Surface-specific bone formation effects of osteoporosis pharmacological treatments

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Abstract

Current anti-osteoporotic pharmacological treatments reduce fracture risk in part by altering bone remodeling/modeling. These effects can manifest on any or all of the bone envelopes – periosetal, intracortical, and trabecular/endocortical – each of which has unique effects on the biomechanical properties of bone. The purpose of this review is to provide an overview of how the most common FDA-approved anti-osteoporosis agents (bisphosphonates, estrogen/hormone replacement therapy, selective estrogen receptor modulators (SERMs), and parathyroid hormone (PTH)) affect tissue-level remodeling/modeling on each of the bone surfaces. Iliac crest biopsy data, the only means of assessing surface-specific bone formation in humans, exist for all of these agents although they predominately focus on trabecular/endocortical surfaces. Data from pre-clinical animal models provide an essential complement to human studies, particuarily for changes on periosteal surfaces and within the intracortical envelope. Although all of the anti-catabolic agents (estrogen replacement therapy, SERMs, bisphosphonates) exert positive effects on the various bone surfaces, the bisphosphonates produce the unique biomechanical combination of allowing normal periosteal expansion while limiting remodeling-induced bone loss on intracortical and trabecular/endocortical surfaces. PTH, the only FDA-approved anabolic agent, exerts biomechanically favorable alterations though enhanced trabecular/endocortical surface activity while also stimulating periosetal expansion. Through understanding how current and future anti-osteoporotic agents influence surface-specific bone activity we will move one step closer to developing agents that could potentially target a particular bone surface.

Key words: bisphosphonates, estrogen/hormone replacement therapy, selective estrogen receptor modulators (SERMs), parathyroid hormone

Introduction

Current osteoporosis pharmacoloical treatments are highly effective in reducing fracture risk [1-3]. The mechanisms underlying fracture risk reduction with the various treatments is not completely understood but is due in large part to the effect these agents have on bone remodeling/modeling. Bone remodeling, the coupled process of bone resorption and formation, serves to renew bone tissue and occurs on trabecular and endocortical bone surfaces and within the cortex (intracortical remodeling) (**Fig. 1**). Bone modeling, an uncoupled process in which formation or resorption occur independent of the other, occurs on trabecular, endocortical, and periosteal surfaces.

Anti-osteoporotic agents can be classified as anti-catabolic or anabolic [4]. Anti-catablic agents, including bisphosphonates, estrogen/hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), and calcitonin work primarily by suppressing bone remodeling. Remodeling suppression slows bone loss, preserving bone architecture and geometry. The only anabolic agent currently approved for treating osteoporosis, parathyroid hormone (PTH), stimulates both modeling and remodeling which preserves, and in some cases enhances, bone architecture and geometry. While the modeling/remodeling effect of each anti-catabolic and anabolic agent is important, the surface(s) on which the effects occur are perhaps more important for bone biomechanics and fracture risk reduction.

The purpose of this review is toprovide an overview of how the FDA-approved anti-osteoporosis agents affect tissue-level remodeling/modeling on eavh of the bone

envelopes - periosteal, intracortical, and endocortical/trabecular - and how this is likely to influence bone biomechanics. As a limiated amount of human data exist (from bone biopsy analyses), the majority of information comes from pre-clinical animal studies. This results in a certain degree of ambiguity with respect to determining how each agent affects the various surfaces as differences among studies, such as species, treatment (dose and duration), and whether or not the animals are intact or ovariectomized, all influence remodeling/modeling effects. Therefore, for each of the bone surfaces, the effects of the various treatments will be summarized for humans, intact animals, and ovariectomized animals, the latter two catagories focusing mostly on large animal models.

