Introduction

Osteoporosis is a common disease where bone mass is reduced, leading to an increased risk of bone fracture. Half of Caucasian women and a fifth of men experience osteoporosis-related bone fracture in the course of lifetime [1]. Treatment of osteoporosis-related fracture causes enormous socio-economic burden, costing nearly $17 billion in 2005 in the U.S.; it is expected to double or triple in the next four decades due to rapidly aging population [2].

Osteoporosis is caused by an imbalance of osteoblastic bone formation and osteoclastic bone resorption. Thus, anti-osteoporosis medications aim to reduce the risk of bone fracture either by increasing osteoblastic bone formation or suppressing bone resorption. Currently, four classes of anti-resorptive agents and one class of anabolic agent are approved by the U.S. Food and Drug Administration for the treatment of osteoporosis (Table 1). However, these medications have failed to increase bone formation or decrease bone resorption in isolation due to the closed coupling of osteoblasts and osteoclasts whereby changes in differentiation or activity of one eventually affects the other [3]. This phenomenon not only limits the therapeutic efficacy but also threatens the safety of osteoporosis drugs. This review will discuss the biological mechanisms of action of currently approved medications for osteoporosis treatment, focusing on the osteoblast–osteoclast coupling.

Anti-resorptive Drugs

1. Bisphosphonates

Bisphosphonates (BPs) are the most common class of medications for the treatment of osteoporosis. They are analogues of pyrophosphate and become highly concentrated in mineral-
ized tissues because the oxygen atoms in the phosphonate groups have a high affinity for divalent cations such as calcium. This leads to the osteoclast-specific effect of BPs, since they are released from bone tissue by osteoclastic bone resorption and internalized by adjacent osteoclasts. Although the mechanism by which BPs inhibit osteoclastic bone resorption is not fully understood, they block farnesyl diphosphate synthase (FPPS) in the mevalonate pathway [5]. Disruption of FPPS prevents formation of farnesol and geranylgeraniol for prenylation of multiple proteins, including small guanosine triphosphatases (GTPases) [6], that are critically involved in the differentiation and survival of osteoclasts [7]. The anti-osteoclastogenic effect of BPs is rescued by the addition of geranylgeraniol, but not farnesol, in vitro [8], supporting the view that interference with protein prenylation may be the underlying mechanism of BP action. Recently, cholesterol has been found to be the endogenous ligand for the estrogen-related receptor alpha (ERRα), originally known as an orphan nuclear receptor [9]. BPs exert their anti-osteoclastogenic effect by blocking the mevalonate pathway and decreasing intracellular cholesterol levels, leading to decreased activation of ERRα. Consequently, hypercholesterolemia-induced bone loss and the osteoprotective effect of BPs are abolished in ERRα knockout mice [9].

BPs effectively reduce the risk of vertebral, non-vertebral, and hip fractures by suppression of osteoclastic bone resorption [10]. Although there is some in vitro evidence that BPs may have an anabolic effect on osteoblasts [11], BPs decrease not only osteoclastic bone resorption but also osteoblastic differentiation in vivo [12]. This is primarily due to the coupling of osteoblasts and osteoclasts: inhibition of osteoclast differentiation and bone resorption decrease production and/or release of osteoblast-stimulating osteoclast-derived growth factors, such as Wnt10a and sphingosine-1-phosphate, and matrix-derived growth factors, such as transforming growth factor-β1 and insulin-like growth factor-1 [4,13]. The excessively low bone turnover caused by BPs has been associated with some rare but serious side effects, such as atypical femoral shaft fracture and medication-related osteonecrosis of the jaw (MRONJ), although the mechanisms of pathogenesis of these are still poorly understood [14].

2. Receptor activator of nuclear factor kappa-B ligand antibody (Denosumab)

Denosumab is a fully humanized monoclonal antibody that targets receptor activator of nuclear factor kappa-B ligand (RANKL) [15]. RANKL, which belongs to the tumor necrosis factor family, binds to the RANK (receptor activator of nuclear factor kappa-B) receptor on myeloid lineage cells and this binding interaction is a key step for the differentiation of osteoclast precursors into mature osteoclasts. Denosumab binds to RANKL and prevents RANKL from binding to RANK, inhibiting differentiation, activation, and survival of osteoclasts.

