The Effect of Antiresorptives on Bone Quality

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Abstract

Background Currently, antiresorptive therapy in the treatment and prevention of osteoporosis includes bisphosphonates, estrogen replacement, selective estrogen receptor modulators (raloxifene), and denosumab (a human antibody that inactivates RANKL). The original paradigm driving the development of antiresorptive therapy was that inhibition of bone resorption would allow bone formation to continue and correct the defect. However, it is now clear increases in bone density account for little of the anti-fracture effect of these treatments.

Questions/purposes We examined the antifracture benefit of antiresorptives deriving from bone quality changes.

Methods We searched the archive of nearly 30,000 articles accumulated over more than 40 years in our research center library using a software program (Refman™). Approximately 250 publications were identified in locating the 69 cited here.

Results The findings document antiresorptive agents are not primarily anabolic. All cause a modest increase in bone density due to a reduction in the bone remodeling space;

however, the majority of their efficacy is due to suppression of the primary cause of osteoporosis, ie, excessive bone remodeling not driven by mechanical need. All of them improve some element(s) of bone quality.

Conclusions Antiresorptive therapy reduces risk of fracture by improving bone quality through halting removal of bone tissue and the resultant destruction of microarchitecture of bone and, perhaps to some extent, by improving the intrinsic material properties of bone tissue. Information presented here may help clinicians to improve selection of patients for antiresorptive therapy by avoiding them in cases clearly not due to excessive bone remodeling.

Introduction

Bone quality is defined as those features of bone tissue that resist physiologic loading other than absolute mass of bone tissue present in an individual adult human. These features include (1) macroarchitecture of bone tissue, (2) microarchitecture of bone tissue, (3) submicroscopic architecture of bone tissue, (3) intrinsic material properties of bone tissue, and (4) efficiency of microdamage repair. However, in the broad sense, the concept of bone quality includes every feature of bone that affects the lifelong ability of the tissue to bear repeated physiologic mechanical loading without failure or fracture and includes the quantity present, ie, its mass.

The macroarchitecture of bone tissue refers to the adult length and shape of the intact skeleton that is largely determined genetically. However, the final adult shape and mass of the skeleton depend on the genetic contribution interacting with modeling and mechanical loading during growth and development [30]. The final product is also influenced by environmental factors, such as nutrition,

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intercurrent illness, and other factors encountered during growth and development. This is best studied by CT and quantitative CT.

The microarchitecture of bone tissue refers to the morphology of trabecular bone tissue. Its features include the number, thickness, shape, connectivity, and volume of trabeculae occupying the marrow space. It is best studied microscopically by bone histomorphometry or micro-CT of iliac biopsy specimens [6, 58] and by high-resolution quantitative CT or MRI of the radius or other sites [22, 42]. The latter continues to be refined.

The intrinsic material properties of bone tissue refer to the elasticity, toughness, and/or strength properties of bone tissue. They are the mechanical engineering properties of the bone tissue that are the products of features described below. These are studied *ex vivo* in bones of animal models by classical engineering methods such as application of measured loads to harvested bone specimens and measuring the relationship between loads and resultant deformation. The technology for measuring this in humans is under development. One promising method is “nano-indentation” where embedded iliac specimens are obtained and an instrument is used to make small indents ($\sim 5\ \mu\text{m}$) while monitoring the force used and the tissue’s ability to return to the preindented state [28]. Of course, this requires iliac biopsy and *ex vivo* measurements on the specimens. Human data so far are scarce.

The submicroscopic architecture of bone tissue refers to the chemical content and form of the bone tissue. Its features include size and morphology of hydroxyapatite crystals; incorporation of other minerals into the mineral phase; the concentration of mineral incorporated into the matrix; the organic makeup of the collagen molecules, ie, the number of crosslinks; and a host of other chemical features. The technology for study of these features includes Raman spectroscopy [23], Fourier transform infrared spectroscopy [13], and electron backscatter microscopy [11]. For human studies, this also requires examination of iliac bone biopsies. It is important to note treatment with bisphosphonates (BPs) results in their continued accumulation in the skeleton during the entire time of treatment. However, they accumulate mostly on bone surfaces and only minimally in the bone tissue distant from surfaces [46], the latter buried by osteoblastic activity at surfaces previously containing BP. Their total body half-life is measured in years [43], and the remodeling suppression continues for extended periods after cessation of treatment, in some reports for 5 years or more [33]. Their location on bone surfaces likely precludes any effect on the intrinsic material properties of bone tissue.

