Exercise Prescription for Osteoporosis: Back to Basics

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BECK, B.R. Exercise prescription for osteoporosis: back to basics. *Exerc. Sport Sci. Rev.*, Vol. 50, No. 2, pp. 57–64, 2022. *This Perspectives provides a back-to-basics rationale for the ideal exercise prescription for osteoporosis. The relevance of fundamental principles of mechanical loading and bone adaptation determined from early animal studies is revisited. The application to human trials is presented, including recent advances. A model of broadscale implementation is described, and areas for further investigation are identified.* **Key Words:** bone, evidence-based practice, exercise, medical reimbursement, minimal trauma fracture, osteopenia, osteoporosis

Key Points

- Osteoporosis is a burgeoning painful, disabling, and expensive public health problem of the modern age linked to inactivity.
- Drug therapy is unpopular because of side effects, dramatic withdrawal-related loss, and lack of universal effectiveness.
- Effective group exercise therapy for osteoporosis has recently been identified but requires expert supervision.
- Reimbursement for evidence-based exercise therapy for chronic disease is economically sound and maximizes access for those who need it.

One of the most spectacular accomplishments of the human body is the capacity of the skeleton to adapt to changes in habitual mechanical loading to maintain structural integrity. The ability to detect damage and repair itself is equally physiologically impressive. The failure of bone due to loss of mass and structural integrity toward the end of life, the condition commonly referred to as osteoporosis, undermines the suggestion that bone has a self-sustaining mechanoadaptive response. A closer look, however, reveals that age-related bone loss is a manifestation of the principle. Bone loss across the lifespan parallels age-related sedentarianism. That is, most people progressively unload their skeleton as they age by becoming considerably less active. In fact, individuals who maintain young adult levels of exercise throughout life tend to maintain their bone mass (1–3) and are therefore at reduced risk of low trauma fracture in their later years. For those diagnosed with osteoporosis — defined as low bone mineral density (BMD) (≤−2.5 T-score from dual-energy x-ray absorptiometry [DXA]) or presence of fragility fracture(s) or both — in older age, however, this knowledge is small comfort.

Primarily a condition of later life, the trend of aging populations will increase the already substantial global personal and financial burden of osteoporosis. In 2010, there were an estimated 137 million women and 21 million men over the age of 50 at high risk of osteoporotic fracture, and this number is expected to double by 2040 (4). Although the global economic cost of osteoporotic fractures is difficult to estimate, in the United States alone in 2018, the total annual cost of osteoporotic fractures was $57 billion and estimated to increase to $95 billion by 2040 (5). Traditionally, first-line treatment for osteoporosis is medication; however, compliance is notoriously poor and efficacy is far from universal. Adverse events, although relatively rare, can be serious (6), and discontinuation of certain medication is associated with rapid bone loss and increased risk of fracture (7,8). Harnessing the natural capacity of bone to optimize its strength through exercise, a therapy with few nonresponders or side effects, is an obvious alternative strategy to manage osteoporosis. The fact that exercise will simultaneously prevent the falls that cause fracture enhances its appeal as a therapeutic agent (Fig. 1).

Determining the best exercise prescription for individuals who have already lost substantial amounts of bone has been a problematic endeavor. Loading a fragile skeleton seems counter to the medical tenet of *primum non nocere* — first, do no harm. The following Perspective will provide the

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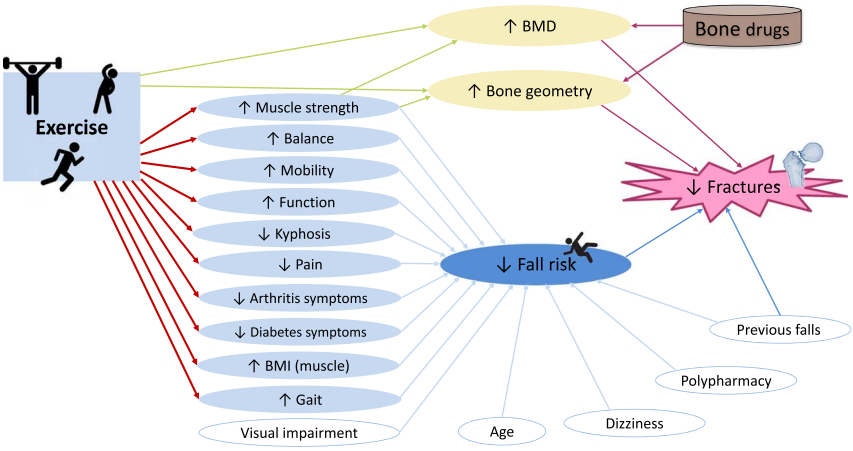