Periosteal surface

Periosteal bone surfaces primarily undergo modeling which is most prominent during growth and development yet continues at a slower rate in adults [5]. Remodeling does occur on periosteal surfaces [6-8] but is generally considered to constitute a small percentage of overall activity on this surface. The addition of bone to the periosteal surface exponentially enhances bone biomechanical properties by increasing the cross-sectional moment of inertia [7, 9]. This is true both for bones made exclusively of cortical bone (e.g. long bone diaphysis) and for those with significant amounts of trabecular bone (e.g. vertebra and femoral neck) [10]. The clinical implications of periosteal expansion are significant as only a small amount of bone needs to be added to this surface to enhance the biomechanical properties [7, 11]. Periosteal expansion can also offset the negative biomechanical effects associated with bone loss from other bone envelopes as only 30% of bone mass lost from the endocortical surface needs to be added

to the periosteal surface to achieve equivalent biomechanical properties [11]. Despite the substantial biomechanical benefit of periosteal apposition, very little clinical data exists concerning the effects of anti-osteoporosis pharmaceutical agents on this surface.

Loss of estrogen increases periosteal expansion while estrogen supplementation suppresses expansion [12-15]. Ample histological data exist concerning the effects of hormone/estrogen replacement therapy (HRT) in humans yet they do not routinely include analyses of the periosteal surface. The available data, published only in abstract form, suggest reduced periosteal formation with HRT [16]. There is no data on the effects of selective estrogen receptor modulators (SERMs) on periosteal bone formation. Raloxifene, one of the most commonly studied SERMs, had no effect on femoral periosteal bone formation in ovariectomized cynomolgus monkeys suggesting it does not inhibit periosteal expansion in estrogen-deplete situations [15]. Conversely, in an intact beagle dog model where endogenous estrogen levels are normal, raloxifene significantly enhanced periosteal bone formation rate compared to controls [17].

Bisphosphonates exert their skeletal effect through suppression of remodeling and therefore would be expected to have minimal direct effect on periosteal surfaces. Clinical data describing bone formation activity on periosteal surfaces, published only in abstract form, suggest no effect of alendronate on the periosteal surface of iliac crest biopsies [16, 18]. Pre-clinical studies with intact beagles [17, 19-21], ovariectomized beagles [22], and intact minipigs [23] have consistently shown no significant effect of bisphosphonates on periosteal bone formation. Significant suppression of periosteal bone formation has been

shown in several rodent studies [24-26] although the absence of similar data in larger pre-clinical models or humans suggest this may a species-specific effect.

As an anabolic agent, intermittent PTH (teriparatide, synthetic PTH [hPTH(1-34)], recombinant human teriparatide [rhPTH(1-34)], or PTH(1-84)), would be expected to have the greatest effect of all the approved osteoporosis agents on periosteal bone [3, 27]. While iliac crest biopsy samples from PTH-treated patients consistently show increased cortical thickness compared to placebo-treated patients [28-31], periosteal surface bone formation results have been conflicting. Following 1 month of treatment, periosteal bone formation rate was significantly higher than controls [32] showed no significant difference between PTH- and placebo-treated patients [28, 33]. Intact rabbits, the only large animal model in which periosteal bone responses to PTH have been examined, have shown significantly higher periosteal bone formation with PTH treatment compared to vehicle [34-36].

Summary- Periosteal surfaces (Table 1)

Periosteal expansion has a significant effect on fracture risk yet there are minimal data describing how anti-osteoporosis agents influence activity on this surface. Beginning at menopause, the loss of endogenous estrogen simulates periosteal expansion. Estrogen/hormone replacement therapy suppresses this periosteal expansion while bisphosphonates have no effect. The human data concerning SERMs and PTH on periosteal bone are insufficient to draw conclusions concerning their effects although

143 some clinical and the majority of pre-clinical data suggest an anabolic effect (or at worst
144 no effect) with PTH.
145
146 **Intracortical envelope**
147 The bone cortex of humans and many large animal research models (non-human
148 primates, dogs, pigs, rabbits) routinely undergoes intracortical (osteonal) [37, 38].
149 Similar to trabecular bone remodeling, the loss of estrogen at menopause is associated
150 with an imbalance in the amount of bone formation relative to resorption within
151 intracortical remodeling units. This negative bone balance, coupled with the increases in
152 intracortical remodeling, result in high levels of cortical porosity in postmenopausal
153 women. Intracortical porosity is inversely related to mechanical properties [39, 40] yet
154 its effect is highly dependent on the spatial location of the pores. In bending or torsion,
155 cortical porosity near the outer periosteal surface has a greater negative effect on
156 biomechanics as compared to if the voids are near the endocortical surface [34, 39]. As
157 with the periosteal surface, few clinical data exist concerning the effects of
158 pharmaceutical agents on intracortical remodeling emphasizing the importance of pre-
159 clinical models. In the case of intracortical remodeling, pre-clinical models are limited
160 exclusively to large animal models as under normal physiological conditions rodents lack
161 intracortical remodeling.
162
163 Reductions in circulating estrogen increase cortical porosity through stimulation of
164 intracortical remodeling [15, 22, 41]. In response to drug-induced or naturally occurring
165 reductions in circulating estrogen, HRT inhibited increased intracortical remodeling and

