The effects of exercise on bone. Basic concepts and implications for the prevention of fractures

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Summary

Osteogenic dynamic loads delivered to the skeleton during exercise prevent aging-associated bone fragility. Moreover, because of its pleiotropic favourable effects on health, exercise improves quality of life, and specific types of exercise increase muscle strength, a known predictor of bone strength, and coordination and balance, and so reduce the risk of fall-related fractures. Exercise should definitely be the mainstay of the prevention and treatment of osteoporosis; often however, physicians don't have enough know-how for evidence-based prescription of exercise. Moreover, the lack of facilities for safe implementation of the exercise programs compound the problem. Scientific societies and health authorities should invest in patient and physicians education about exercise and in promoting facilities (Gyms) devoted to training of persons with, or at risk of, metabolic diseases (osteoporosis, obesity, diabetes), like Metagym in Florence, Italy.

KEY WORDS: exercise, muscle strength, bone strength, falls, osteoporosis, fractures, Gym, Metagym, nutrition adaptation to exercise.

Introduction

Osteoporosis is defined as a condition characterized by reduced bone strength and high propensity to fractures. This definition implies a cause-and-effect relationship between osteoporosis and fragility fractures. Hence, based on DXA measurements as a proxy for bone strength, operative diagnostic criteria for osteoporosis and the intermediate condition, osteopenia, have been established by a WHO study group and widely used in the clinical practice (1). Even if it is known that DXA measurements can be grossly inaccurate, and that this inaccuracy can go undetected, efforts of major research teams and pharmaceutical companies have been directed toward developing (and selling) drugs capable to treat DXA-detected osteoporosis (and osteopenia), with the purpose to prevent fractures (2).
However, the cost and safety of drug treatment to prevent fractures should be carefully considered: if the diagnostic threshold to initiate the treatment is set at -2.5 SD, the cost of preventing one vertebral fracture has been estimated to be more than 30000 dollars, and the cost to prevent one hip fracture even more, and even with this expensive strategy most fractures would still occur (3). Moreover, even drugs like bisphosphonates that have been thoroughly investigated in thousands of patient/years, and have been used for many years in the clinical practice, are not necessarily safe or effective in any single patient (4).
In fact, osteoporotic fractures usually occur in connection with a fall, and anti-osteoporotic drugs have no effect on falls, with the notable exception of high dose vitamin D (5). Indeed, based on the above considerations, a shift in the focus from osteoporosis to falls in the prevention of fractures has been recently proposed (3). This shift is not likely to be easy, given that osteoporosis is diagnosed and treated by clinicians that usually don't assess the risk of falling of their patients but, rather, limit their intervention to prescription of drugs. However, falls can, and should be prevented using evidence-based assessment of risk and intervention (6). The assessment of the risk for falling is relatively simple and could be directly provided by the physician caring for the osteoporotic patient; in fact it includes careful history of past falls, review of medical risk factors including assumption of drugs, and assessment of mobility and physical performance (6).
The chore of the interventions aimed at reducing the risk for falling is, however, a structured exercise program which includes strength and balance training, and requires an adequate facility (i.e. a Gym) and skilled personnel. Although also such exercise programs are expensive they have the merit to positively influence both components of fracture risk: bone strength and falls and therefore deserve careful consideration in every patient with osteoporosis. Moreover, exercise has pleiotropic positive effects on health, including, among others, prevention of diabetes, cardio- and cerebro-vascular disease, improvement of urinary incontinence, reduction in cognitive decline, improvement of mood, self-esteem, and general well-being (7, 8). Because metabolic diseases, including diabetes and osteoporosis, are highly prevalent in the population and are often associated, and because diabetes leads to an increased fracture risk, exercise can reduce fracture occurrence well beyond its direct effects on bone.
According to the above considerations, the careful prescription of exercise should be part of the optimal management of every patient with osteoporosis. However, this is not usually the case: instead, patient are typically given by the caring physician only a generic advise to increase physical activity such as, for instance, walking, swimming or stretching or, at best, they are advised to attend a gym but rarely receive an individualized, clear and detailed prescription of the type and amount of the exercise likely to be effective in his/her particular case. Even more rarely, a follow-up schedule is provided such that exercise-related improvements are recorded and used in the global management of the patient. The reasons for downplaying the value of exercise in the osteoporosis management are both cultural and practical; on one hand physicians often ignore the principles of exercise for metabolic diseases and on the other hand there is a lack of facilities devoted to train these difficult patients: many gyms even exclude from their membership patients with a diagnosed osteoporosis. Moreover, cost-effectiveness and convenience considerations suggest that medical management of osteoporosis and exercise programs adequate to prevent falls through improvement in balance and muscle and bone strength be provided in the same setting. Therefore, I have recently developed in Scandicci (Florence, Italy) Metagym,