Figure 1. Intuitively, fractures occur when trauma exceeds the intrinsic ability of bone to resist the forces on it. Osteoporotic fractures occur when the material or structural properties of a bone are compromised to the extent that only minimal trauma is required to cause a break. A number of medications enhance bone mineral density (BMD) and bone structure, thereby reducing the propensity to fracture. Nevertheless, the trauma associated with a fall is the most common cause of osteoporotic hip fracture, ergo risk factors for falling are indirect, but powerful, factors of risk for fracture unaffected by medications. This schematic illustrates the comparative predominance of influence of exercise (vs drugs) on risk factors for osteoporotic fracture — acting both directly on bone and indirectly on risk of falling (9–14).

evidence, rationale, and current status of safe and effective exercise prescription for osteoporosis.

CURRENT STATE OF THE FIELD

Optimum Mechanical Load Parameters to Build Bone

Julius Wolff's 1982 treatise proposed that mathematical laws can explain the structural objectives of bone remodeling in response to the functional environment. Although Wolff devoted a large proportion of his career to investigating the premise (15–21) and is credited for its formulation, in fact, others before and after him more fully developed the notion of bone functional adaptation (22–29). These historical comments notwithstanding, the basic premise that the skeleton can adapt to alterations in its mechanical environment with optimal morphological efficiency is well accepted and attributed to Wolff. Since the 1970s, a considerable body of evidence from animal research has accumulated to support Wolff's law (30–52) and has established the mechanical load parameters most conducive to the enhancement of bone mass and strength.

Some of the earliest investigations (30,53) demonstrated that static loading is not a remodeling stimulus, and others have since confirmed it has either no measurable effect on bone adaptation or a negative effect similar to a disuse response (30,35,36,54–56). Thus, the first principle of exercise intervention for bone health is that loading should be dynamic or, in other words, *loading must be applied cyclically*.

It then became evident that there was a positive relation between the magnitude of induced strain (bone deformation under load) and the quantity of new bone formed (35–37), culminating in the landmark work of Rubin and Lanyon in 1985 that demonstrated a strong linear relation between load and response ($r = 0.83$) (57). This seminal work underpins the second principle of exercise intervention for bone health; bone loading (at physiological frequencies) must exceed the regular bone strain milieu to induce an adaptive response, in other words, *loading must be greater than that to which a bone is usually exposed*.

Next, frequency of loading (loads per second; Hertz) was recognized as an influential adaptative stimulus (58–62). A complex interaction with load magnitude was revealed in that as frequency of loading increases, the magnitude of load required to stimulate the adaptive response decreases. Low strain magnitudes (250 microstrain) did not maintain bone mass in turkeys when applied at a frequency of 1 Hz, but at 15 Hz, substantial new bone was formed (58). In fact, even lower (50–200 microstrain) strains, such as dominate the skeleton's 24-h strain history (59), become osteogenic if induced in the 15- to 50-Hz domain (60). The physical inability of humans to actively apply mechanical loads at high frequency (*e.g.*, walking and running load frequency is typically only 1–2 Hz (63)) led to the development of vibration technology as a potential passive low-magnitude mechanical intervention for osteoporosis (64). Further discussion of this therapeutic modality is beyond the scope of the current work but has been presented elsewhere (65).

Frequency manifests in two elements that are physiologically interrelated; 1. cycle number (number of times a load is applied in a loading bout) and 2. strain rate (the time taken to reach peak strain under load). Both have relevance for exercise prescription.

