



Advances and Unmet Needs in the Therapeutics of Bone Fragility

Sabashini K. Ramchand^{1,2*} and Ego Seeman^{1,2,3}

¹ Department of Medicine, The University of Melbourne, Melbourne, VIC, Australia, ² Department of Endocrinology, Austin Health, The University of Melbourne, Melbourne, VIC, Australia, ³ Mary Mackillop Institute of Health Research, Australian Catholic University, Melbourne, VIC, Australia

The prevalence of fragility fractures increases as longevity increases the proportion of the elderly in the community. Until recently, the majority of studies have targeted women with osteoporosis defined as a bone mineral density (BMD) T score of < -2.5 SD, despite evidence that the population burden of fractures arises from women with osteopenia. Antiresorptive agents reduce vertebral and hip fracture risk by ~50 percent during 3 years but efficacy against non-vertebral fractures, 80% of all fractures in the community, is reported in few studies, and of those, the risk reduction is only 20–30%. Recent advances in the use of antiresorptives and anabolic agents has addressed some of these unmet needs. Zoledronic acid is now reported to reduce vertebral and non-vertebral fractures rates in women with osteopenia. Studies using teriparatide demonstrate better vertebral and clinical (symptomatic vertebral and non-vertebral) antifracture efficacy than risedronate. Abaloparatide, a peptide sharing amino acid sequences with teriparatide, reduces vertebral and non-vertebral fractures. Romosozumab, a monoclonal antibody suppressing sclerostin, reduces vertebral and non-vertebral fractures within a year of starting treatment, and does so more greatly than alendronate. Some recent studies signal undesirable effects of therapy but provide essential cautionary insights into long term management. Cessation of denosumab is associated with a rapid increase in bone remodeling and the uncommon but clinically important observation of increased multiple vertebral fractures suggesting the need to start alternative anti-resorptive therapy around the time of stopping denosumab. Antiresorptives like bisphosphonates and denosumab suppress remodeling but not completely. Antifracture efficacy may be limited, in part, as a consequence of continued unsuppressed remodeling, particularly in cortical bone. Bisphosphonates may not distribute in deeper cortical bone, so unbalanced intracortical remodeling continues to cause microstructural deterioration. In addition, suppressed remodeling may compromise the material composition by increasing matrix mineral density and glycosylation of collagen. As antiresorptive agents do not restore microstructural deterioration existing at the time of starting treatment, under some circumstances, anabolic therapy may be more appropriate first line treatment. Combining antiresorptive and anabolic therapy is an alternative but whether anti-fracture efficacy is greater than that achieved by either treatment alone is not known.

OPEN ACCESS

Edited by:

Derek LeRoith,
Icahn School of Medicine at Mount
Sinai, United States

Reviewed by:

Jan Josef Stepan,
Charles University, Czechia
Paula H. Stern,
Northwestern University, United States

*Correspondence:

Sabashini K. Ramchand
sabashini.ramchand@austin.org.au

Specialty section:

This article was submitted to
Bone Research,
a section of the journal
Frontiers in Endocrinology

Received: 10 July 2018

Accepted: 10 August 2018

Published: 06 September 2018

Citation:

Ramchand SK and Seeman E (2018)
Advances and Unmet Needs in the
Therapeutics of Bone Fragility.
Front. Endocrinol. 9:505.
doi: 10.3389/fendo.2018.00505

Keywords: anabolic agents, antiresorptive agents, bone fragility, fractures, microstructure, osteoporosis, osteopenia

INTRODUCTION

Bone remodeling, a sequential process of bone resorption and formation, occurs throughout life renewing the composition of the mineralized matrix volume (1). During young adulthood, bone remodeling is balanced—an equal volume of bone is resorbed and subsequently replaced so no net loss or gain occurs (2). Around midlife, bone formation by the osteoblasts of the basic multicellular units (BMUs) decreases, producing remodeling imbalance (3). In addition, as a consequence of the estrogen deficiency accompanying menopause, remodeling imbalance worsens and the rate of remodeling increases—less bone is deposited than was resorbed by each of the many BMUs initiated upon the three (intracortical, endocortical, trabecular) components of the endosteal (inner) bone surface (4). Estrogen therapy, by influencing the lifespan of osteoblasts and osteoclasts, may reverse the estradiol dependent component of the remodeling imbalance (5–7).

There is a reduction in total mineralized bone matrix volume and the decreasing total mineralized bone matrix volume becomes deteriorated in its microstructure. Unbalanced remodeling upon trabeculae cause them to thin, perforate and disappear. Unbalanced intracortical remodeling initiated upon the intracortical canal surfaces enlarge them, they coalesce and fragment the cortex. With advancing age bone loss from the trabecular compartment lessens because trabeculae with their surfaces disappear (remodeling requires a surface to be initiated upon). Bone loss becomes predominantly cortical as intracortical surface area increases facilitating initiation of unbalanced intracortical remodeling (8, 9). The microstructural deterioration produces bone fragility out of proportion to the bone loss producing it (10).

The burden of fragility fractures is increasing in absolute terms because longevity is increasing the proportion of the population over 65 years of age (11). Reducing the burden of fractures is an unmet need because there are unresolved issues in detection of individuals at high risk for fracture that need to be addressed (12). For example, identifying methods able to detect individuals at imminent risk for fracture is a challenge. Commonly used tools such as bone densitometry lack sensitivity. A BMD T score threshold of -2.5 SD designated as “osteoporosis” identifies only 30–40% of women having fragility fractures (13–15).

The word “osteoporosis” is often used synonymously with bone fragility but women with osteopenia are not free of the risk of fracture (13, 15). Indeed, most women and men sustaining fragility fractures have osteopenia and many have so-called “normal” BMD (14). Women with osteopenia at risk for fracture can be identified by measuring microstructural deterioration (16, 17) but high-resolution imaging methods are not yet widely available. The use of clinical risk factor assessment tools such as FRAX have met with variable success (18, 19). Challenges also arise in the uptake and adherence to therapy, in part, because of concerns regarding the serious but uncommon long term adverse effects of therapy (20, 21).

Antiresorptive agents are the first line and most commonly used treatments for prevention and treatment of bone fragility (22). Apart from denosumab, which virtually abolishes

remodeling, most antiresorptives slow unbalanced remodeling so microstructural deterioration continues to occur albeit more slowly (23). This lower rate of remodeling reduces fracture risk compared to untreated women in whom rapid remodeling continues to deteriorate the skeleton. This is a relative risk reduction. In absolute terms, fracture risk does not decrease during antiresorptive therapy because microstructural deterioration present is not reversed and the slow continued unsuppressed and unbalanced remodeling continues to deteriorate bone. This, in part, may explain why fracture risk reduction with antiresorptives is modest. Teriparatide increases bone matrix volume predominantly through remodeling based bone formation (24). It is likely that the anabolic effect of abaloparatide, which acts via the same receptor as teriparatide, is also remodeling based like teriparatide, although rigorous assessment of its mechanism of action has not been undertaken (25). Both reduce the risk of vertebral and non-vertebral fractures (26, 27) but no adequately designed trials have been done to determine whether hip fracture risk is reduced.