a centre specifically designed to meet the demands of patients with metabolic problems including obesity, diabetes, and osteoporosis. Metagym (a Gym for the Metabolism), is equipped to provide strength, balance and vibration exercise; it has personnel qualified and trained to assess physical performance, posture, muscle power, cardiovascular fitness, and capable to devise and implement exercise programs for patients of any age, including nonagenarians, and with physical limitations. Metagym is linked to a medical facility, where medical management of osteoporosis and other metabolic diseases is possible, including endocrinology counselling, assessment of physical performance, anthropometry, bioimpedenziometry, bone densitometry, and medical nutrition therapy. Metagym is also a research centre: it participated in IDES (Italian Diabetes and Exercise Study), a multicenter trial aiming to prove the superiority of combined aerobic and resistance exercise over counselling of exercise in type 2 diabetic patients with metabolic syndrome (9).
This review is focused on the effects of exercise in the adult bone with the aim to prevent falls and bone loss, and to foster favourable geometric bone adaptations. However, it should be noted that exercise interventions in children and adolescents with the aim to optimize the attainment of peak bone mass and the development of a robust bone architecture are also feasible and they are probably an effective strategy to reduce the burden of osteoporotic fractures in the population.

Mechanical loading and bone properties

The main function of the skeleton is to support muscles to allow posture and movement in the space. Architectural properties of the skeleton, including size and shape, are adapted to this function: in any species and at any age, every single bone is rigid proportionally to its habitual loads, without being too massive. A well adapted bone allows movement with a low probability to break during conditions of habitual use.
Because exercise mainly acts through changes in the mechanical environment of the skeleton, it elicits physiologic responses in bone architecture whose knowledge is essential to understand the responsiveness of the osteoporotic patients to exercise, and to prescribe the right exercise program for every single patient.
Habitual loads to bone derive essentially from gravity and, more importantly, muscle contraction (during heavy exercise the latter delivers up to 10 times the gravity force).
In general, the resistance of a given structure is determined by property, amount, and spatial distribution of its constituent material (10). Moreover, in order to optimize resistance, the bone material can change its distribution thus modifying bone size and shape in response to specific challenges. Therefore, assessment of both material properties and architecture of bone are necessary to predict if a bone can resist to a given load. In old age for instance, a reduction in volumetric density of cortical bone (a proxy of material property) or a reduction in the amount of cortical bone (bone mass) is associated with a redistribution of bone material toward the periphery of bone, leading to increased bone size (11-13). This response is homeostatically sound since it maintains bone resistance in the face of a reduction in some bone properties (see later for details).
Bones can be subjected to compressive, tensile, bending and torsional loads. In short bones such as vertebrae and in the metaphyses of long bones compression and tension are the main loads, while bending and torsion are mainly beared by long bones diaphyses. Buckling is a bending secondary to compression; it occurs only in long bones diaphyses and is of uncertain significance in bone pathophysiology.

Resistance to compression and tension

Resistance to compression and tension is determined by the modulus of elasticity (E), whose best proxy is the volumetric density, and the cross-sectional area of the bone, A. Therefore, the formula E*A best describes the resistance to compression and tension. Accordingly, during growth bone metaphyses typically become wider than diaphyses in order to resist their habitual compressive loads (10).

