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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 synergetic 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 ovariectomized (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 ovariectomized 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)

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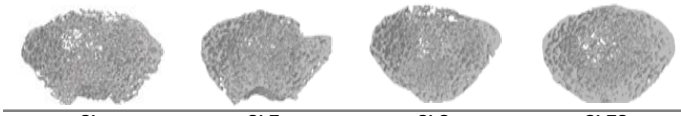
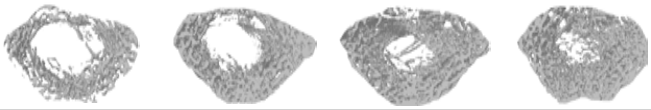
group. Scl-Ab combined with exercise did not further impact bone mass relative to the OVX+S group. Within the cortical femur diaphysis, Scl-Ab prevented decreases in bone strength after OVX, however exercise alone did not affect cortical bone strength. It has been suggested that while running on a treadmill 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 BV/TV and osteocyte lacunae occupancy, while reducing fat mass, the bone resorption marker NTx, and osteocyte apoptosis. Exercise did not affect BMC or cortical microarchitectural parameters. Scl-Ab increased the bone formation marker osteocalcin and prevented the deleterious 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).



			Sh n = 12	ShE n = 12	ShSr n = 12	ShESr n = 12
Left Femurs	Trabecular Bone	BV/TV (%)	22.002 ± 1.647 b c d e f h ***	31.692 ± 1.293 a d e f g h ***	32.091 ± 0.790 a d e f g h ***	35.062 ± 1.057 *vs* all ***
		Tb.Th (mm)	0.103 ± 0.004 *vs* all ***	0.115 ± 0.004 a c d e g h ***, f **	0.138 ± 0.006 a b e f h ***	0.14 ± 0.005 a b e f h ***
		Tb.N (1/mm)	2.143 ± 0.115 *vs* all ***	2.765 ± 0.068 *vs* all ***	2.339 ± 0.102 *vs* all ***	2.499 ± 0.068 *vs* all ***
		Tb.Sp (mm)	0.254 ± 0.022 b e f g h ***, c *	0.216 ± 0.014 *vs* all ***	0.28 ± 0.030 a*, b e f g h ***	0.263 ± 0.019 b e f g h ***
		Tb.Pf (1/mm)	6.556 ± 1.156 *vs* all ***	0.839 ± 0.667 a d e f h ***	0.201 ± 0.923 a d e f h ***	(-)1.91 ± 1.017 a b c e f g ***
		SMI	1.849 ± 0.109 *vs* all ***	1.311 ± 0.103 a e f ***, d**, g h*	1.274 ± 0.105 a e f ***, g**, d*	1.112 ± 0.152 a e f g ***, b**, c *
	Cortical Bone	Ct.Po (%)	0.038 ± 0.015 c **, d h ***	0.031 ± 0.010 d *, h ***	0.020 ± 0.013 a **	0.017 ± 0.013 a ***, b f *
		Ct.Th (mm)	0.475 ± 0.038 c d f g h ***, e **	0.51 ± 0.054 c d e f g h ***	0.534 ± 0.041 a b ***	0.545 ± 0.063 a b ***, e *
		Po.N (1/mm)	0.011 ± 0.004 c d g **, e *, h ***	0.009 ± 0.003 c d g **, h ***	0.005 ± 0.003 a b **	0.005 ± 0.003 a b **
		Po.Sp (mm)	0.971 ± 0.035 e g **, f h ***	0.972 ± 0.048 e g *, f h ***	0.934 ± 0.042 a *, d **, e f g h ***	0.990 ± 0.027 c **, e g *, f h **