The efficiency of microdamage repair refers to the rate of appearance and corresponding repair of microdamage. Microdamage occurs in bone as a result of repeated

submaximal loading, a feature of load-bearing materials throughout nature. Microdamage exists in two forms, linear microcracks that transect lamellae and canaliculi and diffuse damage that leaves the lamellae and canaliculi intact [38]. The lamellar structure of collagen preserves mechanical strength in the presence of load-related microdamage because it tends to limit and deflect microdamage progression. Cement lines, which line the margins of all osteons, also play a role in deflecting and limiting the progression of microcracks [1, 20]. While human data are scarce on the relationship between microdamage accumulation and risk of fracture, the indirect evidence is strong [8, 16, 47, 51, 52]. Targeted bone remodeling is the process that targets and removes microdamage, thus maintaining material properties of bone in long-lived vertebrates. It is important for long-term maintenance of mechanical integrity of the skeleton [63]. Unfortunately, it is nearly impossible to measure in humans because of the inability to obtain tissue suitable for its identification and quantification. However, it has been extensively studied in animal models [18, 49]. The mechanism of targeting microdamage involves osteocyte signaling [67] and regional osteocyte apoptosis [37]. Apparently, emergence of a microcrack results in apoptosis of nearby osteocytes, and in the process of apoptosis, osteocytes emit signaling molecules such as RANKL and other cytokines [53] that target the microcrack for removal and repair. Diffuse damage does not cause osteocyte apoptosis and is not targeted for repair [38]. However, the details of this process are largely unknown [2]. Clinicians and investigators badly need closure of this technical gap for human investigation and clinical care.

Our review was prompted by the fact that the antifracture efficacy of drugs currently used for prevention of fractures in patients with postmenopausal osteoporosis is due largely to positive effects on bone quality rather than bone mass [24]. Thus, we describe those features of bone quality that account for the antifracture effect of antiresorptive drugs. Specifically, we (1) characterize features of bone quality aside from the quantity of bone present, ie, bone mass, that account for the mechanical integrity of the skeleton; (2) examine the defects in bone quality that account for the skeletal fragility in patients with postmenopausal osteoporosis; and (3) examine the mechanisms whereby antiresorptive therapy improves these defects in bone quality, improves the mechanical strength of the skeleton, and reduces the risk of mechanical failure (fracture).

Search Strategy and Criteria

We used the archive of nearly 30,000 articles accumulated over more than 40 years in our research center library.

These articles are catalogued in a software program (RefmanTM) that can be searched by title, author, key word, abstract, date of publication, and journal name. We identified 250 articles by searching for titles including the words, “bone quality”, “microarchitecture”, “material properties”, “fragility”, “bone fragility”, “osteoporosis”, “fracture”, and “low-trauma fracture”. Of those 250 articles, we selected 69 cited in this review by including those with pertinence to the topic, and excluding those that were not. This was not a systematic review, but instead, was a selective review.

Functions of Bone

The main function of bone in humans is to bear the mechanical loads of everyday life without mechanical failure or fracture. This requires considerable adaptability since the range of physiologic loading is quite broad [59, 64]. It also requires mechanisms for ongoing repair of microdamage resulting from repeated physiologic loading.

In addition to bearing loads, bone serves a critically important biologic function in providing a reservoir of mineral, ie, calcium (Ca^{++}), which can be rapidly accessed for maintenance of serum Ca^{++} within a very narrow range [34]. This function competes with the mechanical function of bone and, when it is under stress, can overcome the mechanical function and sacrifice bone quality.