Resistance to bending and torsion

While resistance to compression is proportional to the amount of bone material, the resistance to bending and torsion is critically dependent on the distribution of the material. Moments of inertia and section modulus (I) are geometric variables that strongly depend from the distance of every small particle of material from the bending and torsional axis and best predict the resistance to bending and torsion, according to the formula E*I (10). Please note that I is proportional to the fourth power of the radius. For this reason bone diaphyses, usually loaded in bending and torsion, have evolved ontogenetically into empty cilinders. Moreover, the age-related thinning of bone cortex, potentially leading to a dramatic reduction in mechanical resistance, is compensated for by modeling and consequent periosteal expansion, a strategy capable of increasing the moments of inertia and so maintaining the resistance to bending and torsion into old age. There is evidence that periosteal expansion is less efficient in old women, explaining, at least in part, the greater propensity of older women to fragility fractures (12, 13). There is also evidence that exercise stimulates periosteal expansion leading to architectural adaptation, rather than accumulation of bone material (that is bone mass) (14). For this reason measuring bone mass to verify the effects of exercise on bone may be futile and can underestimate the effects of exercise on bone (10-12).

Assessing the bone mechanical resistance in the laboratory

Mechanical resistance of bones is expressed by the load-deformation curve, obtained applying a progressive load and recording the consequent bone deformation until fracture. The area under the load-deformation curve describes the energy-absorbing capacity of bone. The stress-strain curve, which describes the bone material properties, is obtained dividing both loads and deformations by the cross-sectional area of the bone. The slope of the first, linear, portion of the stress-strain curve describes the *stiffness* of the bone material, while the area under the curve, also influenced by the second, non linear, portion of the deformation is called *thoughness* or capacity to absorb energy before breaking. The stiffness is a function of the degree of mineralization and porosity of bone, while thoughness is strongly influenced by the bone matrix and the collagen structure.

Estimation of bone strength and fracture risk in the clinical practice: beyond bone densitometry

As noted in the introduction, according to the WHO study group guidelines bone strength and fracture risk are usually estimated using DXA bone densitometry. This approach has proved ineffective for two main reasons.
1. *DXA is not capable of detecting changes in bone architecture.* DXA measures bone mass, and therefore it does estimate bone strength. However, as noted in the preceding section, a reduction in bone mass, or the amount of bone material, is ab-

solutely not the only determinant of a reduced bone strength or of the presence of osteoporosis. Rather, an increase in bone size or a more peripheral distribution of bone material, which are putative adaptive processes to aging and bone loss, are disregarded by DXA or, worse, are erroneously detected as reduction in BMD and bone strength (11-13). This occurs because the low BMC value (because of the bone loss) is divided by a wider area (because of the periosteal expansion) yielding a disproportionately lower BMD value. A similar technical and interpretative problem occurs after exercise training; in this case BMD does not change because the moderate increase in bone mass resulting from exercise is obscured by the concomitant periosteal expansion, with the resultant reduction in the calculated BMD (14, 15).

2. *DXA measurements are confounded by differences in bone and body size.* In individuals of low stature DXA, because of its planar nature, attributes erroneously low BMD values.(16) This problem is compounded in subjects with low volumetric density, in which DXA has often difficulty in detecting bone edges and therefore tends to underestimate BMD. As a result of these inaccuracies old ladies of low stature often receive inappropriate diagnoses of osteoporosis and unnecessary treatment aimed at reducing fracture risk. Conversely, osteoporosis in tall people can go undetected (16).

As a result of the above the predictivity of DXA in diagnosing osteoporosis and predicting fracture risk is low.

Because of the limitations of DXA, efforts have been put in the search of alternative methods of estimating fracture risk. Simple clinical risk factors have proved effective in estimating absolute fracture risk and have evolved in the FRAXI algorithm that combines clinical risk factors with DXA derived BMD to yield a 10 years absolute risk of fractures. The development of FRAXI has been an advance for the clinicians, however it needs to be refined since it lacks, for instance, important risk factors for fracture such as assessment of the risk for falling (17).

Bone densitometry methods alternative to DXA have been developed with the objective to improve the prediction of fractures.

- *Quantitative bone ultrasonography (QUS) of the heel* has proven valuable in predicting the risk of fracture in several prospective studies and, in a head to head comparison, it has recently performed better than DXA (18). In particular QUS proved more accurate than DXA in detecting high risk for fracture among individuals with low BMD value (18). Because QUS is portable and it is less expensive than DXA, it probably deserves further consideration as an alternative or adjunctive method for predicting fracture risk. Recently, concomitant use of FRAXI-derived clinical risk factors and QUS has been successful for the improvement of risk prediction over QUS alone (19).
- *Quantitative Computerized Tomography (QCT) of radius and tibia* has considerable advantages over DXA and QUS. In fact, QCT accurately assesses volumetric density (a proxy of the material property stiffness) and Section Modulus (a geometric parameter of material distribution). The combination of volumetric density and section modulus yields a Bone Strength Index (BSI), a realistic predictor of true bone strength that needs to be validated against other bone strength predictors (20). The capability of QCT to assess bone geometry may give advantages in evaluating the effects of exercise on bone (12).