cortical porosity [41, 42]. Similar results have been noted in non-human primates wherein intracortical remodeling increased with estrogen withdrawal leading to increases in cortical porosity [15]. These increases in remodeling and porosity were reduced in animals treated with either estrogen or raloxifene [15]. Treatment of intact beagles with raloxifene had no effect on intracortical remodeling [17].

Bisphosphonates, due to their suppression of remodeling, would be expected to suppress intracortical remodeling. Human data are limited and conflicting. Following 1 to 3 years of risedronate treatment, iliac crest cortical porosity was not different compared to baseline levels or age-matched placebo controls [43, 44]. Conversely, biopsies from women treated for 2-3 years with alendronate had significantly lower cortical porosity in the iliac crest compared to placebo-treated patients [45]. Pre-clinical models consistently document reductions in intracortical remodeling with bisphosphonates. In ovariectomized non-human primates clodronate suppressed tibia intracortical bone formation to control levels [46] while ibandronate reduced intracortical remodeling in the rib and central radius, but not the femoral neck, compared to controls [47]. Suppression of intracortical turnover with bisphosphonates has also been shown in ovariohysterectomized beagles [22], intact beagles [19, 21, 48], and intact minipigs [23].

Of the approved osteoporosis treatments, PTH has the most distinct effect on intracortical remodeling. Using intact female rabbits, PTH has been shown to produce a rapid increase (within the first remodeling cycle) of intracortical bone remodeling [36] which is sustained with continued treatment [35, 36]. This stimulation of remodeling leads to a

189 significant increase in cortical porosity [35, 36]. While an increase in porosity would be
190 predicted to reduce biomechanical properties, the preferential location of intracortical
191 remodeling and porosity near the endocortical surface with PTH minimized any negative
192 biomechanical effects. For example, the increased porosity near the endocortical surface
193 with PTH compromised the cross-sectional moment of inertial (CSMI; an index of
194 biomechanical strength) by less than 2%; if this same amount of porosity were located
195 near the periosteal surface the CSMI would be reduced by almost 10% [35]. Similar
196 results have been documented in ovariectomized non-human primates where intracortical
197 turnover rate was significantly increased in the femur [49], humerus [50], and femoral
198 neck [49] following PTH treatment. The increased porosity with PTH in these non-
199 human primate studies was most notable near the endocortical surface [50], as with the
200 rabbits, and therefore resulted in only minimal consequences to the biomechanical
201 properties of these bones [50]. Increases in cortical porosity with PTH have also been
202 shown in an intact dog model suggesting that similar changes within the cortex occur
203 with PTH treatment when estrogen levels are normal [51]. Human data concerning
204 changes with PTH are limited, yet the porosity data are not consistent with pre-clinical
205 studies. Paired iliac crest biopsies from PTH-treated patients showed a trend toward
206 increased porosity [30] although there was clearly no effect in two other studies of PTH-
207 treatment [28, 29]; these clinical studies did not assess intracortical remodeling.
208
209 *Summary- Intracortical envelope (Table 1)*
210 Intracortical remodeling increases during menopause, leading to higher levels of cortical
211 porosity which reduces biomechanical properties. Anti-catabolic osteoporosis agents,

HRT, SERMs, and bisphosphonates, appear to suppress intracortical remodeling and therefore reduce cortical porosity. Several large animal models show PTH stimulates intracortical remodeling and increases cortical porosity, the biomechanical consequences of which are minimized through preferential location of such activity near the endocortical surface. Based on these data, the anti-catabolic agents provide the most favorable effect on intracortical bone as they reduce cortical porosity in postmenopausal women. However anabolic agents are also attractive for this bone envelope as enhanced remodeling would serve to renew bone tissue and occur spatially such that it has minimal consequences to biomechanics.