Several comprehensive literature reviews are available (28, 29). We confine this manuscript to defining advances that have taken place in existing therapies and new therapies that are available or may become available soon, particularly the development of anabolic agents, therapies that partly reconstruct the skeleton but are also not without their limitations.

ANTI-RESORPTIVE THERAPY

Bisphosphonates

Bisphosphonates are currently first line treatment and the most common antiresorptive therapy used. The antiresorptive efficacy of bisphosphonates depend on inhibition of farnesyl pyrophosphate (FPP) synthase, required for osteoclast resorptive function, as well as their affinity for mineral which influences uptake, distribution, and retention in the bone (30–33). High affinity binding agents, like alendronate, have a reduced ability to penetrate and distribute widely in deeper cortical matrix so that when osteoclasts remodel cortical bone they encounter matrix free of bisphosphonates and continue to resorb bone.

This may partly account for the finding of less reduction in porosity with alendronate than denosumab (34). The reduction in porosity is the net result of fewer cavities being excavated plus the incomplete filling of the resorption cavities excavated shortly before treatment (35). Likewise, ibandronate is avidly bound to matrix mineral and is present in lower concentrations in cortical than trabecular bone. Studies of ibandronate in ovariectomized cynomolgus monkeys demonstrate reduced remodeling and improved trabecular bone strength but not intracortical remodeling suppression or improved cortical bone strength (36). Lower binding affinity of risedronate than alendronate results in wider distribution of risedronate through the bone and may contribute to its earlier suppression of bone remodeling as reported in animal models and claims of possible earlier fracture risk reduction (37, 38).

Several advances have been made in the study of zoledronic acid. This drug is usually given as an annual 5 mg infusion for 3 years. Fracture risk is reduced in postmenopausal women

with osteoporosis, by 77% for clinical (symptomatic) vertebral fractures, 25% for non-vertebral, and 41% for hip fractures (39). Zoledronic acid was also associated with a 28% reduction in mortality after hip fracture, independent of its effects on fracture risk reduction (40, 41).

Discontinuation of zoledronic acid at 3 years, followed by no treatment for 3 years, was associated with minimal reduction in BMD but 30 new morphometric vertebral fractures occurred compared to 14 in those treated for 6 years (odds ratio = 0.51; $P = 0.035$) (42). In further follow-up, women treated for 6 years and 3 years off treatment did not have more fractures than women treated for 9 years. However, the loss of the inception cohort and small numbers of events make interpretation problematic (43).

Several very insightful studies have been published regarding zoledronic acid treatment. In a *post-hoc* analysis of pooled data from the HORIZON studies, there were comparable ~30% reductions in clinical fractures in those who received a single infusion or three or more annual infusions (44). Whether differing baseline characteristics influenced this outcome is not clear, but given the protracted remodeling suppression with this drug, it is of interest to determine the appropriate regimen needed for efficacy and safety.

This has been evaluated by Reid et al. in postmenopausal women with osteopenia randomized to a single dose of zoledronic acid 1, 2.5, or 5 mg. These doses resulted in a similar increase in spine and hip BMD in the 2.5 and 5 mg groups at 2 years but not at 5 years (45), where increases were greater in the 5 mg than 2.5 mg group (46).

More recently, Reid et al. addressed two important unmet needs. There is a lack of information regarding the antifracture efficacy of drugs given to women with osteopenia, the source of over 60% of all fragility fractures (13). There is also little information regarding the prevention of non-vertebral fractures, 80% of all fractures in the community (11). The investigators evaluated 2,000 women with osteopenia, mean age 71 years, treated with zoledronic acid 5 mg or placebo every 18-months for 4 doses. After 6 years of follow up, treated women had a 34% reduction in non-vertebral fractures (HR 0.66, 95% CI 0.51–0.85) (47).

Denosumab

Denosumab is a fully humanized monoclonal antibody directed against RANK-ligand, a major regulator of osteoclast development which inhibits osteoclast recruitment, activity and survival. Denosumab (60 mg subcutaneously administered every 6 months) produces almost complete suppression of bone remodeling. Treatment for 3 years resulted in a 68% reduction in vertebral fractures, 40% reduction in hip fracture and 20% reduction in non-vertebral fractures (48).

Remodeling suppression with denosumab is greater than that achieved with any other antiresorptive agent (49). This greater suppression of remodeling accounts for greater increases in BMD achieved in postmenopausal women treated with denosumab compared to bisphosphonates (34, 50–52). Whether these BMD differences translate to differences in fracture risk reduction between the two groups is not known.

No trials have been conducted with a placebo control group beyond 3 years. Because of this, whatever the fracture rate, it is not possible to infer with confidence that fracture rates reported are attributable to the drug rather than healthy user bias. In the open label extension of the FREEDOM study (53), all participants were treated with denosumab and followed up for 7 years. Ten years of denosumab treatment was associated with an acceptable safety profile, sustained suppression of bone remodeling, continued increase in BMD without plateau and “low” fracture rates. The lack of controls and the large number of participants withdrawn from the trial, suggest that the finding of low and further reductions in fracture rates should be cautiously interpreted.

In the long-term group, BMD increased by 21.7% in the lumbar spine and 9.0% in the femoral neck at 10 years compared to FREEDOM baseline. The mechanism of increase in BMD may be due to progressive secondary mineralization. It is plausible that in the face of suppressed remodeling, continued slow age-related modeling based bone formation becomes detectable as reported in studies of histomorphometry conducted in cynomolgus monkeys (54, 55). Dempster et al. also report some evidence of modest trabecular modeling based bone formation after 3 months of denosumab therapy (56). Further studies are needed to determine whether antiresorptive therapy permits expression of any existing modeling based bone formation when remodeling is suppressed.

An important insight into treatment with denosumab is the report that cessation of denosumab caused a rapid rise in bone remodeling markers with a transitory overshoot above baseline, a decline in BMD in 12 months and, uncommonly, an increased risk in multiple vertebral fractures (57, 58). Occurrence of multiple vertebral fractures were initially reported in several case series (59–64). In a subsequent *post hoc* analysis of the FREEDOM and FREEDOM Extension trials (65), vertebral fracture rate after discontinuation of denosumab increased to 7.1 per 100 participant years vs. 8.5 per 100 participant years in the placebo group. In those who developed one or more vertebral fractures, the proportion of multiple vertebral fractures (>2) was higher in those discontinuing denosumab (60.7%) than in those discontinuing placebo (38.7%, $P = 0.049$). The risk of multiple vertebral fractures after stopping denosumab was greatest in those with a prior vertebral fracture, either before or during treatment (odds 3.9, 95% CI 2.1–7.2) (65). Investigators recommend commencement of an alternative antiresorptive agent soon after cessation of denosumab, although the agent to use and when to start needs further evaluation.

At present, there is no evidence that the increased risk of vertebral fractures is due to the rapid increase in remodeling. The term “rebound” is used but cessation of remodeling suppression produces expansion of the reversible remodeling space with any antiresorptive (66). When an antiresorptive is stopped, the effect has similarities to the onset of menopause. There is a rapid increase in the number of remodeling units starting to excavate bone and hence a rapid rise in remodeling markers. With denosumab, given the drug is not retained in the skeleton like bisphosphonates, the increased number of resorptive cavities is not offset as it is with bisphosphonate cessation. With

bisphosphonate cessation, increased resorption may lead to release of bisphosphonate and reabsorption into matrix slowing the decrease in BMD. In the absence of denosumab, the rapid increase in number of resorption cavities is not inhibited and may create stress concentrators which pre-dispose to microcrack propagation and increased vertebral fracture risk (67, 68). Whether this increase in resorption is amplified by rapid differentiation of existing osteoclast precursors remaining undifferentiated until denosumab is stopped is not known.

