Exercise and Osteoporosis-Related Fractures: Perspectives and Recommendations of the Sports and Exercise Scientist

Wolfgang Kemmler, PhD; Simon von Stengel, PhD

Abstract: **Osteoporosis-related fractures represent a major health concern, particularly in elderly populations. Direct and indirect costs (amounting to nearly $17 billion in 2005), increased morbidity, and loss of independence place substantial burden on the health care system. Observational studies have shown that a physically active lifestyle is associated with a 30% to 50% decrease in vertebral or hip fractures, and a recent meta-analysis that determined the effects of exercise on fracture incidence further confirmed these results. However, because no randomized controlled exercise trials have selected fractures as a primary endpoint, causality between a sedentary lifestyle and fractures may be potentially confounded by participants’ poor health status. With regard to fall reduction and bone strength as the main surrogates for fracture risk, many randomized controlled trials and corresponding meta-analyses have reported significant positive outcomes. Interestingly, no study that has assessed fall-related injuries has focused specifically on interventions that aimed to reduce fall impact. There is ongoing debate as to which factor, osteoporosis or falls, is more important for fracture prevention. This may be dependent on the region prone to fracture and the subjects’ health status. In randomized controlled trials on exercise, the type, mode, and composition of exercise parameters are predictors of study outcome. Unfortunately, many exercise trials on fall prevention have not adequately described the exercise protocol used, which makes it difficult to determine which fall prevention protocol was most effective. A recent meta-analysis recommended Tai Chi and/or a mix of balance and resistance exercises for fall prevention. More sophisticated protocols are required to impact bone strength. Corresponding state-of-the-art protocols have focused on periodized high-impact/high-intensity resistance protocols performed at least twice per week. In the frail elderly, high-frequency/high-cycle number exercise programs with low-to-moderate strain intensity may also positively affect bone strength.**

Keywords: fractures; falls; exercise programs; exercise training

Wolfgang Kemmler, PhD[1]
Simon von Stengel, PhD[1]

[1]Institute of Medical Physics,
University of Erlangen,
Erlangen, Germany

Introduction

Osteoporosis-related fractures are a major health problem, particularly in elderly individuals. About one-third of all men and half of women will sustain a fragility fracture during their lifetime.[1] In the United States, > 2 million osteoporosis-related fractures, costing nearly $17 billion, were recorded in 2005.[2] Increased morbidity and direct and indirect costs associated with rehabilitation, pain medication, and loss of independence place substantial burdens on the health care system.[3] When considering that the number of elderly individuals is increasing, it is important to implement adequate fracture prevention and treatment regimes. There is some evidence to suggest that physical activity, particularly exercise training, may decrease rates of osteoporosis-related fractures. This article aims to 1) provide evidence for the effectiveness of exercise in fracture prevention and 2) describe which exercise strategies and parameters have been effective in reducing fracture rates.

Physical Activity, Exercise, and Fractures

Observational studies have demonstrated that a physically active lifestyle has been associated with a 50% decrease of hip fractures,[4–6] though effects on vertebral fractures[7,8] have been less compelling. Although the consistency of these study results was high, randomized controlled studies are required to ensure that the positive association between physical exercise and fractures was not caused by simple sampling or publication bias, or confounded by preexisting health status.[6] Causality between physical activity and fracture risk cannot be proven because the underlying mechanism for a sedentary

Correspondence:
Wolfgang Kemmler, PhD,
Institute of Medical Physics,
University of Erlangen,
Henkestrasse 91,
91052 Erlangen,
Germany.
Tel: ++ 49-9131-8523999
Fax: ++ 49-9131-8522824
E-mail: wolfgang.kemmler@imp.uni-erlangen.de

lifestyle and fractures may be poor health status. No randomized controlled trial on exercise has focused on fractures as a primary endpoint, which is not surprising, considering that fractures do not occur frequently.[6] Thus, to achieve adequate statistical power, randomized controlled trials with fractures as a primary endpoint require either large sample sizes and/or the inclusion of subjects who are at high risk for sustaining fractures. Moayyeri[6] calculated sample sizes (type I error, 5%; type II error, 20% probability) for a 5-year trial with a cohort at high risk for fractures (women aged > 65 years) using a hip fracture rate ratio of 0.70. This resulted in sample sizes of 2341 subjects per group. It is debatable whether this large sample size could be relevantly reduced by including all fracture types and/or subjects with a higher risk of sustaining fractures. However, it is doubtful whether exercise studies, which generally have low budgets, can recruit, test, and train such large sample sizes. A meta-analysis that reviewed data of randomized controlled trials would be useful in providing a more distinct level of evidence related to the effects of physical activity on fracture risk. Indeed, a recent Cochrane review[9] of 5 exercise studies with a total of 719 participants[10–14] focused on fall-related hip fractures, and reported a risk ratio of 0.36 (95% confidence interval [CI], 0.17–0.70). Thus, according to these results, about two-thirds of fall-related fractures could be prevented by exercise.[9] However, the evidence of this meta-analysis might be limited because of publication bias resulting from the omission of publications with negative results. In addition, recent trials[15–17] with nonsignificant fall reductions not included in this meta-analysis may have favored these positive results.[9]