While the mechanical and Ca^{++} reservoir functions of bone described above are largely the same throughout life, bone cell function changes throughout life to accomplish them under different circumstances. Thus, all of the functions of bone cells are accomplished by the same three cell types, osteocytes, osteoclasts, and osteoblasts, working under different sets of regulatory systems for their different coordinated functions. These discrete functional sets of cell organization were described by Frost [30] as the “intermediary organization” of bone cells. Operating in postfetal life, these functions include (1) growth, (2) modeling, (3) remodeling, and (4) fracture repair. Growth is the elongation of the skeleton, occurring at epiphyses, and ending when growth is completed. Modeling is the shaping or sculpting of the skeleton during growth and development where bone is added on some surfaces and removed from others. In this process, layers of osteoblasts add bone on surfaces in the absence of prior resorption, and layers of osteoclasts remove bone on surfaces in the absence of ensuing formation. The process is mechanically driven and results in net addition of bone. It largely extinguishes at the end of growth and development, although small remnants remain, probably throughout life. Remodeling is the continuous removal and replacement of bone tissue. This functions throughout life to repair microdamage and

maintain mechanical competence for long-lived vertebrates and to provide access to the bone Ca^{++} reservoir. Most bone disease involves defects in remodeling. Fracture repair results in rapid production of endochondral bone, rapidly followed by woven bone at a fracture site, thus quickly restoring mechanical function, followed by removal and replacement by normal lamellar bone through the remodeling system.

These descriptions by Frost [30] survive largely intact. Osteocytes function to regulate the work rules of the osteoblasts and osteoclasts [21]. Remodeling is the predominant bone cell activity during most of life, particularly adult life. It is helpful to examine some of the work rules of the bone cells in the process of remodeling. For example, in remodeling, discreet, rather constant, volumes of bone are removed at selected cortical and trabecular sites, followed by replacement of the same volume of bone at each site. Once initiated, the process proceeds under local control, requiring the ongoing presence of a mechanical loading environment. There are two categories of remodeling, targeted and stochastic [17]. Targeted remodeling is so named because it is targeted to repair microdamage. Stochastic remodeling is so named because the sites for its action are chosen largely at random. Stochastic remodeling is the process whereby the bone Ca^{++} reservoir is accessed to support plasma Ca^{++} concentration.

Bone Remodeling Disease

Osteoporosis, the most common bone disease, affects 1/2 of the female population and 1/5 of the male population older than 50 years [25, 50]; thus, discussion of bone quality must focus on this disease. Low-trauma fracture is the morbid event in the disease. The etiology is not completely understood; however, the pathogenesis is related to postmenopausal changes in bone remodeling and is characterized by defective bone remodeling [57]. It is well known from numerous past studies menopause is accompanied by a substantial increase in bone remodeling [35, 57]. Bone remodeling rates measured by histomorphometry of human transiliac bone biopsies (activation frequency) doubles by 12 months after the last menstrual period and triples by 13 years later [57]. These high rates are maintained in patients with osteoporosis [57]. These increases in remodeling are not associated with increases in mechanical loading; thus, they must be due to increases in stochastic rather than targeted remodeling. Stochastic remodeling is not involved in microdamage repair, except perhaps by chance, and can only weaken the skeleton. A marked increase in stochastic remodeling at menopause causes bone loss, severe deterioration of bone microarchitecture, and reduction in bone quality. This is the most important

etiologic factor in the pathogenesis of postmenopausal osteoporosis. These increases in remodeling are associated with estrogen deprivation at menopause and are reversed by hormone replacement therapy [12]. The morphologic pattern of the bone loss resembles that due to disuse [40] in that trabecular bone and bone at corticoendosteal surfaces are attacked, resulting in bone loss with disruption of trabecular number and connectivity and removal of corticoendosteal bone [41]. The outside dimensions of the cortical bone of the skeleton do not change. In fact, the periosteal surfaces continue to add small amounts of bone throughout the postmenopausal period of bone loss [29, 62].