Denosumab reduces the risk of vertebral, non-vertebral, and hip fractures by suppressing bone resorption [16]. Due to osteoblast-osteoclast coupling, denosumab also decreases osteoblastic bone formation, similarly to BPs, and has also been associated with atypical femoral shaft fracture and MRONJ [17]. With regard to the MRONJ, however, denosumab has an advantage over BPs due to its shorter half-life. BPs are accumulated in bone minerals and slowly released by osteoclastic bone resorption, even years after stopping treatment. In contrast, denosumab reversibly inhibits RANKL, such that bone turnover markers are rapidly recovered within a few months after discontinuation [14,18]. Denosumab increases the risk of infections such as cellulitis, probably due to the inhibition of RANKL in the immune system, although the pathogenesis of this is not fully understood [19].

3. Hormone replacement therapy: estrogen therapy

Menopause is one of the most important risk factors for osteoporosis in middle-aged women [20]. This is because estrogen positively regulates bone and mineral homeostasis,
primarily by suppressing osteoclastic bone resorption [21].

Estrogen has both direct and indirect effects on osteoclasts. The direct effects of estrogen are clearly demonstrated by osteoclast–specific estrogen receptor alpha (ER\(\alpha\)) knockout mice, which show decreased trabecular bone mass [22,23]. Estrogen induces apoptosis of osteoclasts and inhibits RANKL–induced osteoclast differentiation [21]. Besides the direct effects, estrogen decreases production of RANKL and increases production of osteoprotegrin, a decoy receptor for RANKL, by osteoblasts [24,25]. In contrast to the effect on osteoclasts, estrogen has minor effects on osteoblastic bone formation. Although the estrogen has been found to inhibit apoptosis and increase the lifespan of osteoblasts [26], mice in which ER\(\alpha\) was specifically knocked out in osteoblasts using Col1a1-cre showed no discernable bone phenotype. Deletion of ER\(\alpha\) in osteoblast progenitors using Prx1-cre and Osf1-cre led to decreased cortical, but not cancellous, bone mass; however, this effect was due to the estrogen–independent function of ER\(\alpha\) [27]. Overall, estrogen therapy mainly exerts anti-resorptive effects, thereby decreasing osteoblastic bone formation due to osteoblast–osteoclast coupling, although its effects are less profound than the effect of BP or denosumab therapy.

Estrogen is usually used in combination with progesterone to reduce the risk of endometrial cancer in unopposed estrogen therapy [28]. With or without progesterone, estrogen therapy reduces the risk of vertebral, non–vertebral, and hip fractures in post–menopausal women [29]. However, estrogen therapy, even in combination with progesterone, has unwanted side effects in other organs besides the bone. The Women’s Health Initiative trial, a large study of over 27,000 women sponsored by the U.S. government, concluded that the increased risk of breast cancer and stroke caused by estrogen therapy exceeded its beneficial effects, especially in older patients (over the age of 60 at the beginning of treatment) [30,31]. Currently, guidelines recommend the use of estrogen therapy for prevention of bone loss in women with premature menopause or for women with vasomotor symptoms who are younger than 60 years or within 10 years of menopause, in the absence of contraindications [32].

4. Selective estrogen receptor modulators

Selective estrogen receptor modulators (SERMs) are a class of compounds that bind to the estrogen receptor (ER) and act as an agonist or antagonist depending on the target tissue. Raloxifene and bazedoxifene, for example, are estrogenic for the bone and liver, but anti–estrogenic for the breast and endometrium (raloxifene is neutral for the endometrium) [33]. Thus, they have the beneficial effects of estrogen therapy on bone, but may even reduce the risk of invasive breast cancer, although they still increase the risk of venous thromboembolism due to anabolic effects on coagulation factors in the liver [34]. The tissue–selective agonistic or antagonistic effect of SERMs is presumed to be associated with several factors as follows: 1) ligand–dependent promotion or inhibition of recruitment of transcriptional coregulators to the SERM–ER complex and tissue–specific enrichment of those coregulators; 2) regulation of coactivator stability or activity by SERM; and 3) preferential affinity of SERM to ER\(\alpha\) over \(\beta\) and differential tissue distribution of these ER isoforms [35].