Exercise Effects on Fracture Rate

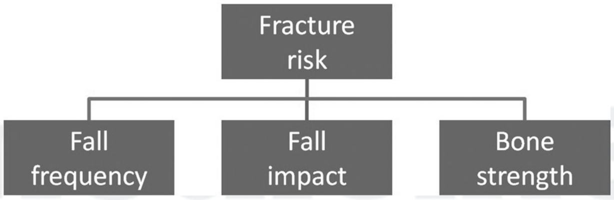
Some of the literature on exercise studies has reported fracture rates as secondary endpoints or simple observations. In a review by Karinkanta et al,[18] authors cited 9 randomized controlled trials on exercise that reported fracture incidence.[10–17,19,20] Of the 9 trials, 8 listed overall fractures (ie, any fractures independent of the site) or serious injuries,[11,15] and 1 study focused on vertebral compression fractures, as assessed by roentgenographic analysis (T4–L5).[20] Each study reported positive outcomes, with 1 exception,[17] but only 3 studies[12,14,20] reached statistical significance. In a study by Korpelainen et al,[12] 160 women (aged 70–73 years) participated in a 30-month exercise regimen focusing on fall reduction and increment of bone strength. Investigators reported significant differences between the exercise group and controls (6 vs 16 fractures; $P = 0.02$) regarding overall fractures. Sinaki et al[20] conducted a study with 50 women (aged 58–75 years) who participated in 2 years of supervised back-strengthening exercise followed by an 8-year period of nonmonitored, self-selected physical activity. Results demonstrated a significant effect (ie, significant difference between the exercise and control groups) for vertebral compression fractures in the women who had continued to exercise (14 vs 6 fractures; $P = 0.03$). In a 12-month study with subjects aged ≥ 75 years who participated in a home-based exercise program, Robertson et al[14] observed significant effects for subjects who sustained a fracture with fewer fractures in the exercise group (2 vs 9 fractures; $P = 0.03$). However, the same exercise program performed with subjects aged < 80 years did not result in significant between-group differences regarding serious fall-related injuries (2 of 120 subjects in the control group vs 15 of 330 subjects in the exercise group[s]; $P = 0.26$).[17] Of interest, the number of serious injuries reported in this multicenter study[17] varied between 3 of 115 subjects and 9 of 120 subjects within the 3 exercise program centers. These results indicate the haphazardness of positive results of studies that were not adequately powered to focus on fracture rates.

Exercise Strategies to Decrease Fracture Risk

Although extensive prospective studies and meta-analyses suggest a high level of evidence concerning the fracture-preventing effect of exercise, the lack of adequately powered studies focusing on fractures as a primary endpoint prevents the definite conclusion that physical activity reduces fracture risk. When reducing the level of evidence by 1 grade, there are many studies that have focused on the effects of exercise on primary risk factors for sustaining fractures. Figure 1 demonstrates predictors of fracture risk.

Although there is ongoing discussion regarding which strategy (strengthening bone or reducing falls) is superior for decreasing fractures,[21–23] it should be noted that the selection

Figure 1. Predictors of fracture risk.



of the exercise strategy used is dependent on the fracture site. Vertebral compression fractures are primarily associated with low bone strength, whereas hip fractures are related to fall frequency, type of fall, and bone strength.[24] Furthermore, the relevance of these strategies differs according to age and functional status of the subject. Both endpoints are important factors in an exercise program involving elderly subjects who are exposed to considerable risk factors for falls.[16] However, it is important to note that in early postmenopausal women who are at low risk for sustaining a fall, increased bone turnover and accelerated bone loss require greater emphasis on bone strength in the exercise program.

Effects of Exercise on Fall Prevention

Most studies[25–29] demonstrated beneficial effects of exercise programs in individuals at high risk of sustaining a fall.[9,30–33] In a recent meta-analysis of community-dwelling subjects aged ≥ 60 years, supervised group exercise programs were demonstrated to reduce fall rate ratio (ie, number of falls/person in the exercise vs control group) by 22% and the corresponding risk ratio (ie, number of fallers in the exercise vs control group) by 17%.[9] Of socioeconomic importance, corresponding home-based exercise programs were also effective in reducing both rate ratios and risk ratios of falls (Table 1).[9]

Effects of Other Interventions in Preventing Falls

It is beyond the scope of this article to extensively review the effects of different interventions on fall prevention; however, a short review is important for the reader to judge the relevance of exercise on fall prevention. A direct comparison of the effect of exercise programs with other interventions on fall prevention is difficult because of differences in cohorts, settings, definitions of "falls,"[34] and assessment methods. However, Gillespie et al[9] provided useful information for several types of interventions within their meta-analysis. When 13 studies (n = 23 100) were reviewed regarding vitamin D/vitamin D analog supplements (with or without calcium), the authors did not demonstrate statistically significant results for rate ratio (0.95; 95% CI, 0.80–1.14) and/or risk ratio of falls (0.96; 95% CI, 0.80–1.14). However, when adjusting for baseline vitamin D status, a corresponding subgroup analysis (3 studies, n = 560) revealed higher effect sizes for the rate ratio (0.57; 95% CI, 0.37–0.89) and risk ratio (0.65; 95% CI, 0.46–0.91) of falls.[9] Bischoff-Ferrari et al[35] conducted a review of 8 randomized controlled trials, which included 2426 subjects aged ≥ 65 years, and assessed the dose-dependent effects of cholecalciferol or ergocalciferol on falls. It was observed that high-dose vitamin D supplementation (700–1000 IU/day) resulted in a 19% reduction in fall risk (pooled relative risk, 0.81; 95% CI, 0.71–0.92), whereas lower doses (200–600 IU/day) did not notably affect falls (relative risk, 1.10; 95% CI, 0.89–1.35).

Table 1. Pooled Effect Sizes of Rate and Risk Ratio for Different Interventional Strategies Based on Randomized Controlled Trials[9]

Type of Intervention	Rate Ratio (pooled) (95% CI)	Risk Ratio (pooled) (95% CI)
Group exercise (overall)	0.78 (0.71–0.86)	0.83 (0.72–0.97)
Group exercise (Tai Chi)	0.63 (0.52–0.78)	0.65 (0.51–0.82)
Home training	0.66 (0.53–0.82)	0.77 (0.61–0.97)

Abbreviation: CI, confidence interval.

In a Cochrane meta-analysis,[9] hormone replacement therapy (2 studies; n = 580) did not show significant results for rate ratio (0.88; 95% CI, 0.65–1.18 for 1 study) and risk ratio (0.94; 95% CI, 0.01–1.08) of falls. Psychotropic medication (1 study; n = 93) was shown to significantly affect rate ratio for falls (0.34; 95% CI, 0.16–0.73); however, corresponding data for risk ratio (2.83; 95% CI, 0.12–67.7) did not confirm this result.[36] Gillespie et al[9] also showed that home safety interventions (6 studies; n = 2700) did not reach statistically significant results for rate (0.90; 95% CI, 0.79–1.03; $P = 0.09$) or risk ratio (0.89; 95% CI, 0.80–1.00; $P = 0.051$). This result was improved to statistical significance when participants were selected based on risk of falling (3 studies; n = 551; rate ratio, 0.56; 95% CI, 0.42–0.76; risk ratio, 0.78; 95% CI, 0.64–0.95).

