Exercise and Anti-Osteoporotic Medication Combined Treatment for Osteoporosis

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Abstract

Antiosteoporotic medications are often used to reduce fracture risk and treat osteoporosis. Similarly, regular physical activity also plays an important role in both maintaining and improving bone density. Recently, it has been shown that exercise combined with osteoporosis medications may produce greater benefits on bone associated with osteoporosis than either intervention alone. This commentary evaluates the current literature mostly produced in our laboratory from animal models to determine the optimal combination of physical exercise and medications on osteoporosis induced by ovariectomy and exogenous glucocorticoids. The data suggest that both approaches enhance bone healing, however the combined effects of these two therapies do not appear to produce any remarkable synergistic or additive effects. Clinical studies are needed to fully understand the effects of exercise and selective medications on bone remodelling in order to optimise treatment of fragility fractures in patients with underlying osteoporosis.

Introduction

Several approaches have been used to treat osteoporosis in order to reduce fracture risk, including therapies and increasing physical activity. Osteoporosis medications increase bone mineral density either by decreasing bone resorption (i.e. Bisphosphonates, Zoledronic Acid, Risedronate, Alendronate), Calcitonin, Selective Estrogen Receptor Modulators, e.g., Raloxifene or bazedoxifene) and their combination (SERM and estrogens), or by increasing bone formation using osteoanabolic agents (i.e. Teriparatide, a recombinant human parathyroid hormone), or by modulating the balance of both approaches (Strontium ranelate) [1-6].

Antibody-mediated inhibition of sclerostin, a pivotal negative regulator of bone formation, represents a promising new therapeutic approach for the anabolic treatment of bone-related disorders including postmenopausal osteoporosis [7]. Sclerostin is a protein produced primarily by osteocytes, and inhibits osteoblastic activity on the surface of bone by binding to low-density lipoprotein receptors and inhibiting the Wnt/β-catenin signalling pathway [7,8]. Disruptions in signalling pathways among these cells and alterations in their activity are considered to be part of the pathophysiology of osteoporosis [9,10].

Physical activity increases mechanical stresses within bone which in turn signals osteoblastic activation and decreased osteoclast resorption [8,11]. The mechanical stresses generated by physical exercise are primarily detected by the osteocytes which transduce these mechanical strains into biological signals [8,12-14]. This anabolic pathway due to mechanical loading has been reported to be mainly related to the modulation of sclerostine levels [15]. In addition up-regulation of RANKL production by the osteocytes might stimulates osteoclast activity [16]. Besides these essential signalling pathways, exercise produces changes in circulating levels of hormones including growth hormone (GH) and insulin-like growth factor (IGF)-1, which together have an anabolic effect on both bone and skeletal muscle [12,13,17].

Several forms of physical activity are known to increase bone mass including high-impact exercise as well as moderate impact activities such as running [18,19]. Animal studies suggest that impact exercise improves bone mass, promotes increases in bone mineral density (BMD) as well as adaptations in the trabecular microarchitecture (increased bone volume/tissue volume, trabecular thickness and number, porosity) [20,21]. Treadmill running is often employed as a strategy to enhance bone remodelling. This approach increases bone formation and decreases bone resorption in the weight bearing sites of rats [20-25]. Similarly, BMD and trabecular bone microarchitecture adapt in growing rats subject to running [22,23,26].

Recently, we have hypothesized that the combined effects of exercise and osteoporosis medications may produce greater benefits on osteoporotic bone than either intervention alone. Several drugs combined with physical exercise have been tested. In the first study, the effects of zoledronic acid, treadmill running and their combination were evaluated in 6 month old ovariectomised (OVX) female rats. zoledronic acid alone prevented the ovariectomy-induced trabecular bone loss and its subsequent trabecular microarchitectural deterioration. Treadmill running was shown to preserve bone strength and to induce bone turnover changes in favor of bone formation. However, the combined effects of zoledronic acid and running together did not produce any additional benefits [27]. More recently, we investigated the effects of anti-sclerostin antibody (Scl-Ab), running and their combination on bone formation in 8 month old ovariectomised female rats [28]. Running decreased fat mass as well as expression of the bone resorption marker Telopeptide N of type I collagen (NTX) relative to the non-exercised control groups. Changes in the latter were associated with a prevention of the deleterious effects of OVX on whole body and femoral BMD. Scl-Ab increased expression of the bone formation marker osteocalcin and also resulted in increases in BMD and femoral metaphyseal bone volume to levels greater than in the Sham (S)
group. Scl-Ab combined with exercise did not further impact bone mass relative to the OVX+S group. Within the cortical femur diaphysis, Scl-Ab prevented decreases in bone strength after OVX, however exercise alone did not affect cortical bone strength. It has been suggested that while running on a treadmill can prevent some bone loss through a modest antiresorptive effect, it did not contribute to the robust bone-forming effects of Scl-Ab observed in our estrogen ablation model.

More recently, the effects of Scl-Ab and interval treadmill training have been tested in a rodent model of glucocorticoid-induced osteopenia. Our findings showed that Exercise alone increased both BMC or cortical microarchitectural parameters. Scl-Ab increased bone resorption marker NTx, and osteocyte apoptosis. Exercise did not affect BV/TV and osteocyte lacunae occupancy, while reducing fat mass, the osteopenia. Our findings showed that Exercise alone increased both effects of glucocorticoids on bone mass, further increasing BMC, BMD and BV/TV to levels above the C group. Scl-Ab increased femoral cortical bone parameters at distal part and midshaft. Scl-Ab prevented the decrease in osteocyte lacunae occupancy and the increase in osteocyte apoptosis induced by glucocorticoid. The addition of exercise to Scl-Ab treatment did not result in additional improvements in bone mass or bone strength parameters [29]. Currently, in a pilot study, we are examining the cumulative effects of SrRan and free-fall impact exercise in an ovariectomised female rat model. Preliminary analysis showed that both SrRan and exercise demonstrated a significant additive effect for these parameters (PC. Aveline, "Cumulative effects of strontium ranelate and free-falol impact exercise in a female ovariectomized rat model", ASBMR Minneapolis, 2012.poster). These results were consistent for the femur, tibia and lumbar vertebrae (Figure 1).

**Table 1:** Trabecular and cortical bone microarchitectures at the left femurs of Wistar female rats. The rats in O groups were ovariectomized. Rats in E groups were running on a treadmill can prevent some bone loss through a modest antiresorptive effect, it did not contribute to the robust bone-forming effects of Scl-Ab observed in our estrogen ablation model.

![Figure 1](image1.png)
However, exercise alone did not significantly reduce osteocyte apoptosis in SHAM and OVX groups while SrRan significantly reduced osteocyte apoptosis in all groups. These data support an additive effect of physical exercise combined with drug treatment and suggest that the modality of exercise may be the key variable. There is also increasing evidence for chronic disease management in the primary care setting and the role of case managers. This may be a strategy to consider implementing in the management of those with bone fragility and osteoporosis [30].

In summary, antosteoporotic drugs (Zoledronic Acid, Scl-Ab and SrRan) or physical exercise increased bone formation, bone mass, and bone strength in fragile bone induced by ovariectomy and glucocorticoid-induced osteopenia models. Yet, combined effects of exercise and osteoporosis medications produced higher benefits only when combined with SrRan. Further research is needed to determine the optimal dose and domain/intensity of physical activity for osteoporosis treatment.

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