Both raloxifene and bazedoxifene reduce the risk of vertebral fractures, but not non–vertebral or hip fractures [36,37]. Thus, these SERMs are recommended for younger postmenopausal women, who have low risk of hip fracture, especially for those who are concerned about the risk of breast cancer [17].

Anabolic Drugs

1. Parathyroid hormone receptor agonists

Currently, the only class of anabolic drug approved for the treatment of osteoporosis is parathyroid hormone (PTH) receptor agonists, which include teriparatide and abaloparatide. Teriparatide is a recombinant protein containing the first 34 amino acids of human PTH, which retain the essential anabolic effect of native PTH. Abaloparatide is a synthetic analogue of parathyroid hormone–related protein with 76% homology. Both drugs bind to the parathyroid hormone 1 receptor (PTH1R), primarily present in the bone and kidney.

The primary physiological function of PTH is to raise the plasma calcium concentration in response to low plasma calcium levels by acting primarily on the bone and kidney. Although conflicting results regarding the direct effect of PTH on the osteoclasts have been reported, it is now widely accepted that PTH binds to PTH1R in osteoblasts and increases RANKL expression to indirectly stimulate osteoclastic bone resorption, thereby liberating calcium into the plasma [38]. PTH, however, also simultaneously increases osteoblastic bone formation by promoting osteoblast differentiation and survival. Thus, PTH has both catabolic and anabolic effects on bone, and the balance is determined by the duration for which PTH remains available to the PTH1R in osteoblasts. While the continuous
elevation of PTH levels in hyperparathyroidism results in increased bone resorption being dominant over increased bone resorption and net bone loss, a brief elevation (1 to 3 hours) of PTH levels by therapeutic intermittent injection primarily stimulates bone formation and increases bone mass [38]. The mechanism of this biphasic effect of PTH (continuous vs. intermittent) is not fully understood, but longer exposure of osteoblasts to PTH seems to be necessary for increasing RANKL expression, in contrast to cell-autonomous anabolic effects [39].

Both teriparatide and abaloparatide reduce the risk of vertebral and non-vertebral fractures [40,41]. However, the use of these drugs is limited to 18 to 24 months for two reasons. First, there is a theoretical concern about increased risk of osteosarcoma because treatment with PTH for two years greatly increased the risk of osteosarcoma in rats [42], although there is no evidence that PTH increases the risk of osteosarcoma in humans. Second, because of osteoblast–osteoclast coupling, the osteoclastic bone resorption slowly begins to increase after several months of PTH treatment. During the first 24 months of treatment, the rate of bone formation is greater than that of bone resorption, making the so-called ‘anabolic window’, but eventually the increasing rate bone resorption equals that of bone formation and there is no net gain in bone mass [43].

**Conclusions**

Bone fractures from osteoporosis can be life-threatening in older people. Current anti-osteoporosis drugs are being successfully used to reduce the risk of these fractures. However, all medications are subject to the effects of osteoblast–osteoclast coupling, limiting treatment efficacy and safety. The recently developed sclerostin antibody, Romosozumab, may be the first medication to uncouple the activities of osteoblasts and osteoclasts and exert simultaneously anabolic and anti-catabolic effects, although there are concerns about the increased risk of cardiovascular disease [44]. Future anti-osteoporosis drugs may target the osteoblast–osteoclast coupling process to develop more effective and safe medications.

**Acknowledgements**

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2016R1D1A1B03931522).

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

**References**

1. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R; National Osteoporosis Foundation. Clinician’s guide to prevention and treatment of osteoporosis. Osteoporos Int 2014;25:2359-81. doi: 10.1007/s00198-014-2794-2.

2. Burge R, Dawson–Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. J Bone Miner Res 2007;22:465–75. doi: 10.1359/jbmr.061113.