Most importantly, corresponding effect sizes of multifactorial interventions, as calculated by the meta-analysis of Campbell and Robertson[30] (rate ratio, 0.78; 95% CI, 0.68–0.89) and Gillespie et al[9] (rate ratio, 0.75; 95% CI, 0.65–0.86) did not differ from exercise interventions. Thus, exercise intervention is one of the most effective and cost-efficient strategies for preventing falls in the elderly.[37,38]

Effective Types of Exercise for Fall Prevention

Despite the amount of evidence on the beneficial effects of exercise on fall prevention, there is only limited evidence concerning the most effective exercise protocol. The type and composition of exercise parameters of fall prevention programs are optiziming patient outcomes. However, most studies performed a single exercise protocol composed of multiple types of exercise, which does not allow comparisons across exercise types. Hence, it is still under discussion as to which type of exercise or combination of exercises is most effective. In their preplanned meta-analysis of The Frailty and Injuries: Cooperative Studies of Intervention Techniques (FICSIT) study, Province et al[39] compared different types of exercise (resistance, Tai Chi, endurance, balance, and flexibility) to determine which type is best for fall reduction. However, only 3 centers (Atlanta,[40] Boston,[41] and Farmington[42]) evaluated the isolated effect of a single type of exercise (resistance, Tai Chi, or balance exercise on fall frequency. A direct, center-specific analysis of balance[40,42] or resistance[41,42] exercise did not demonstrate significant positive effects on falls or fall-related injuries.[39] Concerning the Farmington resistance trial,[42] statistical significance was not reached (incidence rate ratio [IRR], 0.61; 95% CI, 0.34–1.09), possibly because of the low statistical power caused by a low sample size ($n = 27$). Tai Chi, when mixed with different types of exercise, was found to be more effective (IRR, 0.63; 95% CI, 0.45–0.89; $P = 0.01$). After pooling their data and including Tai Chi in the balance intervention section, Province et al[39] compared balance intervention and treatment arms with nonexercise interventions. They reported substantially lower number of falls (IRR, 0.75; $P = 0.01$), but not fall-related injuries, among the balance intervention arm. In this context, other studies have consistently demonstrated beneficial effects of Tai Chi on the risk ratio of falls[43,44] and fall-related injuries.[43] Balance exercise may be particularly effective in subjects with low physical functionality.[45,46] With 1 exception,[47] studies have confirmed beneficial effects of balance exercise on the rate ratio and risk ratio of falls.[11,14,15,17,48–51] However, none of these studies clearly determined the effect of isolated balance exercises, as the interventions did not consist solely of balance exercise.

Resistance exercise is another effective intervention in individuals with decreased lower-limb strength.[52,53] In 3 sub-studies of the FICSIT study,[39] the effects of moderate-to-high–intensity resistance exercise training (~75% 1 repetition maximum [RM]) on fall prevention were compared with balance[39,42] or endurance exercise in elderly subjects with mild deficits in strength and balance.[54] The latter study[54] analyzed the resistance and endurance groups together to increase statistical power (hazard ratio, 0.53; 95% CI, 0.30–0.91). The 2 remaining studies indicated that resistance exercise (IRR, 0.61; 95% CI, 0.34–1.09) affected fall rate more favorably compared with balance exercise (IRR, 0.90; 95% CI, 0.39–1.26) or a combined intervention (IRR, 0.86; 95% CI, 0.49–1.52), though this was nonsignificant.[39,42] Although there is limited corresponding evidence, two-thirds of fall prevention studies with community-dwelling elderly patients included strength training as a main intervention.[11,13–15,17,25,26,29,36,47–50,54–57] One study performed resistance exercise with resistance machines,[54] while the others used elastic belts, ankle weights, or the subjects' own weight. However, the inherent lack of an adequate description of exercise intensity when using elastic belts or gravity makes it difficult to determine whether adequate exercise intensity was used.

Of the 17 studies previously mentioned, 10 observed significant fall reductions.[11,14,15,17,47–50,54,57] Reasons for why the other studies did not observe such reductions may be related to inadequate exercise intensity, although this topic is still debated. It is unfortunate that most (though not all[14,58]) exercise studies that have focused on falls have not described their exercise program in such a way that it can be reproduced, and/or did not use state-of-the-art exercise designs. It should be noted that despite the fact that low strength and balance are some of the most important modifiable risk factors for falls,[33] the evidence that isolated strength or balance exercise training substantially affects fall risk is limited.

Multicomponent exercise strategies that are individually tailored and progressively increased may improve fall prevention most effectively. Besides the inclusion of balance, strength, endurance, and flexibility components, future fall prevention programs for high-risk populations should focus on more specific components.[59] The Nijmegen Falls Prevention Program[60] used an obstacle course that mimicked activities of daily life with potential fall risk (ie, walking over doorsteps, stepping stones) and significantly affected the fall rate (IRR, 0.54; 95% CI, 0.36–0.79) within 5 weeks, which was trend setting. Although the total amount of sessions of the latter program[60] was much lower (ten 90-minute sessions), a recent meta-analysis by Sherrington et al[61] showed that a volume of exercise of > 50 hours over the trial period provided significantly higher relative effects on fall rate ratio (0.80; 95% CI, 0.67–0.96) compared with lower volumes. However, the interpretation of this result is difficult because variables related to exercise volumes (eg, program length, exercise frequency, or adherence) did not predict falls (relative risks, 0.97–1.04).[61]

Exercise Effects on Fall Impact

In addition to fall rate and bone strength, the biomechanics involved when an individual sustains a fall[62] are known to influence the likeliness of a fracture. Thus, an additional strategy for decreasing fall-related injuries is to reduce fall impact on bone via pre-impact movement strategies. There are only a few studies that focus on this area.[60,63–67] Furthermore, most of these studies focus on impact forces rather than on fall-related injuries. The only study that performed fall techniques (derived from martial arts training) determined the number of falls, but not the numer of fall-related injuries.[67] Regarding biomechanical impact, even the "natural fall strategy," in which the arm is used to break the fall, reduced peak impact force values by 12% at the hip and 16% at the shoulder.[66] Using the arm to break the fall, however, may lead to lower-arm and wrist fractures in the elderly.[62] Groen et al[63] investigated more sophisticated fall techniques derived from martial arts in young experienced judokas. Martial art techniques that changed the sideways falling from kneeling height into a rolling movement decreased hip impact force by 30% compared with an arm block technique. Martial arts techniques that reduce fall impact on the hip were easy to learn. After 30 minutes of martial arts exercise training, Weerdesteyn et al[67] observed significantly smaller hip impact forces (17% smaller) compared with a natural fall arrest strategy (arm block) in 15 young adults without any prior experiences in martial arts. Although the effect on hip impact force reduction was lower (8% lower; $P = 0.02$), the same was true for older adults (n = 22; aged 60–81 years) who completed a 5-session martial arts training aimed at reducing fall impact.[64] Interestingly, results from a biomechanical modeling study[65] indicated that a 30% decrease in muscle strength did not markedly affect the effectiveness of these fall techniques.

