstract*).
19. VAN HEIDEKEN WAGERT P, LITTBRAND H, JOHANSSON A, NORDSTRÖM P, GUSTAFSON Y: Jumping exercices with and without raloxifene treatment in healthy elderly women. *J Bone Miner Metab* 2002; 20: 376-82.
20. KELLY PJ, EISMAN JA, SAMBROOK PN: Interaction of genetic and environmental influences on peak bone density. *Osteoporosis Int* 1990; 1: 56-60.
21. SPECKER BL: Evidence for an interaction between calcium intake and physical activity on changes in bone mineral density. *J Bone Miner Res* 1996 ; 11: 1539-44.
22. KELLEY GA: Aerobic exercise and bone density at the hip in post-menopausal women : a meta analysis. *Preventive Medicine* 1998; 27: 798-807.
23. LANYON LE, RUBIN CJ, BOUST G: Modulation of bone loss during calcium insufficiency by controlled dynamic loading. *Calcif Tissue Int* 1986; 38: 209-16.
24. SPECKER B, BINKLEY T: Randomized trial of physical activity and calcium supplementation on bone mineral content in 3 to 5 year old children. *J Bone Miner Res* 2003; 18: 885-92.
25. IULANO-BURNS S, SAXON L, NAUGHTON G, GIBBONS K, BASS SL: Regional specificity of exercice and calcium during skeletal growth in girls : a randomised controlled trials. *Bone Miner Res* 2003; 18: 156-62.
26. UUSI-RASI K, SIEVANEN H, PASANEN M, OJA P, KUORI I: Association of calcium intake and physical activity with bone density and size in premenopausal and postmenopausal: a peripheral quantitative computed tomography study. *J Bone Miner Res* 2002; 17: 544-52.
27. COURTEIX D, JAFFRÉ C, LESPESSAILLES E, BENHAMOU CL: Cumulative effects of calcium supplementation and physical activity on bone accretion in premenarchal children: a

double-blind randomised placebo-controlled trial. *Int J Sports Med* 2004; 25: 1-7.
28. EASTELL R: Treatment of postmenopausal osteoporosis. *N Engl J Med* 1998; 338: 736-46.
29. LANYON LE: Using fonctional loading to influence bone mass and architecture: objectives, mechanisms, and relationship with estrogen of the mechanically adaptative process in bone. *Bone* 1996; 18: 37-43.
30. CHENG MZ, ZAMAN G, RAWLINSON SCF, SUSNILLO RFC, LANYON LE: Mechanical loading and sex hormone interactions in organ cultures rat ulna. *J Bone Miner Res* 1996; 11: 502-11.
31. DAMIEN E, PRICE JS, LANYON LE: The estrogen receptor's involvment in osteoblasts' adaptative response to mechanical strain. *J Bone Miner Res* 1998; 13: 1275-82.
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.
33. JESSOP HL, SJOBERG M, CHENG MZ, ZAMAN G, WHEELER-JONES CP, LANYON LE: Mechanical strain and estrogen activate estrogen receptor alpha in bone cells. *J Bone Miner Res* 2001; 16:1045-55.
34. LEE K, JESSOP H, SUSWILLO R, ZAMAN G, LANYON L: Endocrinology: bone adaptation requires estrogen receptor-alpha. *Nature* 2003; 424: 389.
35. SUURINIEMI M, MAHONEN A, KOVANEN V, ALEN M, LYYTIKAINEN A, WANG Q: Association between exercise and pubertal BMD is modulated by estrogen receptor and genotype. *J Bone Miner Res* 2004; 19:1758-65.
36. YEH JK, LIU CC, ALVIA JF: Additive effect of treadmill exercice and 17 -estradiol replacement on prevention of tibial bone moiss in adult ovariectomized rat. *J Bone Miner Res* 1993; 8: 677-83.
37. KOHRT WM, SNEAD DB, SLATOPOLSKY E, BIRGE SJ: Additive effects of weight-bearing exercice and estrogen on bone mineral density in older women. *J Bone Miner Res* 1995; 10:1303-11.
38. NOTELOVITZ M, MARTIN D, TESAR R *et al*.: Estrogen therapy and variable-resistance weight training increase bone mineral in surgically menopausal women. *J Bone Miner Res* 1991; 6: 583-9.
39. LI CY, JEE WS, CHEN JL *et al*.: Estrogen and « exercise » have a synergistic effect in preventing bone loss – in the lumbar vertebra and femoral neck of the ovariectomized rat. *Calcif Tissue Int* 2003; 72: 42-9.
40. PRINCE RL, SMITH M, DICK IM *et al*.: Prevention of post-menopausal osteoporosis. A comparative study of exercise, calcium supplementation, and hormonal replacement therapy. *N Engl J Med* 1991; 1189-95.
41. HEIKKINEN J, KURTTILA-MATERO E, KYLLONEN E, VUORI J, TAKALA T, VAANANEN HK: Moderate exercise does not enhance the positive effect of estrogen on bone mineral density in post-menopausal women. *Calcif Tissue Int* 1991; 49: S83-S84.
42. CHENG S, SIPILA S, TAAFFE DR, PUOLAKKA J and SUOMINEM H: Change in bone mass distribution induced by hormone replacement therapy and high-impact physical exercice in post-menopausal women. *Bone* 2002; 31: 126-35.
43. LOHMAN TG, CABALLERO B, HIMES JH *et al*.: Effects of exercise on bone mineral density in calcium replete postmenopausal women with and without hormone replacement therapy. *Osteoporos Int* 2003; 14: 637-43.