Relatively few load cycles are necessary to stimulate a bone response. Although unloading bone (0 cycles per day) induces bone loss, only 4 cycles per day of 1200 microstrain of abnormal strain distribution at 0.5 Hz were required to maintain bone mass, and 36 load cycles of the same protocol elicited a 42% increase in bone mineral content in Rubin and Layon's turkey ulna model (40,66). Increasing the number of cycles beyond 36 did not notably increase the response, suggesting that the mechanosensory mechanism saturates quickly. Very low magnitude loads and low strain rates do not initiate remodeling, even with a large number of cycles. These observations not only reinforce the predominance of strain magnitude as the adaptive stimulus but also illustrate the third important principle of exercise prescription for bone, which is, if the load is sufficient to stimulate the adaptive response, *few load cycles are required each bout*.

Speed of loading is intrinsically linked to load frequency as higher frequency loading naturally will increase rate of strain. Thus, it is unsurprising that, like high frequency loading, high strain rates will induce a greater adaptive response than low

strain rates (67). In 1982, O'Connor *et al.* (39) were the first to observe that strain rate predicted 68%–81% of the magnitude of bone deposition on the cortex of sheep bone under bending loads. Crucially though, higher strain rates also cause more microdamage and greater loss of stiffness than lower (68–75). These findings underpin the fourth principle of exercise prescription for bone, which is that a fast rate of loading may be more osteogenic than slow, but the application of this principle is somewhat fraught. Although the effects of loading at different rates is yet to be fully tested in an osteoporotic sample, power training (rapid rate of loading) maintained BMD at the spine and total hip compared with BMD losses in regular strength training (76). In light of these very modest findings, a loading protocol with an increased risk of microdamage arguably represents an unnecessary risk to the fragile bones of osteoporotic individuals when other effective forms of exercise exist.

The ideal method to apply osteogenic loading has not yet been fully determined. Gravity is the single most constant source of loading to which terrestrial skeletons are exposed and without it bone is rapidly lost (77). Muscle is the kinesiological answer to gravity, resisting the loads of body mass and producing movement by applying forces to bones. In fact, muscles have the capacity to exert larger forces on bone than gravity, and the withdrawal of muscle force also is associated with bone loss (78). That elite-level swimming (79) and cycling (80) do not result in higher than average bone mass however, and the human experience in microgravity, suggests that gravity-induced weightbearing loads are a critical element of the bone strain milieu (66). The intrinsic interdependence of gravitational and muscle forces prevents a determination of relative importance for bone, so the point is, in fact, largely academic. Combining impact *and* muscle loading in an exercise prescription for osteoporosis is clearly justified.

Translation to Clinical Trials

In lieu of a comprehensive summary of trials that is not feasible here, findings from a slew of meta-analyses of exercise interventions for bone into the early 21st century illustrate somewhat unimpressive outcomes (81–84). The modesty of effect reported in those findings, however, reflects a number of confounding features of the included studies: 1. almost universal use of BMD as the proxy for bone mass and strength, 2. the practice of excluding individuals with osteoporosis, 3. inadequate load magnitude of exercise interventions, and 4. an absence of fracture data.

To address the first confound, BMD from DXA is a recognized blunt instrument for tracking changes in response to exercise intervention. In fact, clear evidence that the benefit of exercise for bone occurs through morphological changes that influence the strength of bone has long been available. In 1981, in a 1-yr study of pigs that ran for 1 $h \cdot d^{-1}$, no differences were found in bone density, ash weight, or calcium content. Instead, femoral cortical thickness increased 12%, cross-sectional area increased 23%, minimum and maximum area moments of inertia increased 21% and 27%, ultimate bending load increased 35%, and maximum stored energy increased 32% (85)! Clearly, structural adaptation, not adaptation of material properties, improved the ability of bone to withstand increased loading. Thus, the failure of many trials to detect a benefit of exercise for bone is likely related to the preponderance of BMD reporting. Indeed, the recent lifting intervention for training muscle and osteoporosis rehabilitation (LIFTMOR) trial observed only maintenance of BMD at the femoral neck after 8 months of high-intensity resistance and impact training (HiRIT) but marked femoral neck cortical bone thickening (86) (Fig. 2).