Using the hip fracture risk factor (force at impact divided by the load necessary to cause a fracture), Groen et al[64] compared hip impact reduction with proximal femur bone mineral density (BMD) changes to determine their effects on hip fracture prevention.[62] The authors calculated that an 8% impact reduction corresponds to a 4% increase in trochanteric BMD, a change within the range typically described for alendronate treatment.[68–70] This calculation may be somewhat optimistic, and results may differ when fall techniques are applied from a standing position. However, when taking into account the low effort, ease of learning, subjects' reduced fear of falling (which was considered as an independent risk factor of recurrent falling[71]), and the safety of these martial arts techniques from a kneeling position,[64] fall impact reduction techniques should be considered an essential component of fall prevention programs.

Exercise and Bone Strength

Methods of Bone Strength Assessments

The most apparent approach to reduce fractures is to increase bone strength. Bone strength is dependent on mass, geometry, material property, and microstructure.[72] Bone densitometry, as performed by dual-energy x-ray absorptiometry (DXA) or quantitative computed tomography (QCT) is widely used to assess fracture risk.[73] Both techniques determine BMD either as areal density (DXA) or true volumetric density (QCT) with high precision and sensitivity.[74–76] Due to its selective measurements of trabecular bone, QCT is more sensitive to changes in BMD compared with DXA.[75,77] Furthermore, QCT is not affected by factors that confound DXA measurement, such as degenerative diseases of the spine.[78] Computer software for DXA and QCT automatically calculates structural dimensions, such as cross-sectional area and cross-sectional moment of inertia, which are thought to increase power of fracture prediction.[79] Another approach, using the peripheral pQCT (pQCT) technique, determines bone strength via bone strength index or stress strain index based on bone mass and geometric dimensions. Bone strength index showed a much higher association with fracture load in rats compared with BMD as assessed by DXA technique (correlation coefficient, $r = 0.94$ vs $r = 0.70$).[80] The main weakness of pQCT is its peripheral application, predominately at the forearm site. Bone status at this region does not necessarily reflect bone status at other, more important fracture sites, such as the lumbar spine. Furthermore, the forearm is less sensitive to treatment effects when compared with the spine and femur.[76]

Thus, certain methods may exhibit different limitations, which may modify results. For example, although there are exercise trials that determine significant effects on BMD after 6 months,[81] studies that focus on BMD of the lumbar spine or femoral neck, as determined via DXA, should last ≥ 12 months to determine the full extent of changes in BMD.

Evidence of Exercise Effects on BMD

Although DXA may not be the optimal tool for monitoring bone strength due to its widespread implementation and low radiation dose, most studies in humans that have evaluated exercise effects on BMD have applied this method.[82–89] Although age[90–92] and/or menopausal status[93] may impact exercise effects on BMD, most studies have generally reported beneficial effects at clinically relevant skeletal sites, such as the lumbar spine and femoral neck.[82,84–86,88,89] Data from exercise studies assessing bone mass and geometry by peripheral QCT confirmed the positive effects of exercise on bone mass and structure.[94]

Net gain of BMD at the lumbar spine and proximal femur following exercise has been reported to be modest, with levels of 1% to 3% per year among middle-aged and elderly women[82,87,89,95] and men.[96] One study that used the more sensitive QCT technique, however, observed more pronounced differences between the control and exercise groups (QCT trabecular lumbar spine, 8.8% and cortical lumbar spine, 7.9%) after 3 years of exercise.[97] Interventional periods in most exercise studies are relatively short. Thus, it remains unclear whether these positive changes could be maintained over a longer period. In a recent exercise study with an individualized, progressive, and periodized design over a 3-year period,[97,98] and a subsequent study extension over a 2-year period,[99,100] we were able to steadily increase the difference in BMD between the exercise and sedentary control groups. However, the group difference was primarily the result of a continuous decrease in BMD at the lumbar spine and hip among the controls, whereas BMD was maintained (proximal femur) or slightly increased (lumbar spine) in the exercise group.

Exercise Strategies to Increase Bone Strength

Although there are a number of confounders that may affect exercise effects on bone health, in this section we aim to 1) discuss the effects of different strain parameters on bone and 2) identify the most effective exercise strategies for increasing bone strength.

The effectiveness of exercise programs on health-related risk factors is dependent on type (eg, endurance or strength exercise), mode (eg, isometric vs dynamic), and the composition of loading parameters (eg, high vs low exercise intensity). As a matter of course, exercise programs that focus on muscle or bone strength must differ substantially from programs that affect metabolism or coronary heart disease-related risk factors. It is important to note that the classic categorization (eg, endurance-, resistance-type exercise) fails to adequately characterize exercise types with regard to impact on bone. Therefore, we favor the classification of Senn,[101] which distinguished 2 local, mechanically acting factors and 1 systemic, comprehensive-acting bone factor:

1) *Muscle tension*. Muscular tension affects bone by various modes of action. During contraction, muscle directly affects bone at its appendage via the tendon. Furthermore, muscle contractions result in either compression at vertebral bodies or complex compression, bending, torsion, or shear forces at long bones, which serve as a lever system to transfer forces applied by muscles.

2) *Axial loading*. This second locally acting bone factor is characterized by the axial loading of bones by gravitation and resulting ground-reaction forces. Depending on the type of bone, this loading leads to compression, such as in the vertebrae, or compression/bending, such as in the femur or humerus. For example, compressing long bones in artificial loading models will produce axial loading, which induces positive changes of bone parameters, depending on the strain parameters.

