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Optimising Antiresorptive Therapies in Postmenopausal Women

Why Do We Need to Give Due Consideration to the Degree of Suppression?

Morten A. Karsdal,[1,2] *Per Qvist*,[2] *Claus Christiansen*[1] and *László B. Tankó*[2]

1 Center for Clinical and Basic Research (CCBR), Ballerup, Denmark
2 Nordic Bioscience Diagnostics, Herlev, Denmark

Abstract

Accelerated bone turnover with bone resorption exceeding bone formation is a major mechanism underlying postmenopausal bone loss and hence the development of osteoporosis. Accordingly, inhibition of bone resorption is a rational approach for the prevention of osteoporosis. In this context, the most logical option, hormone replacement therapy, reverses the rate of bone turnover to premenopausal levels, whereas the magnitude of inhibition by amino-bisphosphonates and the recently introduced anti-receptor activator of NFκB ligand (RANKL) antibody often exceeds this. As bone turnover has crucial implications for the continuous renewal of bone tissue, the over-suppression of bone turnover has potential consequences for bone quality and strength. Long-term treatment with potent bisphosphonates has recently been associated with osteonecrosis of the jaw and dose-dependent increases in micro-crack accumulation in animals. Although these observations are the subject of ongoing discussions, it is timely to discuss whether the over-suppression of bone turnover below premenopausal levels is really our ultimate goal when defining the success criteria for antiresorptive agents.

In this review, the implications of high and excessively low bone turnover of endogenous origin for bone quality, fracture risk and integrity of the jaw are discussed. In addition, animal and clinical research revealing initial findings regarding the potential adverse effects of drug-induced suppression of bone remodeling are summarised. The inhibition of bone resorption, which is either transient between doses (e.g. with calcitonin) or does not exceed premenopausal levels (with hormone replacement therapy or selective estrogen receptor modulators), is preferable because it not only provides similar antifracture efficacy but can also assist in the maintenance of the dynamic repair of micro-cracks/microfractures.

Bone is a dynamic tissue that is continuously remodelled throughout life not only to maintain circulating calcium homeostasis but also to repair tissue damage (micro-cracks) that impairs bone quality.[1] This continuous remodelling of bone involves the function of cells that are associated with the resorption of old bone (osteoclasts) and formation of new bone (osteoblasts).

The homeostatic balance between bone resorption and formation is influenced by various factors including, but not restricted to, local cytokines, systemic hormones and mechanical stimuli.[2-4] The loss of ovarian sex steroids in postmenopausal women results in an acceleration of bone turnover with a predominance of bone resorption over bone formation. The related negative calcium balance promotes bone loss and increases bone fragility, thereby increasing the risk of osteoporotic fractures.[5] A rational approach to counter these unwanted processes is the inhibition of bone resorption; however, this also leads to the inhibition of bone formation as a result of the coupling of these cellular events.[6-8] Accordingly, pronounced inhibition of osteoclast function can be expected to impair the dynamic renewal of skeletal tissue, leading to an alteration of bone quality and strength.[9]

To draw attention to the need for due consideration of this aspect of antiresorptive therapy, this review summarises selected experimental and clinical observations illustrating the links between bone turnover and the maintenance of the normal skeletal phenotype.

The literature search considered publications on PubMed from 1980 to 2006, as well as abstracts from the American Society of Bone and Mineral Research meetings between 1998 and 2005. The search strategy focused on bone turnover and the pathology of bone, taking into account experimental models of low bone turnover and pharmacological suppression of bone turnover (antiresorptive strategies).