While this “rebound” or “overshoot” in remodeling markers is reported, remodeling returns to its pretreatment level and the reduction in BMD returns to baseline leaving a residual higher BMD than untreated controls (58, 69). If there was accelerated loss of bone, beyond that found early after stopping treatment due to many more excavated cavities than those incompletely refilling after starting denosumab, then BMD should decline to levels no different to untreated controls (70). Bone fragility is likely to occur after stopping treatment because the accelerated remodeling occurs in the setting of an already deteriorated skeleton (as antiresorptive agents do not reverse microstructural deterioration present at the time of starting treatment). This is not the same after menopause where there is little, if any, deterioration before menopause.

Selective Estrogen Receptor Modulators

Raloxifene, a selective estrogen receptor modulator (SERM), reduces the rate of bone remodeling by about 20–30% as determined using circulating bone remodeling markers (71). It produces a modest transitory increase in BMD during early treatment, as fewer new resorption cavities are excavated while the many more cavities excavated before treatment refill, albeit incompletely. With more protracted treatment, unbalanced remodeling continues at 20–30% slower rate than before treatment so microstructural deterioration continues (70). The decline in BMD during prolonged therapy is well documented (71, 72) and probably accounts, in part, for the modest vertebral fracture risk reduction and lack of evidence for non-vertebral fracture risk reduction (71).

Raloxifene appears to reduce vertebral fractures with small and perhaps transient effects on BMD. It is of interest that pre-clinical studies demonstrate an increase in the material strength produced by increases in skeletal-bound water with minimal effect on tissue mineral composition or microdamage accumulation (73–75). These findings provide a novel target for future pharmacological interventions to improve bone strength and lower fracture risk. This is of particular interest given the concerns of protracted remodeling suppression by bisphosphonates and denosumab which are likely to pre-dispose to loss of toughness and atypical femoral fractures (AFFs).

Treatment of osteoporosis in patients with AFFs is challenging; withholding an antiresorptive will result in ongoing structural decay predisposing to fragility fracture, conversely, if an antiresorptive is continued, structural decay will slow but material composition will be compromised predisposing to AFFs (76). One approach may be to use a weaker antiresorptive such as raloxifene, which improves bone toughness with minimal effects

on tissue mineral composition or microdamage accumulation. The efficacy of raloxifene in this context has not been established.

ANABOLIC AGENTS

Teriparatide (PTH 1-34) and abaloparatide are available for clinic use, romosozumab is a modeling based anabolic agent that is still under investigation.

Teriparatide and Abaloparatide

The anabolic effects of PTH 1-34 are ~70% remodeling based. Abaloparatide, which shares amino acid sequences with both parathyroid hormone-related protein (PTHrP) and PTH, acts via the same receptor as teriparatide (PTHr1). Both teriparatide and abaloparatide increase trabecular thickness and improve trabecular microstructure (77–79). There is a transitory phase of increased cortical porosity produced with PTH 1-34 (80, 81). Whether the anabolic effect of abaloparatide is accompanied by less resorptive activity and less cortical porosity needs to be confirmed (27, 82, 83).

Parathyroid hormone analogs have consistently been reported to reduce vertebral fractures but evidence for non-vertebral fracture risk reduction reported by Neer et al. has not been replicated (84). No randomized controlled studies have been done to evaluate anti-hip fracture efficacy, an omission that needs to be addressed.

Abaloparatide also reduces vertebral and non-vertebral fractures (27). In a phase 3 clinical trial, 2463 ambulatory postmenopausal women, of which 1901 completed the study, were randomized to 18 months of abaloparatide (80 µg daily), placebo or open-label teriparatide (20 µg daily). New morphometric vertebral fractures occurred in 0.58% ($n = 4$) of the abaloparatide group, 4.22% ($n = 30$) of the placebo group (relative risk 0.14, 95% CI 0.05–0.39), and 0.84% ($n = 6$) of the teriparatide group. The Kaplan-Meier estimated event rate for non-vertebral fracture was 2.7% for abaloparatide, 4.7% for placebo (HR 0.57, 95% CI 0.32–1.00), and 3.3% for teriparatide ($P = 0.22$ compared to placebo and $P = 0.44$ compared to abaloparatide) (27). Major osteoporotic fractures were reduced with abaloparatide compared to placebo or teriparatide, Kaplan-Meier estimated event rate for placebo was 6.2% (HR 0.30, 95% CI 0.15–0.61) and for teriparatide was 3.1% (HR 0.45, 95% CI 0.21–0.95, $P = 0.03$) (27).

While these findings are encouraging, the claim that abaloparatide produced an earlier and more efficacious fracture risk reduction than teriparatide is problematic because of an increase in number of subjects who fractured in the first few weeks of treatment in the placebo and teriparatide group that is unlikely to be associated with therapy (27). Differences in fracture rates in the two treatment arms in the second and third 6 months of the 18-month trial were minimal (83). In addition, evidence that the anabolic effect is accompanied by less bone resorption with abaloparatide than teriparatide is also not well founded (83).

Increases in BMD with abaloparatide were greater (~1%) than those with teriparatide at the total hip and femoral neck at all time points and ~2% at the lumbar spine at 6 and 12 months (both $P < 0.001$). At 18-months, BMD in the lumbar spine was no different

between the two groups (27). These difference in BMD at the femoral neck and total hip were attributed to the net difference in resorption and formation markers claimed to be surrogates of more net bone deposition with abaloparatide than teriparatide, a problematic interpretation for a range of reasons (83, 85).

Romozosumab

Romozosumab is a humanized monoclonal antibody against sclerostin, an endogenous inhibitor of bone formation. Treatment results in an increase in modeling based bone formation and evidence of decreases in bone resorption. Two studies support the antifracture efficacy of this anabolic agent (86, 87). Cosman et al. enrolled 7,180 postmenopausal women with osteoporosis to monthly romozosumab (210 mg) or placebo for 12 months followed by denosumab (60 mg 6 monthly) for 12 months (86). At 12 months, risk reductions were reported for vertebral fractures by 73% ($P < 0.001$), for clinical fractures by 36% ($P = 0.008$) and non-vertebral fractures by 24% ($P = 0.10$). At 24 months, vertebral fracture risk was reduced by 75% ($P < 0.001$) (86).