Bone and muscle mass and strength

Muscle force is a strong determinant of bone mass and strength. Therefore, assessing both muscle force and an indicator of bone strength (such as bone strength index) in osteoporotic patients may give useful information as to the cause of low bone mass. Based on this premise, several groups have evaluated the relationship between muscle CSA at forearm and calf by pQCT as a surrogate measure of muscle strength and cortical bone CSA or moment of inertia at the same site. As expected, a close relationship linked the muscle and bone parameter both in children and in adults (R2= 0.60-0.95) (21), and studies suggest that osteopenia may be further characterized by investigating the proportionality between muscle and bone mass. In fact, according to this view, bone loss following a hypomobility condition associated with sarcopenia would give origin to a “concordant” osteopenia, in which both muscle mass and bone mass are reduced and the ratio between them remains constant. On the other hand, a bone loss caused by an endocrino-metabolic disorder, such as a “true” osteoporosis or hyperparathyroidism, would lead to a “discordant” osteopenia, in which bone mass is reduced to a greater extent than muscle mass. In one study osteoporotic patients with fractures had a similar cortical bone mass at the tibia diaphysis as age-matched healthy postmenopausal women, however, in the fracture patients the ratio between cortical CSA and muscle CSA was reduced compared with the controls (22). Other studies in children obtained similar results (23). These findings raise the possibility of distinguishing patients with osteoporosis and high fracture risk from osteopenic individuals whose low bone mass is merely a consequence of muscle hypotrophy. In the latter patients the mainstay of treatment is an appropriate “sarcogenic” and “osteogenic” form of physical exercise, not an antiresorptive drug. The aging process is characterized by progressive reduction in trabecular and cortical volumetric density and in cortical bone thinning. In the physically active people, these phenomena lead to greater deformation and greater strains of bones and, as a consequence, activation of adaptive periosteal expansion through modeling, with the purpose to maintain bone strength. In fact, periosteal expansion leads to wider bones that have a more peripheral distribution of bone material, and so greater cross-sectional area and moments of inertia. However, we may speculate that in the sedentary people, the insufficient mechanical stimulation does not produce enough architectural adaptation and bone fragility ensues (13). If this hypothesis is correct, and considering that exercise also improves balance and reduces the risk for falling, promoting and implementing exercise can have the potential to considerably reduce the risk for fracture in the population.

Physical exercise and nutrition therapy to maintain and increase muscle mass and strength

It is well established that muscle strength depends on muscle mass and neuromotor function, and that both of them decrease with aging but can be improved at any age with appropriate exercise. A less known determinant of muscle force is the architecture of muscle fibers in pennated muscle, and this too improves with exercise (24).

Within minutes, and for several hours after each bout of exercise, both protein synthesis and protein breakdown are increased in the muscle fibers. However, only if post-exercise circulating levels of essential aminoacids are sufficient will synthesis prevail on degradation. Different temporal relationships for these processes have been described in old versus young subjects and in males versus females. In fact, compared with the young, in older people higher amount of aminoacids intake, in a closer temporal relationship with the exercise bout are necessary to maximize post-exercise protein synthesis. A thorough discussion of the details of the nutrition-exercise interactions is out of the scope of this article; therefore, the interested reader can refer to recent reviews (25, 26).

Which type of exercise for the bone?