1. Relationship Between Bone Mineral Density (BMD) and Fracture Risk

Bone mineral density (BMD) has been considered the most important determinant of fracture risk. However, the risk of an osteoporotic fracture is approximately 10-fold higher in an old individual than in a young individual with the same BMD.[10] Recent data demonstrate that during antiresorptive therapy the reduction in fracture risk is explained only vaguely by the concomitant increase in BMD.[11] This is illustrated by findings summarised in table I showing that even though drugs have become more effective in terms of increasing BMD, antifracture efficacy does not follow correspondingly. As an example, the mean increase in spinal BMD with alendronate is 7-fold higher than that with calcitonin (8.3% vs 1.2%), yet the reductions in

Table I. Discrepancies between the increase in bone mineral density (BMD) during antiresorptive therapy and the reduction in fracture risk (reproduced from Faulkner,[11] with permission)

Study	Drug	Drug class	Increase in BMD (%)	Reduction in vertebral fracture (%)	Spine T-score[a]
FIT II[16]	Alendronate	Bisphosphonate	8.3	44	−2.1
FIT I[17]	Alendronate	Bisphosphonate	7.9	47	−2.5
RVE[18]	Risedronate	Bisphosphonate	7.1	49	−2.8
RVN[19]	Risedronate	Bisphosphonate	5.4	41	−2.4
MORE[20]	Raloxifene	SERM	2.6	40	−2.6
PROOF[15]	Calcitonin	Natural hormone	1.2	36	<−2.0

a Standard deviation below young adult mean BMD.

FIT = Fracture Intervention Trial; **MORE** = Multiple Outcome of Raloxifene Evaluation; **PROOF** = Prevent Recurrence Of Osteoporotic Fractures trial; **SERM** = selective estrogen receptor modulator.

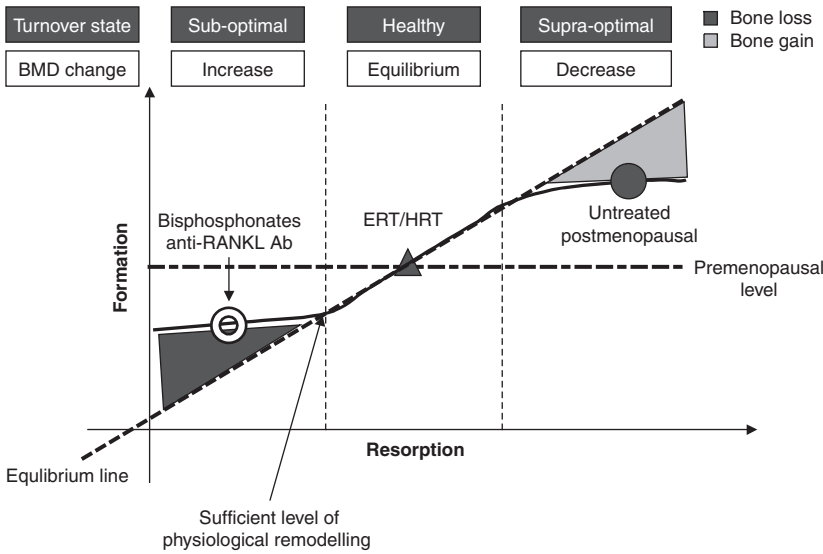

Fig. 1. Association between bone turnover and changes in bone mineral density (BMD). The equilibrium line represents the condition where bone formation and bone resorption are balanced and bone mass is sustained. In postmenopausal women (black circle), bone turnover is supra-optimal, with the rate of bone resorption exceeding the rate of bone formation, collectively leading to bone loss. In women receiving a potent bisphosphonate, bone turnover is often below the premenopausal mean or the mean of those receiving estrogen replacement therapy (ERT), and hence is sub-optimal. The relative over-suppression of bone resorption exceeding the suppression of bone formation promotes greater increases in BMD. The question is whether the lack of corresponding increases in antifracture efficacy is due to a parallel impact on bone quality. **Ab** = antibody; **HRT** = hormone replacement therapy; **RANKL** = receptor activator of NFκB ligand.

vertebral fracture risk are fairly comparable (44% vs 36%, respectively).[11,12] However, this may not be equally true for non-vertebral fractures. A meta-analysis indicates that alendronate and risedronate provide non-vertebral antifracture efficacy, whereas such an effect cannot be claimed for raloxifene or calcitonin.[13] However, it should be noted that neither the MORE (Multiple Outcome of Raloxifene Evaluation) study[14] nor the PROOF (Prevent Recurrence Of Osteoporotic Fractures) study[15] was specifically designed to demonstrate non-vertebral antifracture efficacy, although the MORE study does have the statistical power to provide hints.