Saag et al. (87). assigned 4,093 postmenopausal women with osteoporosis and a fragility fracture to romozosumab (210 mg) or weekly alendronate (70 mg) for 12 months then open label alendronate in both groups. Over 24 months, romozosumab/alendronate reduced vertebral fracture risk by 48% ($P < 0.001$), clinical fractures by 27% ($P < 0.001$), non-vertebral fracture by 19% ($P = 0.04$), and hip fracture by 38% ($P = 0.02$). At 12 months, romozosumab reduced new vertebral (risk ratio 0.63, 95% CI 0.47–0.85) and clinical (HR 0.72, 95% CI 0.54–0.96) fractures compared to alendronate. Non-vertebral fracture risk was also reduced by 26% with romozosumab, but this difference was not statistically significant ($P = 0.06$) (87). The use of romozosumab is under FDA review after results of the trial demonstrated a higher incidence of adjudicated serious cardiovascular events with romozosumab (50/2040) compared to alendronate (38/2014) at the end of 12 months, which did not persist in the 24-month open label extension (87). These findings were not replicated in the much larger placebo-controlled FRAME study (88).

Recent work by McClung et al. (89). report loss of benefit of romozosumab soon after cessation of therapy. Three hundred and sixty-four postmenopausal women with low bone mass were treated with romozosumab for 24 months and then randomized to either denosumab or placebo for a further 12 months. Treatment with romozosumab led to a continued increase in BMD over 2 years with further accrual in those that transitioned to denosumab, whereas BMD returned toward pre-treatment levels in those that transitioned to placebo (89).

Given the inability of antiresorptives to reverse existing microstructural deterioration, and the evidence that anabolic therapy may partly restore bone microstructure, is there evidence supporting better antifracture efficacy using anabolic therapy than antiresorptive therapy. Kendler et al. studied 1360 postmenopausal women with severe osteoporosis randomized to teriparatide (20 μ g daily) or risedronate (35 mg daily) over 2 years (26). Overall, 72% of participants received at

least one bone targeted treatment prior to study entry, most commonly a bisphosphonate (59% in the teriparatide group and 57% in the risedronate group) and median duration of bisphosphonate treatment was 3.5 years (IQR 1.1–7.0) in the teriparatide group and 3.6 years (IQR 1.3–6.1) in the risedronate group. At 2 years, treatment with teriparatide resulted in a 56% (risk ratio 0.44, 95% CI 0.29–0.68) reduction in incident vertebral fractures with a reduction in non-vertebral fractures that did not achieve statistical significance; 25 (4.0%) in the teriparatide group vs. 38 (6.1%) in the risedronate group (hazard ratio (HR) 0.66, 95% CI 0.39–1.10, $P = 0.10$) (26). In a subgroup analyses, these changes were consistent across a range of characteristics of the participants (90).

Combined Antiresorptive and Anabolic Therapy

Combining antiresorptive and anabolic therapy is a missed opportunity for two reasons (70). First, no studies have been done demonstrating greater antifracture efficacy than achieved by either treatment alone. This is a valid reason for a cautionary approach to the uptake of this regimen. The second reason is the widely held belief that antiresorptive therapy suppresses, “blunts,” remodeling based bone formation by PTH (91–93). This is largely based on two influential papers and the accompanying editorial in the New England Journal of Medicine (91, 93, 94). The notion of blunting was based on the assumption that a higher BMD or higher PINP mean more bone formation and a lack of response means less bone formation.

Comparator studies that use changes in BMD and bone remodeling markers as the outcome variable are problematic endpoints. Remodeling based anabolic therapy increases bone matrix volume by replacing more fully mineralized bone with young less fully mineralized bone. Modeling based anabolic therapy adds young less fully mineralized bone to existing older bone. Imaging using radiation transmission often results in a net reduction in BMD because young less mineralized bone transmits rather than attenuates photons leading to the inference that bone “loss” and fragility have occurred. Antiresorptives slow remodeling. Matrix no longer “turned over” undergoes more complete mineralization increasing BMD leading to the inference that bone “volume” or “mass” has increased, and that bone strength has increased even though the matrix becomes less ductile.

As an example, even if an increase or lack of an increase in BMD is accepted on face value, examination of Figures 1 to 3 of the study by Black et al. does not support the notion of blunting (91). Relative to PTH alone, combined therapy (i) did *not* produce a smaller increment in spine or femoral neck BMD, (ii) *did* produce a greater increase in total hip BMD, (iii) *did* reduce the decline in distal radius BMD, (iv) *did* prevent the reduction in total hip and femoral neck vBMD produced by PTH alone. Curiously, the increase in total hip and femoral neck cortical volume by PTH, a *modeling* effect, was prevented by combined therapy. Moreover, combined therapy increased

trabecular vBMD less than PTH alone but this may be a benefit, not blunting. The antiresorptive might prevent PTH mediated increase in intracortical remodeling, cortical porosity and the increase in cortical fragments that look like “trabeculae” (35). Blunting of the rise in P1NP and CTX is likely to be the result of suppressed remodeling, not a reduction in the net volumes of bone deposited or resorbed respectively (85). If blunting of the BMD response was due to fewer BMUs then blunting should be *more* severe with co-administration of PTH with zoledronate, denosumab, or osteoprotegerin (OPG, an endogenous inhibitor of RANKL) than with alendronate. The opposite is reported, and many studies report additive effects (95–98).

The difficulties in using BMD are also present using high-resolution peripheral computed tomography. Tsai et al. (80) report that combined PTH 1-34 and denosumab increased cortical vBMD yet PTH 1-34 reduced it and denosumab had no effect. Combined therapy increased cortical matrix mineral density yet PTH 1-34 decreased it and denosumab had no effect. Combined therapy had no effect on porosity yet PTH 1-34 increased it while denosumab had no effect. These findings do not add up, probably because there are methodological challenges in segmenting (separating) the cortical and trabecular compartments and quantifying porosity and trabecular density because low image resolution and changes in matrix mineral density influence the quantification of microstructure (8, 99).

Sequential Therapy Anabolic to Anti-resorptive

Cessation of anabolic treatment results in loss of the benefits. Antiresorptives maintain or increase BMD, particularly denosumab because it is the most efficacious in suppressing remodeling. In the DATA-Switch study, 2 years of PTH 1-34 followed by 2 years of denosumab resulted in further increases in BMD (100). At 48 months, women treated with combined PTH 1-34 and denosumab for 2 years followed by denosumab alone had greater gains in BMD than those treated with PTH 1-34 followed by denosumab. Whether this results in fewer fractures is not known but it is likely that stopping any of the treatments will result in the loss of benefits and eventual increase in fracture risk.

In another publication of the abaloparatide trial by Miller et al. (27), Bone et al. (101) administered alendronate after abaloparatide which maintained the fracture risk reduction relative to placebo also given alendronate after 18 months. This design does not address the question of whether stopping abaloparatide produces loss of benefits as found with PTH, which requires an arm with abaloparatide given placebo. Any comparisons of abaloparatide/alendronate and placebo/alendronate is flawed as the placebo group is likely to have undergone bone loss and microstructural deterioration during 18 months. The likelihood is however, that stopping abaloparatide will result in loss of benefits. This has recently been reported with romosozumab; where stopping treatment was accompanied by loss of the benefits achieved by the modeling dependent anabolic effect (89).