Since several types of exercise exist it is important to recognise which type of exercise is useful for muscle and bone strength and, in general, for reducing fracture risk.
The classical studies by Rubin and Lanyon (27-29) have established that bone responds to dynamic loads while it is insensitive to static loads, independent of their magnitude, and have defined the following principles of the maximal osteogenic mechanical stimulus:
– a few load cycles are necessary and sufficient (for instance: 4-5 jumps);
– loads must be of high magnitude;
– loads must be applied at high rate;
– loads should produce an unusual distribution of strain (strain is the unit of deformation)

Further studies from the same authors have established that bone responds to loads of a progressively lower magnitude, provided that the frequency of their application increases. In other words, the higher the frequency of load application, the lower the threshold of bone sensitivity to the load itself. This principle forms the basis for the use of vibration exercise to prevent and treat osteoporosis (30-32).
Both endurance and resistance exercise are dynamic and, therefore, both of them are potentially osteogenic. It is known that aerobic exercise stimulates preferentially mitocondrial biogenesis and the synthesis of proteins involved in the oxidative fosforilation, while resistance exercise stimulates preferentially the synthesis of the miofibrillar proteins involved in muscle contraction. Therefore, only resistance exercise significantly increases the cross-sectional area of the trained muscles, and, as a consequence, their force and power (25, 26).
Walking and jogging increase modestly the loads on the skeleton above gravity and do not lead to increase in muscle force and power. Not unexpectedly this type of exercise has proved to be relative ineffective in osteoporosis prevention. On the other hand, resistance exercise increases muscle force and has a greater potential to be useful in osteoporotic patients. Sports like soccer, volleyball and basketball are very effective osteogenic exercises but they are unlikely to be practised by frail osteoporotic individuals.
Vibration exercise is a special form of exercise that consists in standing over a vibrating platform; the high frequency oscillations of the platform elicit reflex muscle contractions of low magnitude that modestly increase O2 consumption. Vibration training has been tested in several trials involving individuals of different age and condition without provoking significant side effects (33). Vibration has been effective in increasing muscle power in young athletes and in sedentary postmenopausal women (34), and in improving physical performance in obese diabetic patients with metabolic syndrome (35) and in frail institutionalised old people (36).
With these premises, vibration exercise has increased femoral BMD in a few trials involving individuals at risk of osteoporosis (37), and, in a recent trial, it proved superior to walking in increasing femoral BMD and reducing fracture risk (38).

Observational studies and clinical trials on the effects of exercise, and lack thereof, on bone

Bone loss is considered a universal feature of aging and is associated with increased fracture risk, especially in older women. However, bone loss may not be an inevitable consequence of aging. Indeed, in the Utterite women, who engage in heavy daily manual work, no age-related decrease in BMD has been detected (39). Moreover, in the longitudinal SOF study, a subset of older women maintained their BMD up to 15 years, and experienced a lower risk of fractures, disability, and mortality. Among other features, these successful aging representatives did not smoke and had higher levels of physical activity and physical performance (40).
The most impressive demonstration of the effects of muscle force on bone is paraplegia. Prospective studies have established that in this condition muscle atrophy is followed by profound bone loss at both trabecular and cortical sites, and consequent high fracture risk (41-43). The causal role of muscle atrophy on microgravity bone loss has been confirmed by space flight and, recently, bed rest studies involving young volunteers (44).
Cross-sectional, retrospective, and prospective observational studies involving elite and amateur athletes have confirmed the major role of exercise, and especially resistance exercise, in the accrual of bone mass and in the development of an optimal bone architecture and high bone strength (14, 15).
Several clinical trials have tested the hypothesis that exercise increases bone mass in children and adults, with mixed results. In children, exercise has consistently shown improvement in mass and architectural parameters assessed by tibial QCT that persist for years after the completion of the intervention (45, 46). On the other hand, results of exercise in adults have usually been modest, and they have often been considered trivial. However, most of the adult trials have used DXA to examine the bone changes after exercise, and this is inadequate, considering that most of the beneficial effects of exercise in the adult bone are characterized by changes in geometry, to which DXA is virtually blind (see above), rather than mass, which is the parameter measured by DXA (47). This notwithstanding, 18 months high-impact exercise in premenopausal women aged 35-45 years was followed by a significant increase (+1.6%) in femoral neck BMD (48). In postmenopausal women aged 50-70 years, high-intensity strength training for one year prevented the significant bone loss that occurred in the control group at femoral neck (-2.5%) and lumbar spine (-2%) (49). Moreover, in the exercise group muscle mass and strength, dynamic balance, and overall physical activity also improved, potentially decreasing fall risk and future fracture risk (49). Furthermore, considering that exercise has established pleiotropic favourable effects on health, besides those on bone, even small improvements in bone characteristics in older individuals should be considered of clinical import. Accordingly, a recent meta-analysis evaluating randomized trials of high quality that involved a total of 256 osteopenic or osteoporotic participants revealed that interventions with combined exercise programs improved physical function, pain, and vitality (i.e. improved quality of life) more in the exercise groups than in the controls (50).
In summary, observational studies and clinical trials in children have consistently shown the beneficial effects of exercise, and the deleterious effects of the lack thereof, on bone characteristics and fracture risk. On the other hand, clinical trials in adults have usually been of limited quality, and therefore they don't allow to draw firm conclusions. Moreover, because of the lack of financial interest, these trials were not powered to detect the effects of exercise on fracture incidence. Nonetheless, Rizzoli et al. in a recent review of the evidence-based strategy for the management of osteoporosis in the elderly listed exercise training in the first line, then vitamin D and calcium supplementation, and use of evidence-based anti-osteoporotic drugs (51).