2. Relationship Between Bone Turnover and BMD

The association between bone turnover and changes in BMD is illustrated in figure 1.

Along the equilibrium line, there is a homeostatic balance between bone resorption and bone formation as in healthy premenopausal women. In postmenopausal women, bone turnover is accelerated (supra-optimal remodelling) and the relative increase in bone resorption exceeding the rate of bone formation leads to a negative calcium balance and hence to bone loss. Estrogen replacement therapy may reverse the acceleration of bone turnover and restore equilibrium in postmenopausal women. In contrast, the suppressive effect of other, more potent antiresorptive drugs such as bisphosphonates or the anti-receptor activator of NFκB ligand (RANKL) antibody, denosumab (AMG-162), may result in the over-suppression of bone remodelling, with turnover rates falling below premenopausal levels (sub-optimal remodelling). Table II provides some examples of steady-state decreases in biomarkers of bone resorption with recommended doses of hormone replacement therapy (HRT), bisphosphonates and denosumab.

Table II. The effect of various antiresorptive therapies on bone resorption measured by biochemical markers (urinary C-telopeptide of type I collagen [CTX-I] and cross-linked N-terminal telopeptide of type I collagen [NTX])[a]

Drug	Treatment period	Change in resorption at the end of the study (%)	References
Hormone replacement therapy	1 year	−45 to 53	21-23
Ibandronate	1 year		24-26
2.5 mg/day		−63	
150mg every 2 months		−57	
Risedronate 5 mg/day	6 months	−60	27
Alendronate 10 mg/day	1 year	−75	6,8,28,29
Zoledronic acid 4mg (single dose)	1 year	−75	30,31
Denosumab (AMG-162)	6 months	−80	32

a Note that the degree of inhibition with alendronate, zoledronic acid and denosumab is well below the inhibition achieved by hormone replacement therapy, which represents premenopausal levels.

To address these apparent quantitative differences more adequately, the results from a randomised clinical trial published by Lindsay et al.,[33] who investigated the effect of alendronate or placebo in postmenopausal women receiving HRT, are worth revisiting. After the initiation of alendronate treatment, bone resorption and bone formation showed significant decreases. In contrast, those who received HRT plus placebo continued to show stable levels of bone resorption. They also provided evidence that the rates of bone formation and resorption in HRT-treated women were within the normal premenopausal range. The significantly more pronounced effect of conventional doses of alendronate and risedronate on bone turnover compared with that of HRT has also been reported by other investigators.[34,35] The stronger effect on bone resorption benefits, in terms of BMD gain, was indicated by a significantly higher spine and hip BMD in the group receiving combined treatment than in the group receiving HRT only (figure 2).

3. Bone Turnover and Fracture Risk

In the large prospective EPIDOS (Epidemiologie de l'Osteoporose) study, elevated biomarkers of bone remodelling were found to be independent predictors of fracture risk.[36-39] Furthermore, a recent study from the Mayo Clinic found that bone turnover accounted for more than half of all vertebral fractures and that the reduction in fracture risk resulting from interventions can to a large extent be ascribed to the inhibition of bone remodelling.[40] As an example, in the MORE trial, 30–40% of the antifracture efficacy of raloxifene was due to the inhibition of bone turnover.[14] Therefore, decreasing bone remodelling is an important therapeutic goal of antiresorptive therapy.