Trabecular/Endocortical surfaces

At menopause, bone remodeling increases on trabecular and endocortical surfaces [52-54] resulting in a significant loss of bone volume and trabecular architecture [44, 55]. Bone formation activity on the trabecular surface is the most studied of the bone envelopes however it is the most complex surface to assess how remodeling/modeling influences biomechanics due to the intimate relationship between trabecular and cortical bone. There is a clear biomechanical benefit of increasing trabecular bone volume with the enhancement of trabecular number having a greater benefit compared to increasing trabecular thickness [56]. Equally important to biomechanics is having a well-connected trabecular network. Therefore, changes in both bone volume and architecture likely determine the ultimate biomechanical effect of anti-osteoporosis treatments on trabecular bone.

The effect of HRT on trabecular surface activity is conflicting. HRT has been shown to significantly suppress trabecular bone remodeling in the majority of human studies [54, 57-60] although other studies have shown no effect [61-64]. Similar discrepancies exist for the effects of HRT on bone volume and architecture with one study showing beneficial effects [62] and others showing no effect [58, 60, 63, 64]. Data from humans treated with SERMs have provided more consistent results compared to HRT, having shown significant [54, 65] and non-significant [58] reductions in trabecular bone remodeling with raloxifene compared to controls. Ovariectomized non-human primates had significantly lower trabecular and endocortical bone formation rates at the iliac crest, vertebra, and tibia when treated with either estrogen or raloxifene [15, 66]. Intact beagle dogs have non-significantly lower trabecular bone remodeling with raloxifene [67].

Studies examining the effect of bisphosphonates on trabecular bone remodeling and bone volume consistently show significant suppression of bone remodeling on both trabecular and endocortical surfaces [43, 68-71]. These reductions in remodeling with bisphosphonate treatment are associated with prevention of the normal loss of bone volume and architecture in placebo-treated patients [43, 44, 55, 71, 72]. Pre-clinical models similarly show that bisphosphonates suppress remodeling and increase bone volume in ovariectomized non-human primates [46, 47, 73], ovariectomized beagles [22, 74], intact minipigs [23], and intact beagles [17, 21, 48, 73, 75-79].

In contrast to anti-catabolic agents, PTH has anabolic effects on trabecular bone formation which are modulated through both bone modeling and remodeling activity

[80]. PTH stimulates trabecular surface modeling [32, 81-83] and affects remodeling by altering the balance at each remodeling site to favor bone formation [28, 51]. Enhancement of trabecular bone volume and bone remodeling have been shown in postmenopausal women treated with intermittent PTH [29, 32, 84] although other studies have shown no significant difference from baseline biopsies in PTH-treated patients for trabecular formation activity or bone mass [28, 85]. In ovariectomized non-human primates, multiple skeletal sites (femoral neck, tibia, distal radius, and vertebra) showed no difference in PTH versus controls for trabecular bone formation rate although bone formation was stimulated on endocortical surfaces of the mid-radius and mid-femur [86]. Conversely, a separate study showed enhanced bone formation activity on trabecular bone surfaces of the femoral neck with PTH [49]. Changes with PTH treatment are most consistent in intact animals, with increases in trabecular/endocortical bone remodeling having been documented in ewes [87], beagles [51, 88], and rabbits [35, 36]. These pre-clinical models have shown enhancement of trabecular bone formation activity with PTH results in increased trabecular bone volume by initially producing thicker trabeculae, and then over time via trabecular tunneling [89], normalizing trabecular thickness and enhancing trabecular number and connectivity [28, 30, 88, 90].