Anti-resorptive to Anabolic

Two recent trials evaluating antiresorptive therapy followed by an anabolic agent have been conducted (100, 102). In the DATA-switch study, women receiving denosumab had a reduction in hip BMD during 12 months of PTH 1-34 followed by a gradual increase in BMD, but remained lower than women in the PTH 1-34 to denosumab group and the PTH 1-34/denosumab to denosumab group (100). Spine BMD decreased in the first 6 months but then increased to a value no different to the above two groups at 48 months. Bone remodeling markers increased in the denosumab to PTH 1-34 group by over 200% relative to baseline values. Whether bone fragility increases is difficult to determine given the decline in BMD may be due to the replacement of more mineralized with less mineralized new bone by remodeling or addition of under mineralized bone by modeling which then becomes mineralized. High remodeling is found using anabolic agents but fracture rates do not increase, they decrease. Nevertheless, cessation of denosumab is associated with rapid increases in remodeling and multiple vertebral fractures; whether this might be prevented or worsened by PTH 1-34 is not known.

In an unblinded study comparing romosozumab (120 mg monthly) vs. PTH 1-34 (20 µg daily) in postmenopausal women previously treated with bisphosphonates, total hip BMD increased with romosozumab by 2.6% compared to a decrease of 0.6% with PTH 1-34 (102). Both drugs increased spine BMD (romosozumab 9.8% vs. PTH 1-34 5.4%). At the hip, romosozumab increased cortical vBMD whilst PTH 1-34 decreased it. Trabecular vBMD was similarly increased with both drugs (102). The comparison of BMD changes is problematic given BMD may decrease when a large volume of bone that is still unmineralized is deposited and the effects on microstructure which contribute disproportionately to bone strength are not taken into account.

CONCLUSION

Fragility fractures are a public health burden. Advances are occurring, but several challenges remain unmet. Most fractures occur in women with osteopenia yet methods of identifying the women forming the population burden of fractures remain to be identified. Even when women at risk are identified, the uptake and adherence to therapy is poor for reasons that are not well defined. Antiresorptive agents are first line approaches to therapy even though these agents do not restore bone volume or the microstructural deterioration present at the time of treatment. Most, if not all, controlled trials are 3 years duration and long-term efficacy is unknown. Anabolic therapies have not been as comprehensively studied. Although newer agents are emerging and vertebral fracture risk reduction is confirmed, less evidence is available for non-vertebral fracture risk reduction, and no anabolic agent has been evaluated for hip fracture risk reduction in randomized controlled studies. Bone densitometry was a good beginning but most fractures in the community arise in persons with a BMD T-score less reduced than -2.5 SD and so they are not offered treatment. Whether assessment of bone

microstructure might help identify and target therapy more effectively remains an unmet challenge, but it is an opportunity in need of exploration because bone fragility is caused by microstructural deterioration.

REFERENCES

- Hattner R, Epker BN, Frost HM. Suggested sequential mode of control of changes in cell behaviour in adult bone remodelling. *Nature* (1965) 206:489–90. doi: 10.1038/206489a0
- Parfitt AM. Skeletal heterogeneity and the purposes of bone remodelling: implications for the understanding of osteoporosis. In: Marcus RFD, Kelsey J, editors. *Osteoporosis*. San Diego, CA: Academic (1996). p. 315–39.
- Lips P, Courpron P, Meunier PJ. Mean wall thickness of trabecular bone packets in the human iliac crest: changes with age. *Calcif Tissue Res.* (1978) 26:13–7. doi: 10.1007/BF02013227
- Vedi S, Compston JE, Webb A, Tighe JR. Histomorphometric analysis of dynamic parameters of trabecular bone formation in the iliac crest of normal British subjects. *Metab Bone Dis Relat Res.* (1983) 5:69–74. doi: 10.1016/0221-8747(83)90004-8
- Vedi S, Compston JE. The effects of long-term hormone replacement therapy on bone remodeling in postmenopausal women. *Bone* (1996) 19:535–9. doi: 10.1016/S8756-3282(96)00227-X
- Vedi S, Purdie DW, Ballard P, Bord S, Cooper AC, Compston JE. Bone remodeling and structure in postmenopausal women treated with long-term, high-dose estrogen therapy. *Osteoporos Int.* (1999) 10:52–8. doi: 10.1007/s001980050194
- Eriksen EF, Langdahl B, Vesterby A, Rungby J, Kassem M. Hormone replacement therapy prevents osteoclastic hyperactivity: a histomorphometric study in early postmenopausal women. *J Bone Miner Res.* (1999) 14:1217–21. doi: 10.1359/jbmr.1999.14.7.1217