Antiresorptives: Mechanism of Action

Bisphosphonates

The first drug approved for treatment of osteoporosis in the United States was alendronate in 1995. It reduced the risk of fracture by about 50% in patients with prevalent low-trauma fracture [45]. Subsequently, three more BPs have been approved: risedronate, ibandronate, and zoledronic acid. The mechanism of action is similar for all of them: a chemical radical anchors the molecule to bone mineral surfaces [60], and a second radical is responsible for the ability to inhibit an enzyme, farnesyl diphosphate synthase, crucial for protein prenylation and function of intracellular osteoclast machinery. The former attaches the molecule to bone surfaces, with higher concentrations gathering on the surfaces where osteoclasts attach, and the latter accounts for the inhibition of osteoclast resorption work after its ingestion into osteocyte cytoplasm. The end result is that osteoclasts' resorption work is inhibited and the remodeling process is stopped before it begins. However, the formation work of previously existing osteoblasts continues. BPs were developed as bone active agents because early cell biology research indicated they would inhibit bone resorption, allowing bone formation to continue. The hope was that bone formation would be uncoupled from bone resorption, with a net bone anabolic effect. However, these molecules seem to behave as remodeling suppressors since bone formation does not continue beyond filling remodeling sites previously created. Thus, the net effect of "antiresorptives" is better described as "antiremodeling."

Denosumab

Denosumab is a human antibody directed at RANKL, the molecule that signals the differentiation of circulating osteoclast precursors into active osteoclasts [26]. It may be

a more robust antiresorptive agent than the BPs [15]. A single subcutaneous injection results in 6 months of remodeling suppression. It has been recently approved in the United States for treatment of postmenopausal osteoporosis. Its antiresorptive effect rapidly declines 6 months after injection, and the treatment regimen calls for repeated injections at intervals of 6 months. It does not accumulate in the skeleton. Experience with denosumab is limited since it has been available for less than a year. Thus far, adverse events have been minimal with its use, and it is a welcome addition to the armamentarium of antiresorptive agents. Its antifracture effect is similar to that seen with BPs.

Selective Estrogen Receptor Modulators

Raloxifene is the only selective estrogen receptor modulator (SERM) approved for treatment and prevention of fractures in patients with postmenopausal osteoporosis [27], although several are under study. Raloxifene, like other SERMs designed to prevent or treat osteoporosis, bind to estrogen receptors; however, postreceptor activity is limited to the skeleton. Postreceptor activity is blocked in soft tissues, giving them other benefits such as prevention of estrogen receptor-positive breast cancer [7] and endometrial cancer. The major therapeutic benefit is through improvement in bone quality since very little of their antifracture effect is attributable to increases in bone mass [24]. However, while they alter collagen [4], few details are known about their effects on bone quality [14] aside from those related to reduction in excessive bone remodeling.

Effects of Antiresorptives on Bone Quality

Effects on Macroarchitecture

BPs do not add bone mass and/or change the shape of the intact adult skeleton; thus, macroarchitecture is not improved or changed. However, the ongoing periosteal bone formation present during aging in postmenopausal women and in patients with osteoporosis [29, 62] continues during BP treatment. This small remnant of the modeling process, otherwise largely extinguished at the end of growth and development, probably accounts for very little antifracture benefit. However, it is not eliminated by BP treatment [29] and may give some benefit to mechanical integrity of long bones given the small increase in the resulting cross-sectional moment of inertia. It suggests, perhaps, research attention should be given to exploiting this phenomenon as a drug target.

Effects on Microarchitecture

Antiresorptive treatment improves microarchitecture in two ways: (1) by preventing further loss of trabecular volume, number, and connectivity and (2) by suppressing activation of remodeling, allowing the remodeling space to fill. This adds mass and strength to trabecular bone and halts erosion of cortical bone on the corticoendosteal surfaces. The pattern of gain in bone mass and its time sequence and quantity after starting BP treatment are concordant with filling the remodeling space [36]. Further, the antifracture effect of this treatment is out of proportion to the overall gain in bone mass. It has been estimated less than 1/2 of the antifracture effect of antiresorptive treatment is attributable to the gain in bone mass [24]. This suggests most of the mechanical benefit of antiresorptive treatment is achieved by suppression of excess bone remodeling and resultant improvement in bone quality, ie, improved microarchitecture.