Summary- Trabecular/Endocortical surfaces (Table 1)

Enhanced trabecular/endocortical remodeling at menopause leads to loss of bone mass and architectural integrity. Anti-catabolic osteoporosis agents, HRT, SERMs, and bisphosphonates, suppress remodeling and result in maintenance of trabecular bone volume and architecture. By suppressing the deterioration of trabecular bone, these

agents all maintain the biomechanical integrity of skeletal sites containing appreciable amounts of trabecular bone. Conversely, anabolic treatment with PTH enhances bone formation activity on trabecular surfaces which positively affects trabecular bone volume and architecture. Based on these effects, both anti-catabolic and anabolic agents have value for trabecular/endocortical bone with the optimal choice depending on whether the goal of treatment is slowing deterioration (anti-catabolic agents) or actively enhancing (anabolic) bone mass and architecture.

Conclusions

Alterations to bone formation activity on the periosteal, intracortical, and trabecular/endocortical surfaces imparted by anti-osteoporosis treatments have unique influences on bone biomechanics. Although all of the anti-catabolic agents (estrogen/hormone replacement therapy, SERMs, bisphosphonates) exert positive effects on the various bone surfaces, bisphosphonates provide a unique biomechanical combination by allowing normal periosteal expansion while limiting bone loss on intracortical and trabecular/endocortical surfaces. PTH, the only FDA-approved anabolic, also exerts biomechanically favorable alterations to bone formation on the various bone surfaces through enhanced activity on trabecular/endocortical surfaces combined with allowing normal periosteal expansion. As new agents gain approval for treatment postmenopausal osteoporosis it will be advantageous to understand how they each affect the various bone surfaces in order to determine the mechanism(s) through which they reduce fracture risk. Equally, if not more important is that this information will help advance our understanding of surface-specific regulation of bone formation

304 which ideally can be utilized to design agents that specifically target a particular bone
305 surface.
306

307

308 **Table 1. Summary of pharmaceutical effects on surface-specific bone formation***

	Estrogen/Hormone Replacement Therapy	Selective Estrogen Receptor Modulators	Bisphosphonates	Parathyroid Hormone
Periosteal				
Postmenopausal women	Decrease	--	No effect	Increase
Ovariectomized animals	Decrease	No effect	No effect	--
Intact animals	Decrease	Increase	No effect	Increase
Intracortical				
Postmenopausal women	Decrease	--	No effect / Decrease	--
Ovariectomized animals	Decrease	Decrease	Decrease	Increase
Intact animals	--	No effect	Decrease	Increase
Endocortical/Trabecular				
Postmenopausal women	Decrease	Decrease	Decrease	Increase
Ovariectomized animals	Decrease	Decrease	Decrease	Increase
Intact animals	--	Decrease	Decrease	Increase

309

310 *In cases where conflicting data exist (see text), the stated effect represents the majority

311 response. (--) signifies there are no data available.

312

Figure Legends

Fig. 1. Anti-osteoporosis pharmaceutical agents impart their skeletal effects in part by altering bone remodeling/modeling on periosteal (B, arrowhead), intracortical (B, arrow), trabecular (C), and endocortical (D) bone surfaces. Scale bar = 1 mm (A) or 500 μm (B-D).