4. Why Do Bisphosphonates Have Lasting Effects on Bone Turnover?

Amino-bisphosphonates bind strongly to hydroxyapatite and become incorporated into bone tissue, with a terminal half-life in bone similar to that of calcium and other minerals.[41] Consequently, small amounts of bisphosphonate accumulate in bone, approximately proportional to the duration of treatment. The retained bisphosphonate is not active until it is subsequently released by bone remodelling, as evident from stable levels of bone turnover with continued treatment. After the discontinuation of therapy, bisphosphonate molecules that are sequestered in bone can be released again as a result of bone resorption during the normal remodelling process. Although the amount of bisphosphonate released by bone remodelling is small compared with the usual oral therapeutic dose, this release from bone is probably responsible for the relatively slow

changes in bone turnover markers and BMD after the withdrawal of treatment.

The study by Wasnich et al.[42] provides an illustration of the much slower and incomplete recovery of bone remodelling over the 2 years after the withdrawal of treatment in alendronate-treated individuals compared with HRT-treated individuals. This lasting suppressive effect of bisphosphonate treatment on bone remodelling was also demonstrated in the extension of FIT (Fracture Intervention Trial). Following re-randomisation of the patients who had received bisphosphonates for 4 years, turnover rates of patients continuing with placebo treatment in the subsequent 3 years were not significantly different from those continuing with bisphosphonate treatment.[28] Interestingly, as shown by Reid et al.,[30] a single injection of zoledronic acid 4mg, the most potent bisphosphonate, was able to evoke a marked suppression of bone resorption that lasted over a 13-month observation period. In a long-term follow-up study, we demonstrated that bone turnover markers were no longer significantly different from baseline levels 5–7 years after the withdrawal of treatment.[43]

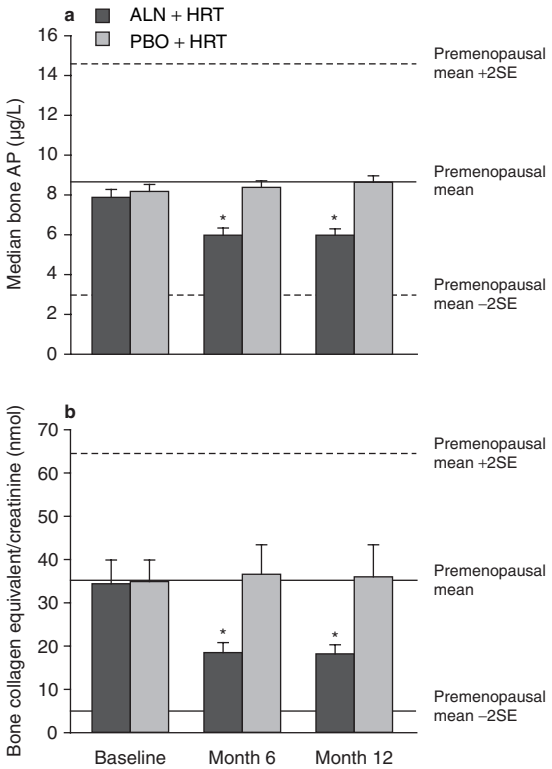

Fig. 2. Median absolute values (± standard error; SE) of bone alkaline phosphatase (AP) [**a**] and urinary cross-linked N-terminal telopeptide of type I collagen (NTX) [**b**] in postmenopausal women treated with alendronate (ALN) 10 mg/day plus hormone replacement therapy (HRT) or placebo (PBO) plus HRT at baseline, month 6 and month 12 of the treatment period (reproduced from Lindsay et al.,[33] with permission; copyright © 1999, The Endocrine Society). * indicates significantly different.

5. Discrepancies

As discussed in sections 1–4, apparent discrepancies exist between the degree of inhibition of bone remodelling and change in BMD (figure 1), and between the change in BMD and reduction in fracture risk (table I). It is tempting to speculate that discrepancies between these parameters might reflect the neglected implications of bone quality and strength. Bone strength, like the strength of any physical construction, is determined by three parameters: (i) the mechanical properties of the material (e.g. degree of mineralisation); (ii) the spatial arrangement of the material (e.g. trabecular microarchitecture); and (iii) the mass of the material (i.e. BMD). BMD increases during prolonged inhibition of bone remodelling, yet we cannot exclude the possibility that parallel alterations of microstructure or mineralisation counter the favourable effects of BMD gain on fracture risk.