3. Chen X, Wang Z, Duan N, Zhu G, Schwarz EM, Xie C. Osteoblast–osteoclast interactions. Connect Tissue Res 2018;59:99–107. doi: 10.1080/03008207.2017.1290085.

4. Cao X. Targeting osteoclast–osteoblast communication. Nat Med 2011;17:1344–6. doi: 10.1038/nm.2499.

5. van Beek E, Lüwik C, van der Pluijm G, Papapoulos S. The role of geranylgeranylation in bone resorption and its suppression by bisphosphonates in fetal bone explants in vitro: a clue to the mechanism of action of nitrogen-containing bisphosphonates. J Bone Miner Res 1999;14:722–9. doi: 10.1359/jbmr.1999.14.5.722.

6. Amin D, Cornell SA, Gustafson SK, Needle SJ, Ullrich JW, Bilder GE, Perrone MH. Bisphosphonates used for the treatment of bone disorders inhibit squalene synthase and cholesterol biosynthesis. J Lipid Res 1992;33:1657–63.

7. Itzstein C, Coxon FP, Rogers MJ. The regulation of osteoclast function and bone resorption by small GTPases. Small GTPases 2011;2:117–30. doi: 10.4161/sgtp.2.3.16453.

8. van beek E, Lüwik C, van der Pluijm G, Papapoulos S. The role of geranylgeranylation in bone resorption and its suppression by bisphosphonates in fetal bone explants in vitro: a clue to the mechanism of action of nitrogen-containing bisphosphonates. J Bone Miner Res 1999;14:722–9. doi: 10.1359/jbmr.1999.14.5.722.

9. Wei W, Schwaid AG, Wang X, Wang X, Chen S, Chu Q, Saghatelian A, Wan Y. Ligand activation of ERRα by cholesterol mediates statin and bisphosphonate effects. Cell Metab
Sung-Jin Kim, et al. Biological characteristics of osteoporosis drugs

www.kijob.or.kr 5

2016;23:479–91. doi: 10.1016/j.cmet.2015.12.010.

10. McClung M, Harris ST, Miller PD, Bauer DC, Davison KS, Dian L, Hanley DA, Kendler DL, Yuen CK, Lewiecki EM. Bisphosphonate therapy for osteoporosis: benefits, risks, and drug holiday. Am J Med 2013;126:13–20. doi: 10.1016/j.ajmed.2012.06.023.

11. Maruotti N, Corrado A, Neve A, Cantatore FP. Bisphosphonates: effects on osteoblast. Eur J Clin Pharmacol 2012;68:1013–8. doi: 10.1007/s00228-012-1216-7.

12. Naylor KE, Bradburn M, Paggiosi MA, Gossiel F, Peel NFA, McCloskey EV, Walsh JS, Eastell R. Effects of discontinuing oral bisphosphonate treatments for postmenopausal osteoporosis on bone turnover markers and bone density. Osteoporos Int 2018;29:1407–17. doi: 10.1007/s00198-018-4460-6.

13. Pederson L, Ruan M, Westendorf JJ, Khosla S, Oursler MJ. Regulation of bone formation by osteoclasts involves Wnt/BMP signaling and the chemokine sphingosine-1-phosphate. Proc Natl Acad Sci U S A 2008;105:20764–9. doi: 10.1073/pnas.0805133106.

14. Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. Bone 2011;48:677–92. doi: 10.1016/j.bone.2010.11.020.

15. McClung MR, Lewiecki EM, Cohen SB, Bolognese MA, Woodson GC, Moffett AH, Peal NFA, McCloskey EV, Walsh JS, Eastell R. Effects of discontinuing oral bisphosphonate treatments for postmenopausal osteoporosis on bone turnover markers and bone density. Osteoporos Int 2018;29:1407–17. doi: 10.1007/s00198-018-4460-6.

16. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoch HB, Austin M, Wang A, Kutilek S, Adams M, Zanchetta J, Libanati C, Siddhanti S, Christiansen C; FREEDOM Trial. Denosumab in postmenopausal women with low bone mineral density. N Engl J Med 2009;361:811–23. doi: 10.1056/NEJMoa0809493.