3) *Systemic*. Resistance- and endurance-type exercise triggers multifaceted reactions of the endocrine system. Both types of exercise were reported to have favorable impact concentrations of hormones interacting with bone metabolism and calcium homeostasis, dependending on the intensity and duration of exercise.[102–104] Furthermore, a higher concentration of agents such as testosterone and 17-β-estradiol was detected in trained versus sedentary subjects.[104,105] Although it has not been established whether these discrete changes of hormonal concentration directly affect bone, acute bone marker changes reflect this favorable alteration of osteoanabolic agents after exercise.[104]

Some authors have proposed an interaction between mechanical and systemic factors. It is suggested that exercise-induced effects of bone formation may be more beneficial in the presence of higher levels of certain hormones or corresponding agents by changing the sensitivity of bone cells to mechanical loading.[106,107] Although this effect is still under discussion, studies[108–111] have indicated a positive synergistic effect of exercise and nonmechanical agents on bone.

Using this categorization, the exercise specialist was able to determine the ways in which different sports can increase bone strength. For example, weightlifting includes all of the bone factors previously described, whereas swimming is characterized by nonaxial loading, below-threshold muscular tension,

Table 2. Measures of Bone Strength Parameters in Athletes[113–120]

Lumbar Spine		**Femoral Neck**
Weightlifting/gymnastics/sports games[a]	+	Gymnastics/sports
Unspecific exercising allrounders[b]		Weightlifting
Running		Unspecific allrounders/ballet/dancing
Ballet/dancing		Running
Swimming/cycling/untrained	–	Swimming/cycling/untrained

[a]Basketball, volleyball, tennis, squash; [b]Individuals who participate in several different types of exercise, or individuals who participate in different sports.

and (if practiced excessively) negative impact on the endocrine system.[112] Table 2 demonstrates the relevance of different sports on BMD according to cross-sectional studies that compared different sports.[113–120] The causal link between sports and bone strength/BMD cannot be clearly determined by cross-sectional studies because pre-exercise status was not assessed. However, studies that focus on sports with unilateral load distribution and compare dominant and nondominant upper limbs (eg, tennis or volleyball) have observed substantial differences between the loaded and unloaded site.[121–125] Thus, in accordance with Wolff's law,[126] different types of exercise impact bones differently and induce site-specific adaptations.

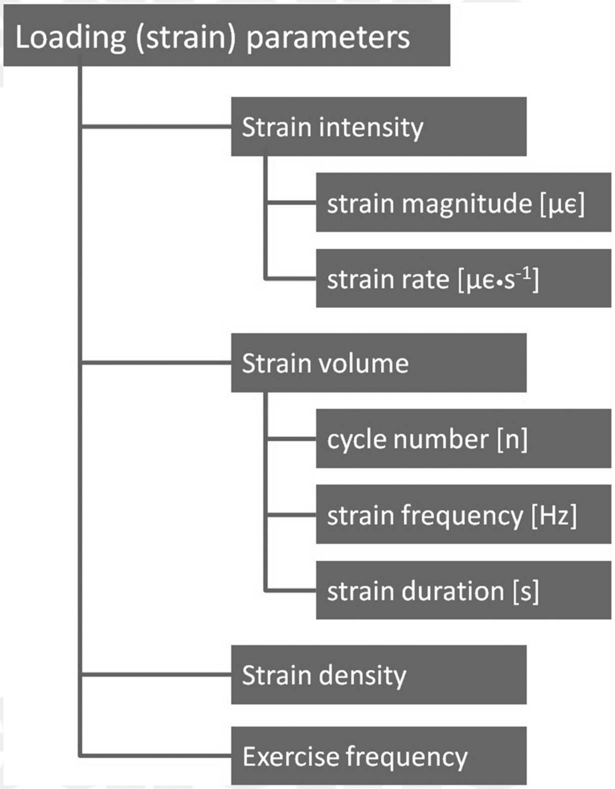
Exercise Parameters

The optimum specification and composition(s) of exercise parameters (eg, exercise intensity, cycle number, duration, frequency) are the major determinants when designing exercise programs that favorably impact bone strength. For example, although animal trials and cross-sectional studies with athletes[127–129] have typically demonstrated beneficial effects of resistance exercise on bone strength parameters, results differ between exercise programs using different loading strategies, such as low versus high intensity[130] or low versus high movement velocity.[100] In this context, nomenclature used when describing exercise/mechanical loading parameters related to bone adaptation differ from the nomenclature usually used in sport sciences. Figure 2 categorizes mechanical exercise parameters related to bone adaptation.

Strain Magnitude

Strain magnitude is the extent of deformation applied by loading (μΣ = microstrain: deformation of 0.1% ~1000 μΣ; fracture threshold averages 25 000 μΣ). According to Frost's mechanostat theory,[131] strain magnitude is the most critical parameter for the adaptive response of bone to exercise. In early animal studies, Rubin and Lanyon[132] and Hsieh and Turner[133] demonstrated that bone formation increases linearly to its deformation magnitude at strain magnitudes of > 1000 μΣ (Figure 3). When this is translated to human movement, strain magnitudes of 1000 to 1500 μΣ, which is the modeling threshold according to the Mechanostat theory,[131] are achieved by fast walking or jogging.[134] However, recent studies suggest that thresholds for modeling/remodeling differ between skeletal sites according to their habitual loading history.[135–137] Furthermore, other strain parameters also impact bone adaptation and thus affect the threshold for loading magnitude (Table 3).

Figure 2. Categorization of exercise parameters that are related to bone.