With respect to the second common confound of past exercise trials, individuals with the lowest bone mass exhibit the largest response to mechanical load interventions, a phenomenon that was coined by the late Barbara Drinkwater as the principle of initial values (87,88). This observation is a clear illustration of Wolff's law in that an inadequately strong bone will deform more under load and therefore receive a stronger adaptive stimulus to resist future loading than a bone that is already able to withstand the load. Thus, an exercise trial including participants with "normal" bone mass/strength would be less likely to observe an effect than one including participants with lower-than-average bone mass.

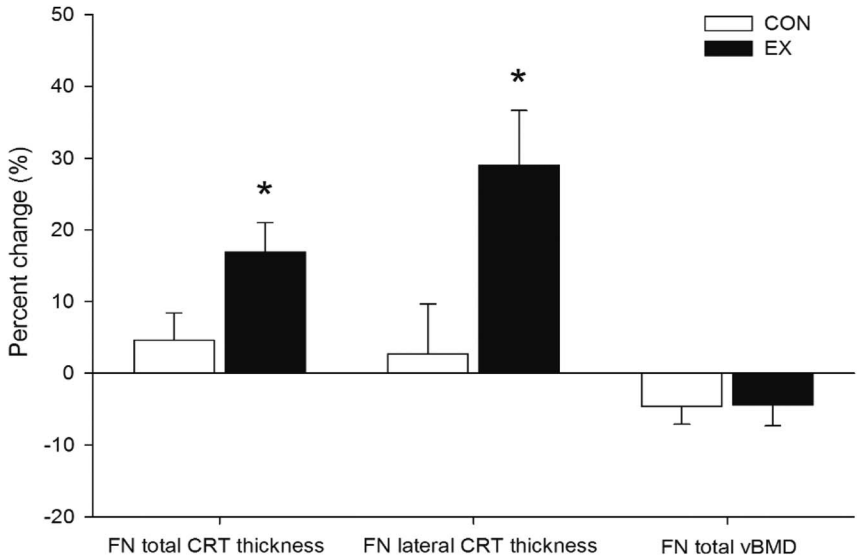

Figure 2. Eight months of high-intensity resistance and impact training (HiRIT) improved total and lateral femoral neck cortical thickness (net benefit: 12.3%, $P = 0.014$ and 29.3%, $P = 0.003$, respectively) in the absence of bone mineral density (BMD) change (unpublished plot from the LIFTMOR trial (86)). CON, control group; EX, HiRIT group; FN, femoral neck; CRT, cortical; vBMD, volumetric BMD.

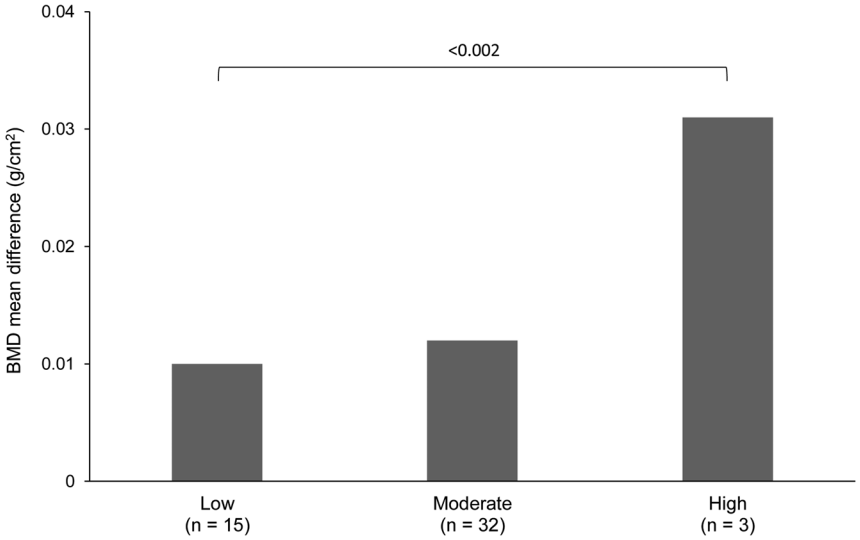

Figure 3. High-intensity exercise improves lumbar spine bone mineral density (BMD) more effectively than low- or moderate-intensity exercise (unpublished plot from comprehensive meta-analysis; Kistler-Fischbacher *et al.* (9)).