- Zebaze RM, Ghasem-Zadeh A, Bohte A, Iuliano-Burns S, Mirams M, Price RI, et al. Intracortical remodelling and porosity in the distal radius and post-mortem femurs of women: a cross-sectional study. *Lancet* (2010) 375:1729–36. doi: 10.1016/S0140-6736(10)60320-0
- Parfitt AM. Misconceptions (2): turnover is always higher in cancellous than in cortical bone. *Bone* (2002) 30:807–9. doi: 10.1016/S8756-3282(02)00735-4
- Schaffler MB, Burr DB. Stiffness of compact bone: effects of porosity and density. *J Biomech.* (1988) 21:13–6. doi: 10.1016/0021-9290(88)90186-8
- Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int.* (2006) 17:1726–33. doi: 10.1007/s00198-006-0172-4
- Khosla S, Cauley JA, Compston J, Kiel DP, Rosen C, Saag KG, et al. Addressing the crisis in the treatment of osteoporosis: a path forward. *J Bone Miner Res.* (2017) 32:424–30. doi: 10.1002/jbmr.2888
- Siris ES, Chen YT, Abbott TA, Barrett-Connor E, Miller PD, Wehren LE, et al. Bone mineral density thresholds for pharmacological intervention to prevent fractures. *Arch Intern Med.* (2004) 164:1108–12. doi: 10.1001/archinte.164.10.1108
- Sanders KM, Nicholson GC, Watts JJ, Pasco JA, Henry MJ, Kotowicz MA, et al. Half the burden of fragility fractures in the community occur in women without osteoporosis. When is fracture prevention cost-effective? *Bone* (2006) 38:694–700. doi: 10.1016/j.bone.2005.06.004
- Pasco JA, Seeman E, Henry MJ, Merriman EN, Nicholson GC, Kotowicz MA. The population burden of fractures originates in women with osteopenia, not osteoporosis. *Osteoporos Int.* (2006) 17:1404–9. doi: 10.1007/s00198-006-0135-9
- Bala Y, Zebaze R, Ghasem-Zadeh A, Atkinson EJ, Iuliano S, Peterson JM, et al. Cortical porosity identifies women with osteopenia at increased risk for forearm fractures. *J Bone Miner Res.* (2014) 29:1356–62. doi: 10.1002/jbmr.2167
- Boutroy S, Van Rietbergen B, Sornay-Rendu E, Munoz F, Bouxsein ML, Delmas PD. Finite element analysis based on *in vivo* HR-pQCT images of the distal radius is associated with wrist fracture in postmenopausal women. *J Bone Miner Res.* (2008) 23:392–9. doi: 10.1359/jbmr.071108
- Shepstone L, Lenaghan E, Cooper C, Clarke S, Fong-Soe-Khioe R, Fordham R, et al. Screening in the community to reduce fractures in older women (SCOOP): a randomised controlled trial. *Lancet* (2018) 391:741–7. doi: 10.1016/S0140-6736(17)32640-5
- Rubin KH, Rothmann MJ, Holmberg T, Hoiberg M, Moller S, Barkmann R, et al. Effectiveness of a two-step population-based osteoporosis screening program using FRAX: the randomized Risk-stratified Osteoporosis Strategy Evaluation (ROSE) study. *Osteoporos Int.* (2018) 29:567–78. doi: 10.1007/s00198-017-4326-3
- Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* (2014) 29:1–23. doi: 10.1002/jbmr.1998
- Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* (2007) 22:1479–91. doi: 10.1359/jbmr.07070nj
- Russell RG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int.* (2008) 19:733–59. doi: 10.1007/s00198-007-0540-8
- Seeman E, Delmas PD, Hanley DA, Sellmeyer D, Cheung AM, Shane E, et al. Microarchitectural deterioration of cortical and trabecular bone: differing effects of denosumab and alendronate. *J Bone Miner Res.* (2010) 25:1886–94. doi: 10.1002/jbmr.81
- Lindsay R, Cosman F, Zhou H, Bostrom MP, Shen VW, Cruz JD, et al. A novel tetracycline labeling schedule for longitudinal evaluation of the short-term effects of anabolic therapy with a single iliac crest bone biopsy: early actions of teriparatide. *J Bone Miner Res.* (2006) 21:366–73. doi: 10.1359/JBMR.051109
- Moreira CA, Fitzpatrick LA, Wang Y, Recker RR. Effects of abaloparatide-SC (BA058) on bone histology and histomorphometry: the ACTIVE phase 3 trial. *Bone* (2017) 97:314–9. doi: 10.1016/j.bone.2016.11.004
- Kendler DL, Marin F, Zerbini CAF, Russo LA, Greenspan SL, Zikan V, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet* (2018) 391:230–40. doi: 10.1016/S0140-6736(17)32137-2
- Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, et al. 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
- Khosla S, Hofbauer LC. Osteoporosis treatment: recent developments and ongoing challenges. *Lancet Diabetes Endocrinol.* (2017) 5:898–907. doi: 10.1016/S2213-8587(17)30188-2
- Reid IR. Short-term and long-term effects of osteoporosis therapies. *Nat Rev Endocrinol.* (2015) 11:418–28. doi: 10.1038/nrendo.2015.71
- van Beek E, Pieterman E, Cohen L, Lowik C, Papapoulos S. Farnesyl pyrophosphate synthase is the molecular target of nitrogen-containing bisphosphonates. *Biochem Biophys Res Commun.* (1999) 264:108–11. doi: 10.1006/bbrc.1999.1499
- Kavanagh KL, Guo K, Dunford JE, Wu X, Knapp S, Ebetino FH, et al. The molecular mechanism of nitrogen-containing bisphosphonates as antiosteoporosis drugs. *Proc Natl Acad Sci USA.* (2006) 103:7829–34. doi: 10.1073/pnas.0601643103
- Fisher JE, Rogers MJ, Halasy JM, Luckman SP, Hughes DE, Masarachia PJ, et al. Alendronate mechanism of action: geranylgeraniol, an intermediate in