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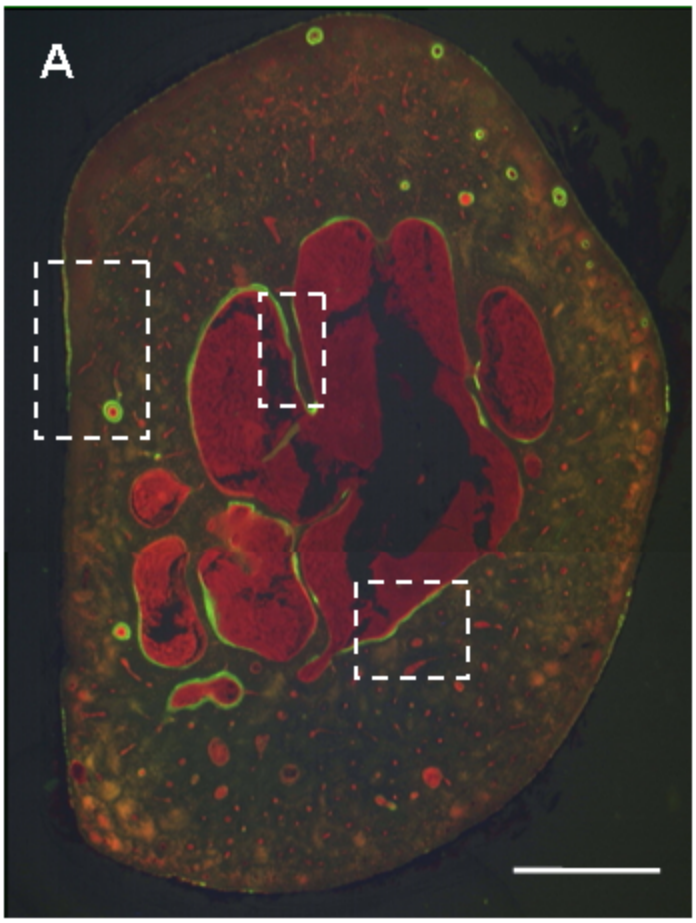
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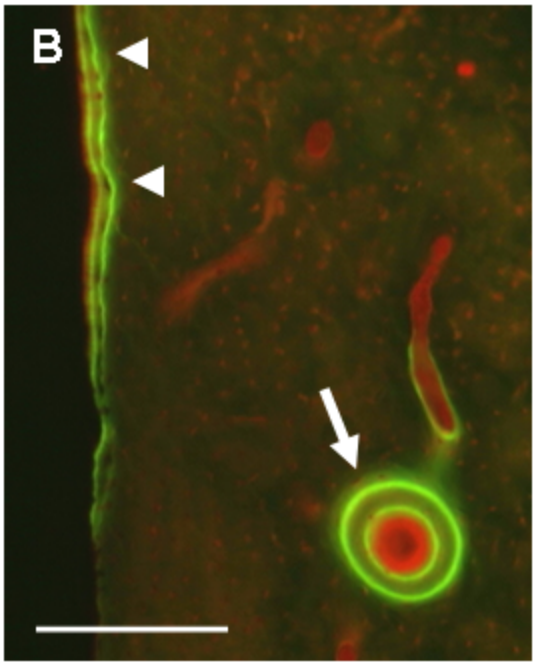
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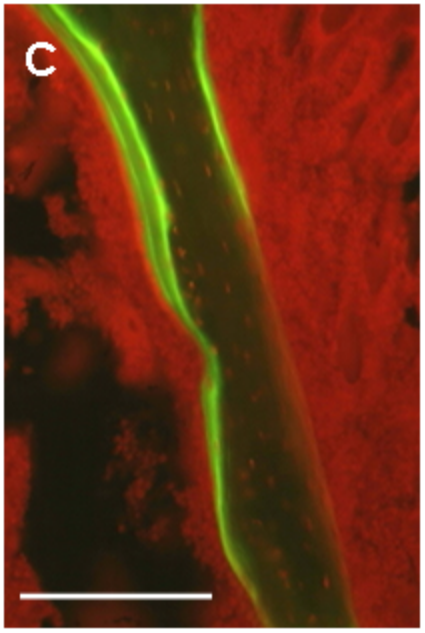
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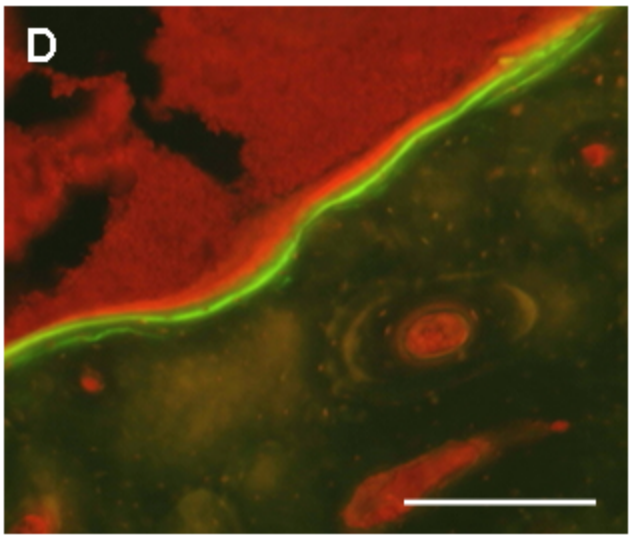
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