Summary and conclusions

In summary, the effects of exercise on bone health are complex and fascinating. The following take-home messages are proposed:
1. The clinically meaningful objective of the management of os-

teopenia and osteoporosis is the prevention of fracture occurrence; therefore, both preservation of bone strength and reduction in fall risk should be explicitly set as the target of the interventions. Because of its favourable effects on both bone strength and fall risk, exercise should be the first choice intervention in the management of osteopenia and osteoporosis;

2. The ontogenetic adaptations of bones to mechanical forces, and the effects of exercise on bone geometry described in the above sections suggest that bone has a unique plasticity that can be therapeutically exploited in the osteoporosis prevention and management. The bone plasticity is present at any age, including old age, but it is more evident in children, suggesting that the prevention of osteoporosis is indeed primarily a pediatric, rather than geriatric, task.

3. Muscle and bone are strongly linked, both anatomically and functionally; unsurprisingly therefore, differences in muscle mass and force explain most of the differences in bone mass and strength in both children and adults of any age. As a consequence, interventions aimed at increasing bone strength should be primarily aimed at improving muscle force and power, not directly delivering mechanical loads on the skeleton.

4. The effects of different types of exercise on muscle and bone properties have been studied and characterized. Clinicians should refer to these studies to choose appropriate exercise interventions for their patients; it not acceptable any more that physicians prescribe walking or swimming or chalistenics to their osteoporotic patients as the only exercise intervention. Instead, based on the scientific evidence available, resistance and vibration exercise should have the highest priority. Moreover, prescribing exercise for balance, coordination, endurance, and stretching may allow to exploit the whole range of beneficial effects of exercise on bone and general health.

5. Adequate nutrition intervention should complement the exercise prescription. Besides the well known recommendations on adequate intake of calcium and other macro and micronutrients, nutrition intervention should include the chronologic adaptation of meals to the training sessions. In particular, it is recommended that within 1-2 hours after each training session the patients consume a meal that contains abundant high quality proteins and adequate amounts of carbohydrates. If this is not possible, the prescription of additional essential aminoacids to the post-exercise meals should be considered.

6. Several difficulties often hinder the application of the principles of exercise to the practice. Particularly unusual is the availability of Gyms that accept the membership of osteoporotic patients, and offer adequate supervision of the exercise. Therefore, the example of Metagym in Scandicci (Florence, Italy), a Gym dedicated to the training of patients with metabolic problems, and connected to a medical facility where diagnosis and medical management of osteoporosis is ensured, should be followed. Such centres should be supported by the health authorities because of their strong potential for improvement in the care of the patients with osteoporosis and other metabolic diseases, and for reduction in health costs for the community.

In conclusion, exercise improves physical performance and quality of life, and reduces fracture risk, disability, and mortality. The rationale to use exercise as a therapeutic intervention in individuals at risk for fracture is strong and it should be the mainstay of the management of osteopenia and osteoporosis. However, exercise is seldom prescribed with evidence-based criteria; moreover, the quantitative, qualitative, and chronologic adaptation of nutrition therapy to exercise is largely ignored by both physicians and dieticians, often precluding the unique opportunity to derive from exercise the maximal benefit. An effort is required by physicians and politicians to make rational, evidence-based choices for the patients and to make exercise interventions feasible and effective.

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