17. Compston JE, McClung MR, Leslie WD. Osteoporosis. Lancet 2015;386:3212–24. doi: 10.1016/S0140-6736(15)61224-8.

18. Khan SA, Kanis JA, Viskaslan S, Kline WF, Matzulak B, McCloskey EV, Beneton MN, Gertz BJ, Sciberras DG, Holford TR, Orgerie J, Coombes GM, Rogers SR, Porras AG. Elimination and biochemical responses to intravenous alendronate in postmenopausal osteoporosis. J Bone Miner Res 1997;12:1700–7. doi: 10.1359/pmr.1997.12.12.1700.

19. Watts NB, Roux CF, Modlin JF, Brown JP, Daniels A, Jackson S, Smith S, Zack DJ, Zhou L, Grauer A, Ferrari S. Infections in postmenopausal women with osteoporosis treated with denosumab or placebo: coincidence or causal association? Osteoporos Int 2012;23:327–37. doi: 10.1007/s00198-011–1755-2.

20. Finkelstein JS, Brockwell SE, Mehta V, Greendale GA, Sowers MR, Ettinger B, Lo JC, Johnston JM, Cauley JA, Danielson ME, Neer RM. Bone mineral density changes during the menopause transition in a multiethnic cohort of women. J Clin Endocrinol Metab 2008;93:861–8. doi: 10.1210/jc.2007–1876.

21. Khosla S, Oursler MJ, Monroe DG. Estrogen and the skeleton. Trends Endocrinol Metab 2012:23:576–81. doi: 10.1016/j.tem.2012.03.008.

22. Nakamura T, Imai Y, Matsumoto T, Sato S, Takeuchi K, Igarashi K, Harada Y, Azuma Y, Krust A, Yamamoto Y, Nishina H, Takeda S, Takayanagi H, Metzger D, Kanno J, Takaoka K, Martin T, Chambon P, Kato S. Estrogen prevents bone loss via estrogen receptor alpha and induction of Fas ligand in osteoclasts. Cell 2007:130:811–23. doi: 10.1016/j.cell.2007.07.025.

23. Martin–Millan M, Almeida M, Ambrogini E, Han L, Zhao H, Weinstein RS, Jilka RL, O’Brien CA, Manolagas SC. The estrogen receptor-alpha in osteoclasts mediates the protective effects of estrogens on cancellous but not cortical bone. Mol Endocrinol 2010:24:323–34. doi: 10.1210/me.2009–0354.

24. Eghbali–Fatourechi G, Khosla S, Sanyal A, Boyle WJ, Lacey DL, Riggs BL. Role of RANK ligand in mediating increased bone resorption in early postmenopausal women. J Clin Invest 2003:111:1221–30. doi: 10.1172/JCI17215.

25. Hofbauer LC, Khosla S, Dunstan CR, Lacey DL, Spelsberg TC, Riggs BL. Estrogen stimulates gene expression and protein production of osteoprotegerin in human osteoblastic cells. Endocrinology 1999:140:4367–70. doi: 10.1210/endo.140.9.7131.

26. Kousteni S, Bellido T, Plotkin LI, O’Brien CA, Bodenner DL, Han L, Han K, DiGregorio GB, Katzenellenbogen JA, Katzenellenbogen BS, Roberson PK, Weinstein RS, Jilka RL, Manolagas SC. Nongenotropic, sex-nonspecific signaling through the estrogen or androgen receptors: dissociation from transcriptional activity. Cell 2001:104:719–30. doi: 10.1016/S0092–8674(01)00268–8.

27. Almeida M, Iyer S, Martin–Millan M, Bartell SM, Han L, Ambrogini E, Onal M, Xiong J, Weinstein RS, Jilka RL, O’Brien CA, Manolagas SC. Estrogen receptor–α signaling in osteoblast progenitors stimulates cortical bone accrual. J Clin Invest 2013:123:394–404. doi: 10.1172/JCI65910.
icz CD, Aragaki AK, Thomson CA, Howard BV, Wactawski-Wende J, Chen C, Rohan TE, Simon MS, Reed SD, Manson JE. Continuous combined estrogen plus progestin and endometrial cancer: the Women’s Health Initiative randomized trial. J Natl Cancer Inst. 2015;108:djv350. doi: 10.1093/jnci/djv350.

29. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, LeBoff M, Lewis CE, McGowan J, Neuner J, Pettinger M, Stefanick ML, Wactawski-Wende J, Watts NB: Women’s Health Initiative Investigators. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women’s Health Initiative randomized trial. JAMA 2003;290:1729–38. doi: 10.1001/jama.290.13.1729.

30. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J: Writing Group for the Women’s Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women’s Health Initiative randomized controlled trial. JAMA 2002;288:321–33. doi: 10.1001/jama.288.3.321.

31. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Bryzsky R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O’Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van Horn L, Wactawski-Wende J, Wallace R, Wassertheil-Smoller S: Women’s Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women’s Health Initiative randomized controlled trial. JAMA 2004;291:1701–12. doi: 10.1001/jama.291.14.1701.

32. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause 2017;24:728–53. doi: 10.1097/GME.0000000000000921.

33. Pickar JH, Boucher M, Morgenstern D. Tissue selective estrogen complex (TSEC): a review. Menopause 2018;25:1033-45. doi: 10.1097/GME.0000000000001095.

34. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, Norton L, Nickelsen T, Bjarnason NH, Morrow M, Lippman ME, Black D, Glusman JE, Costa A, Jordan VC. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 1999;281:2189–97. doi: 10.1001/jama.281.23.2189.

35. Musa MA, Khan MO, Cooperwood JS. Medicinal chemistry and emerging strategies applied to the development of selective estrogen receptor modulators (SERMs). Curr Med Chem 2007;14:1249–61. doi: 10.2174/092986707780598023.

36. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, Christiansen C, Delmas PD, Zanchetta JR, Stakkestad J, Güler CC, Krueger K, Cohen FJ, Eckert S, Ensrud KE, Avioli LV, Lips P, Cummings SR. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999;282:637–45. doi: 10.1001/jama.282.7.637.

37. Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, de Villiers TJ, Constantine GD, Chines AA. Efficacy of bazofoxifen in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo-, and active-controlled clinical trial. J Bone Miner Res 2008;23:1923–34. doi: 10.1359/jbmr.080710.

38. Aslan D, Andersen MD, Gede LB, de Franca TK, Jørgensen SR, Schwarz P, Jørgensen NR. Mechanisms for the bone anabolic effect of parathyroid hormone treatment in humans. Scand J Clin Lab Invest 2012;72:14–22. doi: 10.3109/00365513.2011.624631.

39. Locklin RM, Khosla S, Turner RT, Riggs BL. Mediators of the biphasic responses of bone to intermittent and continuously administered parathyroid hormone. J Cell Biochem 2003;89:180–90. doi: 10.1002/jcb.10490.

40. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsmab AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434–41. doi: 10.1056/NEJM200105103441904.

41. Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, Alexandersen P, Zerbini CA, Hu MY, Harris AG, Fitzpatrick LA, Cosman F, Christiansen C: ACTIVE Study Investigators. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA 2016;316:722–33. doi: 10.1001/jama.2016.11136.

42. Vahle JL, Sato M, Long GG, Young JK, Francis PC, Engelhardt JA, Westmore MS, Linda Y, Nold JB. Skeletal changes
in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1–34) for 2 years and relevance to human safety. Toxicol Pathol 2002;30:312–21. doi: 10.1080/01926230252929882.

43. Pleiner-Duxneuner J, Zwettler E, Paschalis E, Roschger P, Nell-Duxneuner V, Klaushofer K. Treatment of osteoporosis with parathyroid hormone and teriparatide. Calcif Tissue Int 2009;84:159–70. doi: 10.1007/s00223-009-9218-x.

44. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, Maddox J, Fan M, Meisner PD, Grauer A. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med 2017;377:1417–27. doi: 10.1056/NEJMoa1708322.