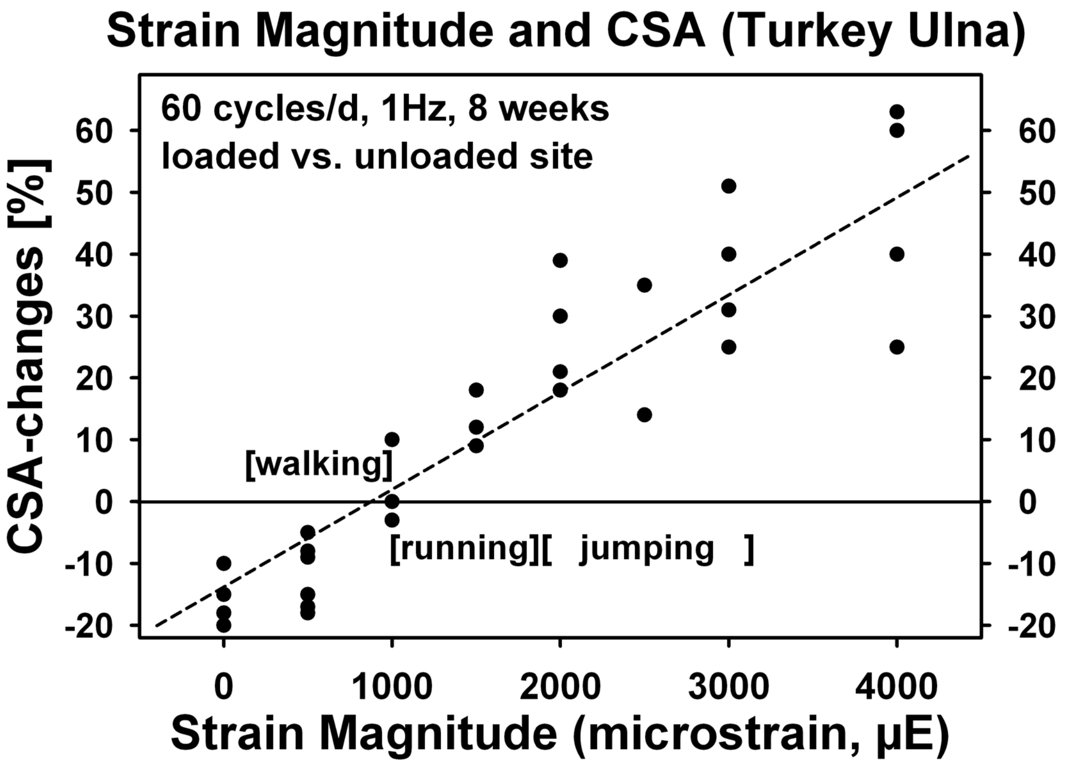
Strain Rate

Strain rate is the change in strain magnitude (acceleration or deceleration of loading) per second (μΣ/s). Recently, studies determined the effect of strain magnitude and rate on ovine radii and ulnae, and observed that strain rate predicts most (68%–81%) variation concerning bone formation. Two studies[138,139] demonstrated that the loading and unloading rate affects bone similarly. Turner et al[140] observed a linear increase of bone formation rate with higher strain rates (0.013 Σ/s, ~50 $\mu m^3/\mu m^2$ vs 0.026 Σ/s, ~180 $\mu m^3/\mu m^2$ vs 0.039 Σ/s, ~250 $\mu m^3/\mu m^2$) using a protocol (2 Hz, 36 reps/day, 2 weeks) with constant strain magnitude but different strain rates. In this study, different strain rates were generated during sinusoidal loading by different strain amplitudes (range between 36–54 N vs 18–54 N vs 0–54 N vs static loading with 54 N). Thus, the positive effect may be attributed to both strain rate and strain amplitude. Mosley and Lanyon[141] cyclically loaded rat ulnae (4000 μΣ, 2 Hz, 1200 reps/day) using 3 different strain rates (~0.018 Σ/s vs ~0.030 Σ/s vs ~0.100 Σ/s). In this experiment, the protocol with the highest strain rate resulted in a 54% higher relative bone formation rate compared with the moderate strain rate, which showed a 13% larger response than the low strain rate group. In 2 studies with roosters, Judex and Zernicke[142,143] determined the effect of strain rates on bone formation via jumping, running, and walking. Drop-jumps (200 jumps/day, 5–6 days/week for 3 weeks) resulted in peak strain rates of $>$ 740% compared with walking, or $>$ 370% compared with running. Strain magnitudes were only slightly higher compared with walking or running ($>$ 30% and $>$ 11%, respectively) and strain distribution was comparable. As a result, bone formation rate significantly increased in the drop-jumpers only. The favorable effect of high strain rates on BMD was observed by 2 exercise studies,[144,145] which directly compared low- versus high-impact exercises (ground-reaction forces $<$ 1.5 vs 2–2.5 × body weight) and 1 additional study that compared strength versus power training in postmenopausal women.[99]

Cycle Number

Cycle number is the overall number of loading cycles per set or session. Rubin and Lanyon[146] demonstrated that at high strain

Figure 3. Strain magnitude and percentage changes of ulna cross-sectional area. Strain magnitudes that resulted from different types of movements were inserted for a better comparison.



Adapted from Rubin et al.[146]

Table 3. Relationship Between Strain Magnitude, Cycle Number, and Strain Frequency Adequate to Maintain Parameters Related to Bone Strength

Study	Region of Interest	Type of Loading	Magnitude Cycle (μΣ)	Cycles, n	Frequency (Hz)
Rubin and Laynon[146]	ulna (chicken)	Axial compression	2000	4	0.5
Rubin and Lanyon[132]	ulna (turkey)	Axial compression	1000	100	1
Cullen et al[150]	ulna (rat)	4-point-bending	1000	40	2
Cullen et al[150]	ulna (rat)	4-point-bending	800	120	2
McLeod and Rubin[195]	ulna (turkey)	Axial compression	700	600	1
Hsieh and Turner[133]	ulna (rat)	Axial compression	580	360	10
McLeod and Rubin[195]	ulna (turkey)	Axial compression	400	18 000	30
McLeod and Rubin[195]	ulna (turkey)	Axial compression	270	36 000	60
Qin et al[196]	ulna (turkey)	Axial compression	70	108 000	30

magnitudes (2000 μΣ), the effect of the cycle number was negligible. These results were confirmed by exercise studies in animals[147] and humans,[148] which applied high strain magnitudes/rates and determined positive effects on bone after marginal cycle numbers (5 jumps/day[147]; 10 jumps/day[148]). Thus, the relevance of this parameter was previously underestimated (Table 3). However, the impact of cycle number increases when strain magnitude or rate is applied at lower levels (Table 3).[149] In this context, Cullen et al[150] demonstrated that 40 reps with a strain magnitude of 1000 μΣ (2 Hz) did not affect bone formation, whereas 120 or 400 reps showed significant increases in these bone formation rate parameters (Table 3). These results were also confirmed by an animal study by McDonald et al,[138] who compared 2 protocols with 4 versus 40 reps with approximately 200 μΣ. The authors observed positive effects on the mid-tibia cross-sectional area at higher cycle numbers only. To estimate the isolated effect of the cycle number at very low strain magnitudes/rate is difficult because most studies applied high cycle numbers and high frequencies (Table 3). To summarize this section, higher-repetition/lower-loading protocols may be an option for elderly patients to safely increase bone strength.