The third confound is intrinsically related to the second. An exercise load must impose greater strains in bone than regular loading to provoke an adaptive response, so habitual interventions such as walking and light resistance training will be ineffective stimuli for most normally active individuals, even older adults. That exercise trials have routinely applied interventions of insufficient magnitude to stimulate a bone response was recently demonstrated in a very comprehensive systematic review (89) and meta-analysis (9) where the influence of exercise intensity was parsed out. These reviews clearly demonstrated both the historical predominance of low- to moderate-intensity exercise trials, and the greater efficacy of higher-intensity exercise for improving lumbar spine BMD (Fig. 3).

The fourth and final confounding feature of most exercise randomized controlled trials, the lack of fracture data, is function of trial feasibility. Health care providers understandably make therapeutic decisions based on available evidence. Osteoporosis medications can be tested in very large-scale trials that are powered to detect antifracture efficacy because they are funded by pharmaceutical companies with deep pockets. Exercise trials do not have the same commercial or pecuniary implications and, thus, do not attract large-scale funding. In 2008, Moayyeri *et al.* (90) calculated a sample size of 4812 per group would be required to examine fracture end points in an exercise intervention in European women. As an exercise trial involving nearly 10,000 participants is generally thought to be

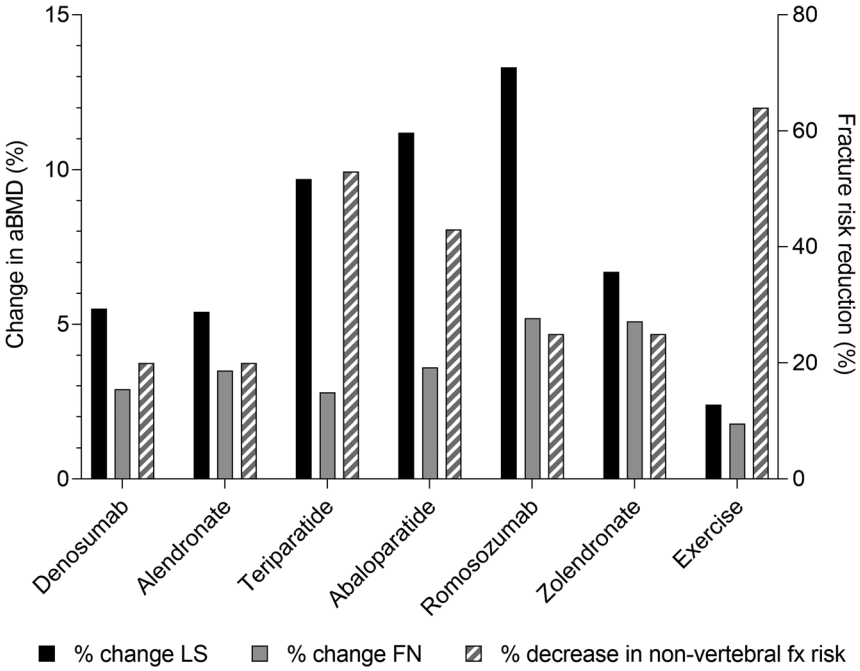

Figure 4. Data from drug trials testing common osteoporosis medications show that although drugs may improve bone mineral density (BMD) at the spine and hip more than exercise (not including high intensity resistance and impact training [HiRIT]), exercise provides superior protection from fracture. [NB. A degree of heterogeneity exists in the drug study durations, ranging from 12 to 36 months (96–103); exercise data was drawn from meta-analyses (10,83)].

unfundable, we rely instead on the results of meta-analyses of randomized controlled trials (10) and cohort studies (90–95). Those data suggest a dramatic benefit of exercise for fracture prevention; better even than the best medication (Fig. 4). A meta-analysis, including 13 controlled trials and 1424 participants over 45 yr of age, found exercise more than halved the incidence of fracture (10). Primary care providers have been slow to recognize these data.