			O n = 12	OE n = 12	OSr n = 12	OESr n = 10
Left Femurs	Trabecular Bone	BV/TV (%)	6.287 ± 0.866 *vs* all ***	19.017 ± 3.074 a *, b c d e g h ***	22.227 ± 0.631 b c d e h ***, f *	26.675 ± 0.534 *vs* all ***
		Tb.Th (mm)	0.092 ± 0.004 *vs* all ***	0.124 ± 0.008 *vs* all ***	0.141 ± 0.006 a b e f ***, h **	0.154 ± 0.009 a b c d e f ***, g **
		Tb.N (1/mm)	0.683 ± 0.099 *vs* all ***	1.522 ± 0.195 a b c d e ***, h **	1.577 ± 0.083 a b c d e h ***	1.739 ± 0.092 a b c d e g ***, f **
		Tb.Sp (mm)	1.150 ± 0.260 a b c d ***, g h **	0.995 ± 0.177 a b c d ***, g *, h **	0.811 ± 0.152 a b c d ***, e **, f *	0.779 ± 0.165 a b c d ***, e f **
		Tb.Pf (1/mm)	16.644 ± 2.005 *vs* all ***	3.231 ± 1.976 a b d e h ***, b g *	0.508 ± 1.442 a d e h ***, f **	(-)1.978 ± 1.309 a b c e f g ***
		SMI	2.385 ± 0.106 *vs* all ***	1.654 ± 0.091 *vs* all ***	1.452 ± 0.112 a d e f h ***, b c *	1.19 ± 0.124 a e f g ***, b *
	Cortical Bone	Ct.Po (%)	0.026 ± 0.012 h **	0.031 ± 0.017 h **, d *	0.026 ± 0.016 g **	0.010 ± 0.007 a b ***, e f g **
		Ct.Th (mm)	0.413 ± 0.026 b ***, a g **, d h *	0.398 ± 0.032 a b ***	0.503 ± 0.044 a b ***, e **	0.512 ± 0.035 a b ***, e *
		Po.N (1/mm)	0.007 ± 0.003 h **, a *	0.008 ± 0.004 h **	0.006 ± 0.003 a h **, b *	0.003 ± 0.002 a b ***, e f g **
		Po.Sp (mm)	1.021 ± 0.025 c ***, a **, b d f h *	1.064 ± 0.054 a b c d ***, e*	1.031 ± 0.055 a b d *, c ***	1.069 ± 0.043 a b c d ***, e *

Figure 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 submitted to 10 free-fall impact exercise per day, 5 days a week during 8 weeks. Rats in Sr groups received 625 mg/kg/day of SrRan. The critical p-value were p = 0.05: *, p < 0.01: **, p < 0.001: ***, NS: non significant and a: vs Sh, b: vs ShE, c: vs ShSr, d: vs ShESr, e: vs O, f: vs OE, g: vs OSr and h: vs OESr.

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, antiosteoporotic 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.