Strain Frequency

Strain frequency is defined as the number of loading cycles per second. Several animal studies have demonstrated the sensitivity of bone to strain frequency. Rubin and McLeod[151] found that the bony ingrowth of titanium implants in functionally isolated turkey ulnae was accelerated by the application of vibration, and higher frequencies (20 Hz) were more potent than lower frequencies (1 Hz). Using different loading frequencies, McDonald et al[152] determined bone formation rates in the loading model of rabbit tibia. The authors found an increased formation rate with increasing frequency (4, 10, 40 Hz). Judex et al[153] showed that, for bone adaptation, the loading frequency was even more critical than the strain magnitude/rate. In this study, whole-body vibration 90-Hz signals were more effective for inducing bone adaptation in the metaphysis of the proximal tibia of rats than 45-Hz signals, despite the significantly lower strain rate and magnitude at 90 Hz compared with 45 Hz. However, it is arguable whether the observed bone formation was induced more by the increased strain frequency or the cycle number, which was increased simultaneously because of invariant loading periods.

Turner et al[154] examined the effect of loading frequencies between 0.1 and 2.0 Hz but constant cycle number on bone formation rate, using the rat ulna model. Only frequencies of $>$ 0.5 Hz resulted in increased bone formation. In another study, at a constant cycle number, an increase in the strain magnitude (360–4.680 mΣ) as well as the frequency (1, 5, 10 Hz) resulted in an increase in the bone formation rate (Figure 4).[133]

Combined results of different in vivo animal loading studies have confirmed the interaction between strain frequency, cycle number, and strain magnitude. In studies that used lower frequencies or cycle numbers, higher strain magnitudes were required to maintain bone mass in immobilized animals. In studies that used high frequencies and cycle numbers, low-strain magnitudes also resulted in preservation of bone (Table 3).

With the exception of Turner et al,[154] it is debatable whether these results can be transferred to clinical practice because frequencies of $>$ 2.5 Hz are difficult to acehieve in exercises such as aerobic dance, running, jumping, and resistance training. In this context, whole-body vibration training on vibration platforms is a promising new training method that uses bone sensitivity to high-frequency, low-intensity strain. All animal studies demonstrated positive results of high-frequency, low-intensity signals on trabecular or cortical bone.[153,155–160] Study results suggest that the sensitivity and adaptative response of trabecular and cortical bone to mechanical loading differ,[161] while high-frequency, low-magnitude strains are more effective for trabecular bone.[155,157] In contrast to the favorable results of animal studies, results of whole-body vibration studies in humans are inconsistent, with positive[162–166] and negative findings.[167–171]

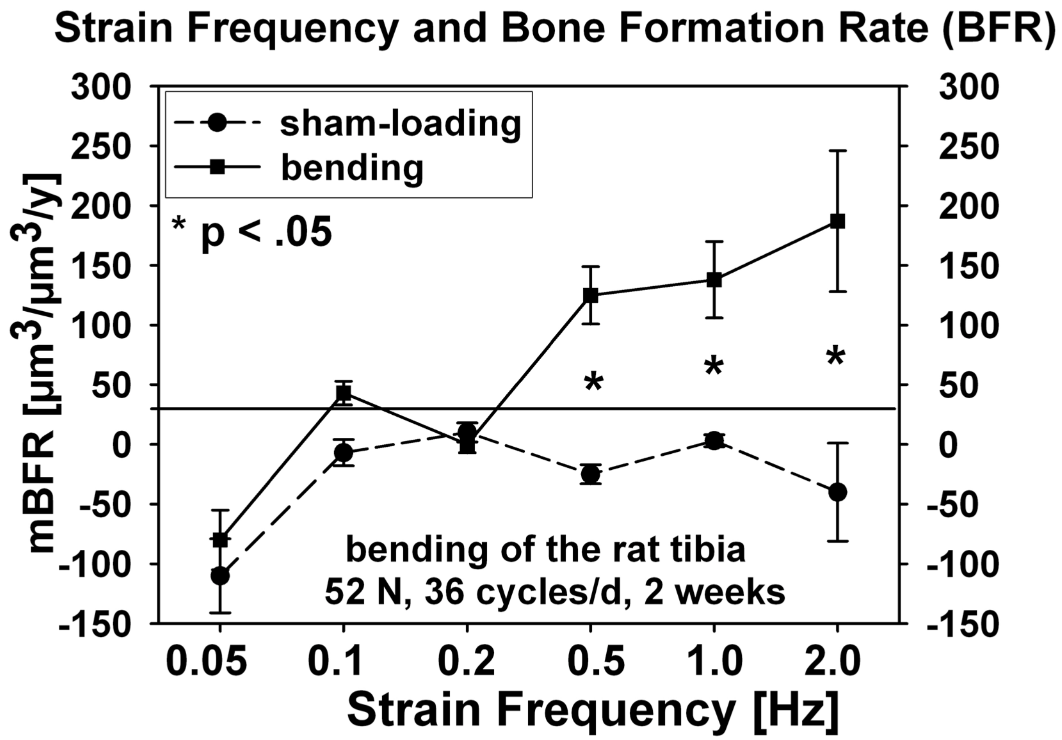
Strain Duration

Strain duration is the duration of a single loading cycle. The relevance of strain duration in exercise programs realted to bone strengthening has not been properly assessed. There is some evidence that static loading was suboptimal to induce relevant positive changes of bone dimensions.[172] However, some studies generated positive effects on bone by static loading protocols.[152,173,174] Although intermittent (dynamic) loading was generally more favorable, a study by McDonald et al[152] demonstrated that static loads (10 N bending of the tibia, 45 minutes/day for 4 weeks) also generate significant positive increases of the mid-tibial cross-sectional area, depending on the strain magnitude. The authors attributed this result to the shorter loading period compared with most other studies with static loading protocols. However, using a protocol with 17 N for 2 weeks, Robling et al[175] observed that 10 minutes per day of static loading had an inhibitory effect on appositional bone formation in rat tibia. In addition, shorter static loading with higher strain magnitude (18 sec, 54 N, for 2 weeks) did not result in relevant changes in bone formation rate.[140] These data indicate that dynamic rather than static exercises should be favored in clinical practice.