Effects on Submicroscopic Architecture

There is evidence BPs substantially alter the chemistry of bone tissue. For example, BPs change collagen crosslinking, polymerization, degree of mineralization, and collagen maturity [3, 61, 66, 68]. Any of these are candidates for change in the intrinsic mechanical properties of bone tissue, for better or for worse [61]. However, little is known about the contribution of these changes to any of the mechanical properties of bone, and much more work is needed in this area.

Effects on Intrinsic Material Properties of Bone Tissue

In this discussion, the concept of intrinsic material properties of bone tissue does not include microdamage, which has its effect locally and on the whole-bone material properties. The effect of microdamage is studied by *in vivo* or *ex vivo* whole-bone bending experiments. Intrinsic material properties here refer to the stress-strain relationships of bone tissue in the absence of microdamage studied *ex vivo* by obtaining carefully milled bone specimens. This has not been adequately studied in patients on antiresorptive treatment. The effects of antiresorptive therapy on intrinsic material properties of bone seem limited to that resulting from a change from excessive remodeling rates to normal remodeling rates. The accumulation of BPs on bone surfaces would not be expected to change intrinsic material properties of bone tissue. One possible change to the intrinsic material properties of skeletal tissue is that the mineral density of the collagen matrix becomes more

homogenous compared to pretreatment [10] due to the marked decrease in remodeling rates.

Effects on Microdamage Repair

It is well established bone remodeling targets and repairs microdamage in vertebrate animals [17]. While it has been assumed the same process for microdamage repair occurs in humans, there are no human studies available characterizing it adequately because of difficulties in obtaining adequate bone specimens from living humans. Nevertheless, it is reasonable to assume microdamage occurs in humans, and remodeling functions to target and repair it. Further, although difficult to demonstrate, it is reasonable to assume, at some level of excess accumulation in humans, unrepaired microdamage will cause mechanical failure and inappropriate fracture. The recent reports of “atypical” fractures occurring during BP treatment [44] have focused attention on the possibility that antiresorptive therapy may have a downside. Perhaps, in suppressing the excessive stochastic remodeling in osteoporosis patients, their targeted remodeling can be oversuppressed by BP treatment, allowing accumulation of unrepaired microdamage and return of the fracture diathesis.

There are numerous uncertainties and difficulties in evaluating the importance of microdamage in the mechanical integrity of the skeleton in animals and humans. Microdamage can be both good and bad for mechanical integrity [69]. Some animal studies of BPs show whole-bone mechanical strength and toughness are improved by BP treatment despite an increase in the amount of microdamage [5, 48]. Extensive reviews of the physiology of microdamage and its mechanical effects are available [18, 19, 39, 48, 65].

It is not clear how signaling for targeted remodeling is separate and distinct from signaling for stochastic remodeling. There are no serum biochemical markers discriminating between rates of targeted remodeling and stochastic remodeling. It is not possible to know whether stochastic remodeling can be selectively suppressed, allowing targeted remodeling to continue unchanged.

Therefore, it is difficult to understand the relationship between suppression of remodeling during BP treatment and the occurrence of “atypical” fractures [54]. Fortunately, they are rare in patients receiving BP therapy, and since they occur rarely in patients not exposed to BPs [9], the etiology may not be associated with antiresorptive therapy. Further, about 5% of iliac biopsies from untreated patients with osteoporosis show very low or absent remodeling [57]. Thus, the “atypical” fractures in patients on BPs may be due to a pre-existing remodeling defect, and the treatment with BPs may not have been responsible. Alternatively, a pretreatment partial defect in targeted repair of microdamage in patients with osteoporosis may

give them risk of oversuppression of remodeling when exposed to BP therapy.