6. Manifestations of Low Bone Remodelling

Osteopetrosis or ‘brittle bone disease’ is the collective name for conditions of diverse origin that are characterised by over-mineralisation of bone tissue, alterations of bone quality and bone strength, and a relatively high incidence of fragility fractures. Although the aetiology of osteoporosis is diverse, the underlying common cause is abrogated osteoclast

function and disruption of the physiological processes of bone remodelling.[44,45] For example, loss-of-function mutations in the *Cathepsin K* (an osteoclast-specific protease) gene are associated with osteopetrotic bone phenotype, disorganised bone structure and extensive fragility fractures.[44,45] Similarly, the genetic ablation of genes essential for osteoclast function, such as *a3V-ATPase*, *RANK*, *RANK-L*, *ClC-7* and *M-CSF* are also associated with characteristics of osteopetrosis.[46-52] Manolios et al.[53] described necrotic bone lesions in the femoral heads of osteopetrotic patients (pseudo-avascular necrosis). Interestingly, the genetic problems of osteoclast function are frequently associated with different malformations of the jaw, periodontal diseases and impaired tooth development, etc.,[54,55] suggesting that physiological bone remodelling is particularly important for the maxilla and mandibular.

Having discussed the implication of extremely low bone turnover for bone abnormalities, it is relevant to ask whether the chronic inhibition of bone resorption by pharmacological agents may lead to similar abnormalities. The reason for asking this is provided by recent reports describing an increased incidence of osteonecrosis of the jaw (ONJ) among long-term recipients of bisphosphonates.[56-63] According to Hoff et al.,[64] 1.3% of patients receiving intravenous bisphosphonates develop ONJ or ONJ-like symptoms. It is to be emphasised that many of the ONJ cases occurred in cancer patients who had received immunosuppressive therapy. Immunosuppression can decrease the number of osteoclast progenitors,[65,66] suggesting that its synergism with the effects of bisphosphonates in terms of decreasing the number of osteoclasts might actually be a crucial factor in the pathogenesis of ONJ. Bisphosphonates also induce programmed cell death (apoptosis) of osteoclasts via the inhibition of the mevalonate pathway, which is involved in the regulation of various cell survival signals.[67-69] While this serious adverse effect may be of less concern when considering the treatment of osteoporotic postmenopausal women with bisphosphonates, it needs to be documented adequately.

Finally, observations indicate that high doses of intravenous bisphosphonates may promote decreased angiogenesis.[70] As the jaw is a highly vascularised area (corresponding to its high physical challenge and remodelling rate), decreased angiogenesis would also be a limitation in maintaining homeostatic balance and thus a triggering mechanism for the manifestation of ONJ.

Animal experiments have shed light on the causal links between long-term bisphosphonate treatment and dose-dependent increases in micro-crack accumulation in bone tissue.[71-76] Interestingly, the sustained suppression of bone resorption with selective estrogen receptor modulators (SERMs) does not promote micro-crack accumulation in monkeys,[71] indicating that a more moderate suppression of bone turnover not exceeding premenopausal levels maintains the structural integrity of skeletal tissue. Micro-crack accumulation affects the mechanical and material properties of cortical bone, which in turn may have consequences for the development of skeletal fragility and stress fractures. Currently, there is no definitive evidence that long-term treatment with bisphosphonates increases the risk for fragility fractures (the 10-year follow-up of alendronate-treated patients was not sufficiently powered to provide insights).[29] However, some observations point to a likely impact on bone quality.[76] A recent report by Odvina et al.[9] described nine patients who sustained spontaneous non-vertebral fractures while receiving alendronate therapy, six of whom displayed either delayed or absent fracture healing for 3 months to 2 years while receiving antiresorptive therapy. The investigators performed a thorough histomorphometric analysis of the cancellous bone, which showed signs of markedly suppressed local bone formation with a reduced or