The first investigations to control for three of the above confounds were the LIFTMOR (postmenopausal women) (86), the LIFTMOR-M (older men) (104), and the medicine and exercise for osteoporosis (MEDEX-OP) trials (postmenopausal women on or off medications) (105). In those studies, only osteopenic and osteoporotic participants were included, bone geometry was examined in addition to BMD, and a program of truly HiRIT was implemented. Those trials revealed a consistently positive BMD effect at the spine, structural improvement at the hip (84,106), and, importantly, a high level of safety (no increased risk of fracture from HiRIT) (107,108). Coupled with impressive improvements in functional performance and posture, this HiRIT intervention addressed risk of osteoporotic fracture both by improving bone strength and by reducing the risk of falls — the nemesis of osteoporosis (Fig. 1). In effect, this series of trials finally connected the fundamental principles of effective exercise loading determined from animal trials to safe and effective exercise therapy for osteoporosis.

Translation to Clinical Practice

Highly controlled clinical trials are, by their very nature, artificial environments and, therefore, rarely represent "real life." The safety of the HiRIT program in the LIFTMOR and MEDEX-OP trials was mediated by expert supervision with close attention to technique, graduated introduction, and appropriate progressions. This need for expert supervision in the real world introduces cost, which some consider to be a hurdle to broadscale implementation. There are two obvious flaws in such reasoning. The first is medications involve cost that does not preclude their adoption. The second is *not* implementing a known effective intervention because of perceived cost is the therapeutic equivalent of throwing the baby out with the bath water. Many people are willing to pay for exercise therapy and indeed prefer to do so than take medications. Furthermore, if governments already reimburse drug therapy for osteoporosis, why not an equally effective treatment with fewer side effects and more ancillary benefits?

The questions of translational (will it be as effective in the real world?) and public health efficacy (will people do it of their own accord?) could be answered only by testing the HiRIT program in clinical practice. To do so, in 2015, a translational research clinic (The Bone Clinic, Brisbane, Australia) was established in the community. In this novel real-world experiment, the HiRIT program (dubbed Onero, from the Latin for overload) is delivered by trained exercise professionals to clients who pay for classes, which are run in groups with a coach-to-client ratio of 1:8. In this way, true feasibility can be determined for the target demographic. Effectiveness can be determined by comprehensive assessment and monitoring, including compliance and adverse events. Preliminary evidence (4-year data) indicates the HiRIT program continues to be as safe and effective under real-world supervised conditions as in the clinical trials (Fig. 5) (109). The HiRIT program has been licensed for delivery by independent physiotherapists and exercise physiologists to extend reach of the program nationally and internationally, including the research elements.

It is well-recognized that individuals with limited income access lifestyle interventions, such as gym memberships, less frequently than those with higher incomes. It also is well accepted that many governments subsidize medications to level the playing field and ensure that drugs are available to all who need them. Considering the known substantial and almost ubiquitous benefits of exercise for chronic disease, there is an undeniable argument for similar reimbursement of evidence-based therapeutic exercise. The burden of chronic disease to taxpayer-funded