These questions are important for clinicians. For example, if serum biochemical markers were available that would identify insufficient targeted remodeling before selecting treatment, one might be able to avoid using antiresorptives that result in accumulation of excess microdamage and in return of the fracture diathesis. The currently available serum biochemical markers of bone remodeling do not distinguish between targeted and stochastic remodeling and are weak in distinguishing between normal and abnormally low overall remodeling rates. Considerable work is required to characterize the physiology of bone microdamage and its repair.

Antiresorptives in Diseases Other Than Osteoporosis

Osteogenesis imperfecta is due to genetic defects in Type I bone collagen. It is an example of defective intrinsic material properties of bone tissue with poor mechanical integrity of the skeleton and a variable, but usually severe, fracture diathesis [56]. It is also characterized by short stature and reduced skeletal mass. The latter is likely due to excessive stiffness of the abnormal bone tissue resulting in poor adaptation to mechanical load. Treatment with antiresorptive agents is most effective in childhood during growth and development because of their effect on bone modeling. These agents suppress the resorptive feature of modeling, presumably leaving formation intact. This results in striking increases in bone mass and reduction in fracture risk, even though the intrinsic bone tissue defect remains. The current nomenclature includes other childhood diseases of low bone mass such as osteoporosis pseudoglioma [32] and others.

Paget's disease is another bone disease characterized by increased remodeling localized to discreet areas of the skeleton. Its clinical consequences include bone deformity, compressive symptoms, fracture, and pain. Antiresorptive therapy with BPs has been extremely successful in relieving symptoms and halting the progression of disease [55]. Long-term problems from BP therapy are minimized because of the rather short courses of treatment that need to be used only during periods when the disease is active. Antiresorptive therapy has also been widely used in oncology for treatment of hypercalcemia and prevention of bone metastases [31].

Discussion

While osteoporosis is associated with reduced bone mass resulting from decades of bone loss, the advent of antiresorptive therapy has led to the understanding that age-related bone loss is a product of the destructive effect of

excessive rates of bone remodeling. It is now clear increases in bone density account for little of the anti-fracture effect of antiresorptive therapy. Thus, the benefit of antiresorptive therapy must be largely due to suppression of excessive bone remodeling and resultant improvement in bone quality. In this review, we characterized the features of bone quality, examined the defects in bone quality accounting for excessive skeletal fragility, and examined the mechanisms whereby antiresorptive therapy improves bone quality and reduces the risk of fracture.

There are certain limitations to the literature in our review: (1) uncertainty regarding the role and character of defects in bone quality in the cause of bone fragility in osteoporosis; (2) uncertainty regarding the role of excessive nonmechanically driven bone remodeling in the cause of bone fragility in osteoporosis; (3) lack of knowledge concerning the mechanism of excessive bone remodeling; and (4) lack of understanding concerning the mechanism of improved bone quality by intervention with antiresorptive (antiremodeling) agents.

Excessive remodeling causes loss of bone tissue in a pattern that disrupts the quality of trabecular microstructure and the thickness of cortices. This pattern of bone loss creates skeletal fragility out of proportion to the amount of bone lost. Antiresorptive treatment results in partial correction of the principal bone quality defect in osteoporosis, disruption in bone microarchitecture, but cannot completely restore mechanical integrity because of the absence of an anabolic effect.

The literature has not focused sufficient attention on the disruption of trabecular elements in osteoporosis. Further, there has not been sufficient research on the effect of excessive bone remodeling on the intrinsic material properties of bone tissue, such as changes in the collagen molecules, size and integrity of mineral crystals, composition of mineral crystals, concentration of mineral in the collagen matrix, effect of microdamage, and defective signaling for remodeling. Research is needed on the contributions of the various defects in bone quality contributing to excessive fragility and how to identify them in living humans.

Research is also needed to discover methods of quantifying targeted remodeling as distinct from stochastic remodeling. In addition, research is badly needed to discover and develop anabolic treatments for osteoporosis that hold promise of reducing fracture risk even more than antiresorptive therapy.

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