- the mevalonate pathway, prevents inhibition of osteoclast formation, bone resorption, and kinase activation *in vitro*. *Proc Natl Acad Sci USA*. (1999) 96:133–8. doi: 10.1073/pnas.96.1.133
33. Dunford JE, Thompson K, Coxon FP, Luckman SP, Hahn FM, Poulter CD, et al. Structure-activity relationships for inhibition of farnesyl diphosphate synthase *in vitro* and inhibition of bone resorption *in vivo* by nitrogen-containing bisphosphonates. *J Pharmacol Exp Ther*. (2001) 296:235–42.
 34. Zebaze RM, Libanati C, Austin M, Ghasem-Zadeh A, Hanley DA, Zanchetta JR, et al. Differing effects of denosumab and alendronate on cortical and trabecular bone. *Bone* (2014) 59:173–9. doi: 10.1016/j.bone.2013.11.016
 35. Zebaze R, Seeman E. Cortical bone: a challenging geography. *J Bone Miner Res*. (2015) 30:24–9. doi: 10.1002/jbmr.2419
 36. Smith SY, Recker RR, Hannan M, Muller R, Baus F. Intermittent intravenous administration of the bisphosphonate ibandronate prevents bone loss and maintains bone strength and quality in ovariectomized cynomolgus monkeys. *Bone* (2003) 32:45–55. doi: 10.1016/S8756-3282(02)00923-7
 37. Allen MR, Turek JJ, Phipps RJ, Burr DB. Greater magnitude of turnover suppression occurs earlier after treatment initiation with risedronate than alendronate. *Bone* (2011) 49:128–32. doi: 10.1016/j.bone.2010.07.011
 38. Silverman SL, Watts NB, Delmas PD, Lange JL, Lindsay R. Effectiveness of bisphosphonates on nonvertebral and hip fractures in the first year of therapy: the risedronate and alendronate (REAL) cohort study. *Osteoporos Int*. (2007) 18:25–34. doi: 10.1007/s00198-006-0274-z
 39. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. (2007) 356:1809–22. doi: 10.1056/NEJMoa067312
 40. Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med*. (2007) 357:1799–809. doi: 10.1056/NEJMoa074941
 41. Colon-Emeric CS, Mesenbrink P, Lyles KW, Pieper CF, Boonen S, Delmas P, et al. Potential mediators of the mortality reduction with zoledronic acid after hip fracture. *J Bone Miner Res*. (2010) 25:91–7. doi: 10.1359/jbmr.090704
 42. Black DM, Reid IR, Boonen S, Bucci-Rechtweg C, Cauley JA, Cosman F, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res*. (2012) 27:243–54. doi: 10.1002/jbmr.1494
 43. Black DM, Reid IR, Cauley JA, Cosman F, Leung PC, Lakatos P, et al. The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res*. (2015) 30:934–44. doi: 10.1002/jbmr.2442
 44. Reid IR, Black DM, Eastell R, Bucci-Rechtweg C, Su G, Hue TF, et al. Reduction in the risk of clinical fractures after a single dose of zoledronic acid 5 milligrams. *J Clin Endocrinol Metab*. (2013) 98:557–63. doi: 10.1210/jc.2012-2868
 45. Grey A, Bolland MJ, Horne A, Mihov B, Gamble G, Reid IR. Duration of antiresorptive activity of zoledronate in postmenopausal women with osteopenia: a randomized, controlled multidose trial. *CMAJ* (2017) 189:E1130–6. doi: 10.1503/cmaj.161207
 46. Grey A, Bolland M, Mihov B, Wong S, Horne A, Gamble G, et al. Duration of antiresorptive effects of low-dose zoledronate in osteopenic postmenopausal women: a randomized, placebo-controlled trial. *J Bone Miner Res*. (2014) 29:166–72. doi: 10.1002/jbmr.2009
 47. Reid I, Horne A, Mihov B, Stewart A, Garratt L, Bolland M, et al. Abstracts of the ECTS Congress 2018 - P068 Zoledronate every 18 months for 6 years in osteopenic postmenopausal women reduces non-vertebral fractures and height loss. *Calcif Tissue Int*. (2018) 102:S1–159. doi: 10.1007/s00223-018-0418-0
 48. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. (2009) 361:756–65. doi: 10.1056/NEJMoa0809493
 49. Reid IR, Miller PD, Brown JP, Kendler DL, Fahrleitner-Pammer A, Valter I, et al. Effects of denosumab on bone histomorphometry: the FREEDOM and STAND studies. *J Bone Miner Res*. (2010) 25:2256–65. doi: 10.1002/jbmr.149
 50. Miller PD, Pannacciulli N, Brown JP, Czerwinski E, Nedergaard BS, Bolognese MA, et al. Denosumab or zoledronic acid in postmenopausal women with osteoporosis previously treated with oral bisphosphonates. *J Clin Endocrinol Metab*. (2016) 101:3163–70. doi: 10.1210/jc.2016-1801
 51. Brown JP, Roux C, Ho PR, Bolognese MA, Hall J, Bone HG, et al. Denosumab significantly increases bone mineral density and reduces bone turnover compared with monthly oral ibandronate and risedronate in postmenopausal women who remained at higher risk for fracture despite previous suboptimal treatment with an oral bisphosphonate. *Osteoporos Int*. (2014) 25:1953–61. doi: 10.1007/s00198-014-2692-7
 52. Roux C, Hofbauer LC, Ho PR, Wark JD, Zillikens MC, Fahrleitner-Pammer A, et al. Denosumab compared with risedronate in postmenopausal women suboptimally adherent to alendronate therapy: efficacy and safety results from a randomized open-label study. *Bone* (2014) 58:48–54. doi: 10.1016/j.bone.2013.10.006
 53. Bone HG, Wagman RB, Brandi ML, Brown JP, Chapurlat R, Cummings SR, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol*. (2017) 5:513–23. doi: 10.1016/S2213-8587(17)30138-9
 54. Kostenuik PJ, Smith SY, Jolette J, Schroeder J, Pyrah I, Ominsky MS. Decreased bone remodeling and porosity are associated with improved bone strength in ovariectomized cynomolgus monkeys treated with denosumab, a fully human RANKL antibody. *Bone* (2011) 49:151–61. doi: 10.1016/j.bone.2011.03.769
 55. Ominsky MS, Libanati C, Niu QT, Boyce RW, Kostenuik PJ, Wagman RB, et al. Sustained modeling-based bone formation during adulthood in cynomolgus monkeys may contribute to continuous BMD gains with denosumab. *J Bone Miner Res*. (2015) 30:1280–9. doi: 10.1002/jbmr.2480
 56. Dempster DW, Zhou H, Recker RR, Brown JP, Recknor CP, Lewiecki EM, et al. Remodeling- and modeling-based bone formation with teriparatide versus denosumab: a longitudinal analysis from baseline to 3 months in the AVA study. *J Bone Miner Res*. (2018) 33:298–306. doi: 10.1002/jbmr.3309
 57. Miller PD, Wagman RB, Peacock M, Lewiecki EM, Bolognese MA, Weinstein RL, et al. Effect of denosumab on bone mineral density and biochemical markers of bone turnover: six-year results of a phase 2 clinical trial. *J Clin Endocrinol Metab*. (2011) 96:394–402. doi: 10.1210/jc.2010-1805
 58. Bone HG, Bolognese MA, Yuen CK, Kendler DL, Miller PD, Yang YC, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. *J Clin Endocrinol Metab*. (2011) 96:972–80. doi: 10.1210/jc.2010-1502
 59. Anastasilakis AD, Makras P. Multiple clinical vertebral fractures following denosumab discontinuation. *Osteoporos Int*. (2016) 27:1929–30. doi: 10.1007/s00198-015-3459-5
 60. Aubry-Rozier B, Gonzalez-Rodriguez E, Stoll D, Lamy O. Severe spontaneous vertebral fractures after denosumab discontinuation: three case reports. *Osteoporos Int*. (2016) 27:1923–5. doi: 10.1007/s00198-015-3380-y
 61. Popp AW, Zysset PK, Lippuner K. Rebound-associated vertebral fractures after discontinuation of denosumab-from clinic and biomechanics. *Osteoporos Int*. (2016) 27:1917–21. doi: 10.1007/s00198-015-3458-6
 62. Lamy O, Gonzalez-Rodriguez E, Stoll D, Hans D, Aubry-Rozier B. Severe rebound-associated vertebral fractures after denosumab discontinuation: 9 clinical cases report. *J Clin Endocrinol Metab*. (2017) 102:354–8. doi: 10.1210/jc.2017-00096
 63. Polyzos SA, Terpos E. Clinical vertebral fractures following denosumab discontinuation. *Endocrine* (2016) 54:271–2. doi: 10.1007/s12020-016-1030-6
 64. Anastasilakis AD, Polyzos SA, Makras P, Aubry-Rozier B, Kaouri S, Lamy O. Clinical features of 24 patients with rebound-associated vertebral fractures after denosumab discontinuation: systematic review and additional cases. *J Bone Miner Res*. (2017) 32:1291–6. doi: 10.1002/jbmr.3110
 65. Cummings SR, Ferrari S, Eastell R, Gilchrist N, Jensen JB, McClung M, et al. Vertebral fractures after discontinuation of denosumab: a *post hoc* analysis of the randomized placebo-controlled freedom trial and its extension. *J Bone Miner Res*. (2018) 33:190–8. doi: 10.1002/jbmr.3337
 66. Parfitt AM. Morphological basis of bone mineral measurements: transient and steady state effects of treatment in osteoporosis. *Miner Electrolyte Metab*. (1980) 4:273–87.