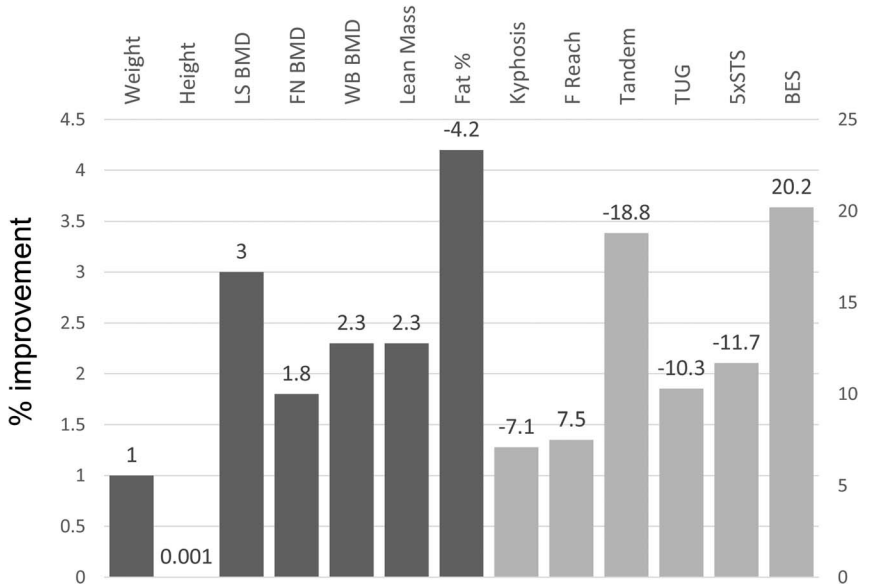

Figure 5. Twelve-month mean percent improvement in bone and functional outcomes after supervised high intensity resistance and impact training (HiRIT) in the real-world clinical setting (n = 415; mean age 63.4 ± 7.7 yr, 6% men, 60.4 ± 32.4% compliance) (109). BES, back extensor strength; BMD, bone mineral density; FN, femoral neck; F Reach, functional reach; LS, lumbar spine; STS, sit to stand; T, total; TUG, timed up and go; WB, whole body.

health care systems is enormous and growing. Economic evaluations of exercise therapy for multiple conditions, but particularly musculoskeletal conditions, show clear financial advantage in addition to the population health benefit (110,111).

GAPS IN KNOWLEDGE AND KEY QUESTIONS TO MOVE THE FIELD FORWARD

Future research endeavors should focus on fine-tuning important remaining aspects of exercise prescription for osteoporosis. Dose response is a fundamental element of any exercise recommendation and remains to be determined for HiRIT. The LIFTMOR and MEDEX-OP trials showed that 2 $d \cdot wk^{-1}$ is sufficient to elicit benefit, but it is not known whether 1 $d \cdot wk^{-1}$ is enough, nor whether 3 $d \cdot wk^{-1}$ provides greater benefit. The interaction between HiRIT and osteoporosis medications also is not well understood and would be a major clinical advance. The recent meta-analysis (9) and the MEDEX-OP trial (105) made some inroads into this question, but more data are needed. The question as to whether HiRIT can prevent the loss of bone that occurs with discontinuation of certain bone medications (7) also is clinically relevant. Finally, the ability of HiRIT to protect bone from conditions and therapies known to be harmful to bone, such as rheumatoid arthritis and chemo and corticosteroid therapies, is worthy of investigation to improve patient outcomes. No doubt additional data reporting safety and compliance of HiRIT will reassure clinicians and exercise professionals to recommend/adopt high-intensity exercise for osteoporosis therapy. Efforts to increase awareness of primary care providers of the presence of clinical exercise practitioners who are trained to manage patients with prevalent fractures are indicated.

FUTURE PERSPECTIVES

My intentional focus in the current Perspectives on what some might consider to be the ancient history of our field was to reconnect modern-day exercise prescription for osteoporosis with the fundamental principles of effective bone loading identified many years ago. Until recently, the application of those principles to the human condition was eschewed by fears that high-magnitude loading would cause fractures in frail osteoporotic skeletons. However, applying low-magnitude loading as an alternative has been an abject failure as a bone stimulus. It is, therefore, hardly surprising that when the recent LIFTMOR trials applied true principles of effective bone loading in older adults with low bone mass, they showed great efficacy. To have done so safely was the final clinical barrier, and practice changing.

The volume of data demonstrating the undeniable benefits of targeted therapeutic exercise for chronic disease, the paucity of adverse effects, and the myriad of ancillary benefits suggest exercise is a veritable panacea for the innumerable diseases and conditions attributed to sedentary lifestyles in the 21st century. Some conditions respond to exercise programs that require no supervision and few require no resources, such as walking. Others, including osteoporosis, require a much higher-intensity exercise protocol that is inherently hazardous unless expertly supervised. Access to evidence-based therapy, be it exercise or medication, is an egalitarian issue. That is, government medical reimbursement schemes have been established on the grounds that treatment should not be based on whether or not a person can afford it. Inclusion of evidence-based exercise therapy in such schemes is long overdue for many chronic diseases, to which we now confidently can add osteoporosis.

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