References

1. Boyce BF, Rosenberg E, de Papp AE, Duong LT (2012) The osteoclast, bone remodelling and treatment of metabolic bone disease. Eur J Clin Invest 42: 1332-1341.
2. Lippuner K (2012) The future of osteoporosis treatment - a research update. Swiss Med Wkly 142: w13624.
3. Ng KW (2009) Future developments in osteoporosis therapy. Endocr Metab Immune Disord Drug Targets 9: 371-384.
4. Migliaccio S, Brama M, Spera G (2007) The differential effects of bisphosphonates, SERMS (selective estrogen receptor modulators), and parathyroid hormone on bone remodeling in osteoporosis. Clin Interv Aging 2: 55-64.
5. Ohtori S, Inoue G, Orita S, Yamauchi K, Eguchi Y, et al. (2013) Comparison of teriparatide and bisphosphonate treatment to reduce pedicle screw loosening after lumbar spinal fusion surgery in postmenopausal women with osteoporosis from a bone quality perspective. Spine (Phila Pa 1976) 38: E487-492.
6. Kaufman JM, Audran M, Bianchi G, Braga V, Diaz-Curiel M, et al. (2013) Efficacy and safety of strontium ranelate in the treatment of osteoporosis in men. J Clin Endocrinol Metab 98: 592-601.
7. Li X, Ominsky MS, Warmington KS, Morony S, Gong J, et al. (2009) Sclerostin antibody treatment increases bone formation, bone mass, and bone strength in a rat model of postmenopausal osteoporosis. J Bone Miner Res 24: 578-588.
8. Bonewald LF (2011) The amazing osteocyte. J Bone Miner Res 26: 229-238.
9. Boyce BF, Rosenberg E, de Papp AE, Duong LT (2012) The osteoclast, bone remodelling and treatment of metabolic bone disease. Eur J Clin Invest 42: 1332-1341.
10. Cary RL, Waddell S, Racioppi L, Long F, Novack DV, et al. (2013) Inhibition of ca(2+) /calmodulin-dependent protein kinase kinase 2 stimulates osteoblast formation and inhibits osteoclast differentiation. J Bone Miner Res 28: 1599-1610.
11. Robergs RA, Icenogle MV, Hudson TL, Greene ER (1997) Temporal inhomogeneity in brachial artery blood flow during forearm exercise. Med Sci Sports Exerc 29: 1021-1027.
12. Klein-Nulend J, Bacabac RG, Veldhuijzen JP, Van Loon JJ (2003) Microgravity and bone cell mechanosensitivity. Adv Space Res 32: 1551-1559.
13. Klein-Nulend J, Nijweide PJ, Burger EH (2003) Osteocyte and bone structure. Curr Osteoporos Rep 1: 5-10.
14. Uzbekov RE, Maurel DB, Aveline PC, Pallu S, Benhamou CL, et al. (2012) Centrosome fine ultrastructure of the osteocyte mechanosensitive primary cilium. Microsc Microanal 18: 1430-1441.
15. Tu X, Rhee Y, Condon KW, Bivi N, Allen MR, et al. (2012) Sost downregulation and local Wnt signaling are required for the osteogenic response to mechanical loading. Bone 50: 209-217.
16. Wijenayaka AR, Kogawa M, Lim HP, Bonewald LF, Findlay DM, et al. (2011) Sclerostin stimulates osteocyte support of osteoclast activity by a RANKL-dependent pathway. PLoS One 6: e25900.
17. Toumi H, Higashiyama I, Suzuki D, Kumai T, Bydder G, et al. (2006) Regional variations in human patellar trabecular architecture and the structure of the proximal patellar tendon enthesis. J Anat 208: 47-57.
18. Ju YI, Sone T, Ohnaru K, Choi HJ, Fukunaga M (1985) Differential effects of jump versus running exercise on trabecular architecture during remobilization after suspension-induced osteopenia in growing rats. J Appl Physiol 112: 766-772.
19. Umemura Y, Ishiko T, Tsujimoto H, Miura H, Mokushi N, et al. (1995) Effects of jump training on bone hypertrophy in young and old rats. Int J Sports Med 16: 364-367.
20. Honda A, Sogo N, Nagasawa S, Shimizu T, Umemura Y (2003) High-impact exercise strengthens bone in osteopenic ovariectomized rats with the same outcome as Sham rats. J Appl Physiol (1985) 95: 1032-1037.
21. Honda A, Umemura Y, Nagasawa S (2001) Effect of high-impact and low-repetition training on bones in ovariectomized rats. J Bone Miner Res 16: 1688-1693.
22. Iwamoto J, Shimamura C, Takeda T, Abe H, Ichimura S, et al. (2004) Effects of treadmill exercise on bone mass, bone metabolism, and calciotropic hormones in young growing rats. J Bone Miner Metab 22: 26-31.
23. Iwamoto J, Takeda T, Sato Y (2005) Effect of treadmill exercise on bone mass in female rats. Exp Anim 54: 1-6.
24. Iwamoto J, Yeh JK, Aloia JF (1999) Differential effect of treadmill exercise on three cancellous bone sites in the young growing rat. Bone 24: 163-169.
25. Hagihara Y, Nakajima A, Fukuda S, Goto S, Iida H, et al. (2009) Running exercise for short duration increases bone mineral density of loaded long bones in young growing rats. Tohoku J Exp Med 219: 139-143.
26. Joo YI, Sone T, Fukunaga M, Lim SG, Onodera S (2003) Effects of endurance exercise on three-dimensional trabecular bone microarchitecture in young growing rats. Bone 33: 485-493.
27. Lespessailles E, Jaffré C, Beaupied H, Nanyan P, Dolléans E, et al. (2009) Does exercise modify the effects of zoledronic acid on bone mass, microarchitecture, biomechanics, and turnover in ovariectomized rats? Calcif Tissue Int 85: 146-157.
28. Toumi H, Lespessailles E (2015) Proceedings of the first musculo-skeletal imaging by clinical micro CT symposium. IBMS BONEKEY 13.
29. Achiou Z, Toumi H, Touvier J, Boudenot A, Uzbekov R, et al. (2015) Sclerostin antibody and interval treadmill training effects in a rodent model of glucocorticoid-induced osteopenia. Bone 81: 691-701.
30. Ciccone MM1, Aquilino A, Cortese F, Scicchitano P, Sassara M, et al. (2010) Feasibility and effectiveness of a disease and care management model in the primary health care system for patients with heart failure and diabetes (Project Leonardo). Vasc Health Risk Manag 6: 297-305.