Strain Density

Strain density indicates the rest periods between loading periods or cycles, set of cycles, training sessions, or training blocks. The relevance of this parameter is strongly related to desensitization of bone after loading. Some studies suggest that sensitization of bone to mechanical loading may decrease after several loading cycles, at least at higher strain magnitude or rate.[146,176] However, bone desensitization may occur in different time frames.[177] In regards to isolated loading bouts, short rest periods between single loading cycles have been shown to increase osteoanabolic reaction of bone.[178–182] Robling et al[179]

Figure 4. Effect of different strain frequencies on bone formation rate in the rat tibia.



Adapted from Turner et al.[154]

compared the effect of 0.5, 3.5, 7, and 14 seconds of rest between each loading cycle (54 N, 36 cycles, 2 Hz, 4-point bending rat tibia protocol) and observed a substantially higher increase in relative bone formation ratio (66%–190%) for the 14-second approach compared with the other protocols. In addition to the short time effect on bone desensitization, the partitioning of a single session into more frequent, shorter bouts of loading improved the osteogenic response to loading.[179,183,184] After 8 hours of rest between each set of 90 cycles, bone sensitization seemed to be fully restored.[179] In regards to long-term desensitization, a recent study by Saxon et al[185] compared the effects of three 15-week protocols (15 wks of axial compression of the rat ulna with 15 N, 2 Hz, and 360 cycles/day at 3 days/week) on bone strength parameters. However, the 3 protocols differed according to periodization stategy (5 wks of loading/10 wks of rest vs 5 wks of loading with 5 wks of rest 5 wks of loading vs 15 wks of loading, without rest periods). Although all 3 protocols resulted in comparable increases in bone mass and geometry, the effect of the time-off protocol (protocol 2) on bones' work to failure was substantially higher than in the other 2 trials. After 15 weeks, the intermittent program maintained significant changes in bone formation rate, in contrast with the continuous program, which did not show substantial changes in bone formation rate in the last study period. These results may indicate the relevance of periodized exercise programs to maintain or restore bone sensitization.

Exercise Frequency

Due to the generally sedentary nature of Western society, exercise frequency is a critical paramenter when implementing an exercise program; however, few exercise studies have focused on exercise frequency.[186] One study of premenopausal women showed that daily hopping exercises (50 jumps/day with 2.5–2.8 × body weight) significantly increased femoral neck BMD (loaded vs unloaded side), whereas lower frequencies (2–4 sessions/wk) were not effective.[187] In animal studies,[188,189] however, 3 to 4 sessions per week were equally or even more effective than daily protocols. It is difficult to suggest a minimum exercise frequency for effective bone adaptation because other strain parameters confound this relationship. However, exercise studies in humans with attendance rates of $<$ 2 sessions per week[89,95] have failed to demonstrate positive effects on bone parameters. Indeed, a further direct comparison (1–2 vs 2–4 sessions/wk) by retrospective assessment[190] demonstrated the superiority of $>$ 2 sessions per week on BMD changes. After 4 years of resistance exercise with a maximum of 3 sessions per week, Cussler et al[191] confirmed the close positive association between exercise frequency and BMD changes at the lumbar spine, hip, and total body by multiple linear regression analysis. Thus, in addition to a favorable loading composition, the primary factor in successful exercise programs is a moderate-to-high attendance rate.

Summary of Exercise Strategy

When taking together the exercise strategy to reduce fractures, the first step is to identify subject-specific risk factor(s) to adequately address these factors as primary training aims (ie, fall reduction and bone strengthening). In younger subjects, exercise should focus on nonlinear, periodized, high-impact (eg, high-impact aerobic, multidirectional jumps) and high-loading (eg, strength training $\geq$ 70% 1 RM) exercises. Exercises performed with higher movement velocities and adequate rest periods should be carried out $\geq$ 2 times per week.[192] In a periodized mode, "bone blocks" (ie, phases that focus on bone strength) of 6 to 8 weeks should be broken up by periods with lower strain rates/strain magnitudes to restore bone sensitization, prevent overload and injuries, and maintain participant compliance.[98] Ideally, during the rest periods, other aims that are more sensible to exercise volume, such as overweight/adiposity, can be focused on.[193]

In frail elderly patients who are prone to falls, focus should be on exercises that benefit bone strength and fall/impact reduction. Low-impact aerobic or dances that load bone in a multidirectional mode and further train general coordination are of high importance. Depending on the individual's health status, a more specific coordination sequence aimed at improving functional abilities to prevent falls should also be considered.[60] Specific 4- to 5-week blocks of dedicated fall and impact reduction training[60,64] taught by specialists should be offered in addition to a general exercise program. Periodized resistance exercise training performed on machines may be a safe option for achieving high muscular tension and strain magnitudes. Elderly patients who are very frail may use a combined exercise/vibration approach with slow dances, specific fall prevention/impact reduction practice, low-intensity resistance exercise on machines, and whole-body vibration.

Conclusion

Exercise is very effective in reducing the risk of osteoporosis-related fractures. Although there is limited evidence to suggest that exercise interventions provide statistically significant decreases in impact fracture rates, many studies have demonstrated beneficial effects of exercise on addressing risk factors of fractures, such as fall frequency and bone strength. As demonstrated, it is essential to carefully arrange exercise strategy, type of exercise, and strain parameters to optimally reduce fracture risk. When considering that elderly populations often have multiple morbidities,[194] fracture prevention protocols should be included in multicomponent exercise programs so that all important risk factors/diseases of this cohort are addressed. Such protocols may encourage individuals to perform several weekly specific exercise sessions to prevent events related to coronary heart disease, decrease risks of diabetes, prevent sarcopenia and osteoporosis, and reduce low back pain.[186]

Conflict of Interest Statement

Wolfgang Kemmler, PhD and Simon von Stengel, PhD disclose no conflicts of interest.

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