absent osteoblastic surface in most patients. Biochemical markers did not indicate reduced levels of bone formation, illustrating that regional alterations are not necessarily reflected by the measurement of circulating levels of biomarkers, which represent the integration of bone turnover of the entire skeleton. The osteoclastic surface was reduced in eight patients and the eroded surface showed a decrease in four patients. In addition, matrix synthesis was markedly diminished, with the absence of a double-tetracycline label and an absent or reduced single-tetracycline label in all patients. These trends were also applicable to intracortical and endocortical surfaces. As the study was fairly small and participants may not be considered as typical for the average postmenopausal woman, more extensive histomorphometric data are needed to draw definitive conclusions.

7. Anti-RANKL Antibody

Denosumab is a human monoclonal antibody to RANKL that blocks the binding of RANKL to RANK. The drug has an efficacy comparable to that of the most potent bisphosphonate, zoledronic acid. Indeed, a recent single-dose placebo-controlled study by McClung et al.[77] that assessed the effect of denosumab (0.3–3.0 mg/kg) on biochemical markers of bone turnover, demonstrated a dose-dependent, rapid (within 12 hours) and profound (up to 84%) decrease in urinary cross-linked N-terminal telopeptide of type I collagen (NTX), which was sustained for 6 months. The impact of long-term treatment with denosumab on bone quality and strength is unknown. Experimental studies investigating the effects of treatment with osteoprotegerin (OPG) – a competitor ligand of RANKL – provide some indirect hints.[78,79] One of these studies showed that a single injection of human OPG (5 mg/kg) causes an approximately 95% reduction in the osteoclast surface per bone surface after 10 days.[78] Ulrich-Vinther and Andreassen[79] investigated fracture healing in rats receiving either OPG or placebo. They showed that OPG treatment evoked marked decreases in the number of osteoclasts by 93%. This change was accompanied by augmented callus dimensions, hampered deposition of new woven bone at the fracture line of the genuine cortical bone and, interestingly, severely hampered integration of newly formed bone into cortical bone. They also reported altered mechanical properties of bones with an impaired number/function of osteoclasts marked by a 50% decrease in ultimate stress,[79] which translates to decreased bone strength and bone quality in the callus. The importance of a sufficient number of osteoclasts for the maintenance of bone formation and remodelling to ensure proper bone quality is also emphasised by various animal models lacking osteoclasts, such as the Csf1r−/− mice or the op/op mice.[80,81]

8. Conclusions and Perspectives

While more clinical data are needed to establish evidence-based links between the marked suppression of bone markers, changes in bone quality and their implications for ONJ or fragility fractures, authorities stay alert to the possibility that the marked and sustained inhibition of bone turnover is part of the pathogenesis of these clinical conditions.[56] The use of constantly improving methods to address the different aspects of bone quality will hopefully help to answer many of the remaining questions.

While the differences between HRT or SERM and bisphosphonates or denosumab are apparently only quantitative and can be solved by dose adjustment, the effect of the latter two in promoting a marked reduction of the number of osteoclasts might be an important pathogenic factor, especially when synergising with other medications (e.g. immunosuppression). Collectively, in our opinion, it is timely to revisit our strategic approach to the definition of therapeutic goals for medications targeting

the inhibition of bone resorption. Physiological modulators of osteoclast function – calcitonin and estrogen (and SERMs) – are preferable, not only because they provide similar antifracture efficacy but also because they maintain sufficient bone remodelling and the reparation of micro-cracks/microfractures. To provide evidence for these assumptions in the human context, further studies using advanced techniques of bone quality measurements are awaited.

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Correspondence and offprints: Dr *Morten A. Karsdal*, Nordic Bioscience A/S, Herlev Hovedgade 207, DK-2730 Herlev, Denmark.
E-mail: mk@nordicbioscience.com