67. Dempster DW. Exploiting and bypassing the bone remodeling cycle to optimize the treatment of osteoporosis. *J Bone Miner Res.* (1997) 12:1152–4. doi: 10.1359/jbmr.1997.12.8.1152
68. Einhorn TA. Bone strength: the bottom line. *Calcif Tissue Int.* (1992) 51:333–9. doi: 10.1007/BF00316875
69. Miller PD, Bolognese MA, Lewiecki EM, McClung MR, Ding B, Austin M, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone* (2008) 43:222–9. doi: 10.1016/j.bone.2008.04.007
70. Seeman E, Martin TJ. Co-administration of antiresorptive and anabolic agents: a missed opportunity. *J Bone Miner Res.* (2015) 30:753–64. doi: 10.1002/jbmr.2496
71. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. 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
72. Kaufman JM, Palacios S, Silverman S, Sutradhar S, Chines A. An evaluation of the Fracture Risk Assessment Tool (FRAX(R)) as an indicator of treatment efficacy: the effects of bazedoxifene and raloxifene on vertebral, nonvertebral, and all clinical fractures as a function of baseline fracture risk assessed by FRAX(R). *Osteoporos Int.* (2013) 24:2561–9. doi: 10.1007/s00198-013-2341-6
73. Allen MR, Iwata K, Sato M, Burr DB. Raloxifene enhances vertebral mechanical properties independent of bone density. *Bone* (2006) 39:1130–5. doi: 10.1016/j.bone.2006.05.007
74. Allen MR, Hogan HA, Hobbs WA, Koivuniemi AS, Koivuniemi MC, Burr DB. Raloxifene enhances material-level mechanical properties of femoral cortical and trabecular bone. *Endocrinology* (2007) 148:3908–13. doi: 10.1210/en.2007-0275
75. Gallant MA, Brown DM, Hammond M, Wallace JM, Du J, Deymier-Black AC, et al. Bone cell-independent benefits of raloxifene on the skeleton: a novel mechanism for improving bone material properties. *Bone* (2014) 61:191–200. doi: 10.1016/j.bone.2014.01.009
76. Ramchand SK, Chiang CY, Zebaze RM, Seeman E. Recurrence of bilateral atypical femoral fractures associated with the sequential use of teriparatide and denosumab: a case report. *Osteoporos Int.* (2016) 27:821–5. doi: 10.1007/s00198-015-3354-0
77. Chen P, Miller PD, Recker R, Resch H, Rana A, Pavo I, et al. Increases in BMD correlate with improvements in bone microarchitecture with teriparatide treatment in postmenopausal women with osteoporosis. *J Bone Miner Res.* (2007) 22:1173–80. doi: 10.1359/jbmr.070413
78. Bahar H, Gallacher K, Downall J, Nelson CA, Shomali M, Hattersley G. Six weeks of daily abaloparatide treatment increased vertebral and femoral bone mineral density, microarchitecture and strength in ovariectomized osteopenic rats. *Calcif Tissue Int.* (2016) 99:489–99. doi: 10.1007/s00223-016-0171-1
79. Bilezikian JP, Hattersley G, Fitzpatrick LA, Harris AG, Shevroja E, Banks K, et al. Abaloparatide-SC improves trabecular microarchitecture as assessed by trabecular bone score (TBS): a 24-week randomized clinical trial. *Osteoporos Int.* (2018) 29:323–8. doi: 10.1007/s00198-017-4304-9
80. Tsai JN, Uihlein AV, Burnett-Bowie SM, Neer RM, Derrico NP, Lee H, et al. Effects of two years of teriparatide, denosumab, or both on bone microarchitecture and strength (DATA-HRPQCT study). *J Clin Endocrinol Metab.* (2016) 101:2023–30. doi: 10.1210/jc.2016-1160
81. Macdonald HM, Nishiyama KK, Hanley DA, Boyd SK. Changes in trabecular and cortical bone microarchitecture at peripheral sites associated with 18 months of teriparatide therapy in postmenopausal women with osteoporosis. *Osteoporos Int.* (2011) 22:357–62. doi: 10.1007/s00198-010-1226-1
82. Leder BZ, O'Dea LS, Zanchetta JR, Kumar P, Banks K, McKay K, et al. Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab.* (2015) 100:697–706. doi: 10.1210/jc.2014-3718
83. Martin TJ, Seeman E. Abaloparatide is an anabolic, but does it spare resorption? *J Bone Miner Res.* (2017) 32:11–6. doi: 10.1002/jbmr.3042
84. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. 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
85. Seeman E, Nguyen TV. Bone remodeling markers: so easy to measure, so difficult to interpret. *Osteoporos Int.* (2016) 27:33–5. doi: 10.1007/s00198-015-3374-9
86. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med.* (2016) 375:1532–43. doi: 10.1056/NEJMoa1607948
87. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med.* (2017) 377:1417–27. doi: 10.1056/NEJMoa1708322
88. Cosman F, Crittenden DB, Ferrari S, Khan A, Lane NE, Lippuner K, et al. FRAME Study: the foundation effect of building bone with 1 year of romosozumab leads to continued lower fracture risk after transition to denosumab. *J Bone Miner Res.* (2018) 33:1219–26. doi: 10.1002/jbmr.3427
89. McClung MR, Brown JP, Diez-Perez A, Resch H, Caminis J, Meisner P, et al. Effects of 24 months of treatment with romosozumab followed by 12 months of denosumab or placebo in postmenopausal women with low bone mineral density: a randomized, double-blind, phase 2, parallel group study. *J Bone Miner Res.* (2018) 33:1397–406. doi: 10.1002/jbmr.3452
90. Geusens P, Marin F, Kendler DL, Russo LA, Zerbini CA, Minisola S, et al. Effects of teriparatide compared with risedronate on the risk of fractures in subgroups of postmenopausal women with severe osteoporosis: the VERO trial. *J Bone Miner Res.* (2018) 33:783–94. doi: 10.1002/jbmr.3384
91. Black DM, Greenspan SL, Ensrud KE, Palermo L, McGowan JA, Lang TF, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med.* (2003) 349:1207–15. doi: 10.1056/NEJMoa031975
92. Finkelstein JS, Leder BZ, Burnett SM, Wyland JJ, Lee H, de la Paz AV, et al. Effects of teriparatide, alendronate, or both on bone turnover in osteoporotic men. *J Clin Endocrinol Metab.* (2006) 91:2882–7. doi: 10.1210/jc.2006-0190
93. Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM. The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med.* (2003) 349:1216–26. doi: 10.1056/NEJMoa035725
94. Khosla S. Parathyroid hormone plus alendronate—a combination that does not add up. *N Engl J Med.* (2003) 349:1277–9. doi: 10.1056/NEJMe038143
95. Cosman F, Eriksen EF, Recknor C, Miller PD, Guanabens N, Kasperk C, et al. Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1-34)] in postmenopausal osteoporosis. *J Bone Miner Res.* (2011) 26:503–11. doi: 10.1002/jbmr.238
96. Tsai JN, Uihlein AV, Lee H, Kumbhani R, Siwila-Sackman E, McKay EA, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. *Lancet* (2013) 382:50–6. doi: 10.1016/S0140-6736(13)60856-9
97. Kostenuik PJ, Capparelli C, Morony S, Adamu S, Shimamoto G, Shen V, et al. OPG and PTH-(1-34) have additive effects on bone density and mechanical strength in osteopenic ovariectomized rats. *Endocrinology* (2001) 142:4295–304. doi: 10.1210/endo.142.10.8437
98. Samadifard R, Xia Q, Goltzman D. Co-treatment of PTH with osteoprotegerin or alendronate increases its anabolic effect on the skeleton of oophorectomized mice. *J Bone Miner Res.* (2007) 22:55–63. doi: 10.1359/jbmr.060915
99. Zebaze R, Ghasem-Zadeh A, Mbala A, Seeman E. A new method of segmentation of compact-appearing, transitional and trabecular compartments and quantification of cortical porosity from high resolution peripheral quantitative computed tomographic images. *Bone* (2013) 54:8–20. doi: 10.1016/j.bone.2013.01.007

100. Leder BZ, Tsai JN, Uihlein AV, Wallace PM, Lee H, Neer RM, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. *Lancet* (2015) 386:1147–55. doi: 10.1016/S0140-6736(15)61120-5
101. Bone HG, Cosman F, Miller PD, Williams GC, Hattersley G, Hu MY, et al. ACTIVEExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis. *J Clin Endocrinol Metab.* (2018) 103:2949–57. doi: 10.1210/jc.2018-00163
102. Langdahl BL, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS, et al. Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. *Lancet* (2017) 390:1585–94. doi: 10.1016/S0140-6736(17)31613-6

Conflict of Interest Statement: ES has received research support and lecture fees from Amgen, Allergan, and Eli Lilly; he is a director of the board and shareholder of StraxCorp.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Ramchand and Seeman. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.