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Review

Effects of osteoporosis medications on bone quality

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Abstract

In clinical practice, the quantitative evaluation of bone tissue relies on dual-energy X-ray absorptiometry (DXA) measurements of bone mineral density (BMD) values, which are closely associated with the risk of osteoporotic fracture. However, only a small fraction of the antifracture effect of bone resorption inhibitors is ascribable to BMD gains (4% with raloxifene and 16–28% with alendronate and risedronate). Bone quality encompasses a number of bone tissue properties that govern mechanical resistance, such as bone geometry, cortical properties, trabecular microarchitecture, bone tissue mineralization, quality of collagen and bone apatite crystal, and presence of microcracks. All these properties are dependent on bone turnover and its variations. In populations, the decreases in bone resorption markers achieved with resorption inhibitors may predict in part the decrease in fracture risk. At the spine, however, this correlation exists down to a 40% fall in bone resorption markers; larger drops did not provide further protection against fractures in patients taking risedronate in one evaluation of this relationship.

Osteoporosis medications can exert favorable effects on bone size and cortical thickness. Such effects have been documented with teriparatide (PTH 1–34), which is the unique purely anabolic treatment for osteoporosis available to date. More surprising are the favorable effects on bone size seen with some of the bone resorption inhibitors such as neridronate in adults with osteogenesis imperfecta. Similarly, estrogens and alendronate can increase femoral neck size in postmenopausal women. Preservation of the trabecular microarchitecture was demonstrated first with risedronate and subsequently with alendronate. In placebo-controlled studies, a deterioration in trabecular microarchitecture occurred within 1 to 3 years in the placebo groups but not in the bisphosphonate groups. Teriparatide, in contrast, improves trabecular microarchitecture, in particular by increasing connectivity and improving the plate-rod distribution.

The minerals within trabecular or cortical bone can be evaluated using microradiography or synchrotron micro-computed tomography. Marked or prolonged secondary mineralization may result in poor bone quality. Increased bone mineralization is among the key effects of bone resorption inhibitors, most notably bisphosphonates. Prolonged use of the most potent bisphosphonates may lead to unwanted effects related to excessive mineralization. Microcracks may play a physiological role; however, a large number of microcracks may be deleterious via an effect on osteocytes. Excessive mineralization may promote the development of multiple microcracks. Studies of bone crystal and collagen properties with several bone resorption inhibitors, including risedronate and raloxifene, showed no harmful effects.

An increasing number (several hundreds) of mandibular osteonecrosis associated with bisphosphonate therapy has been reported. The typical patient was receiving injectable bisphosphonate therapy for bone cancer and had undergone dental work shortly before bisphosphonate administration. The mechanism of this adverse effect is poorly understood.

Keywords: Osteoporosis; Strontium ranelate; Selective estrogen receptor modulator (SERM); PTH; Bone quality; Bisphosphonates; Microarchitecture

1. Introduction

Quantitative bone tissue parameters were initially thought to be acceptable surrogate markers for bone strength. Bone mass per unit volume can be determined, although the most widely used parameter in clinical practice is bone density per unit surface area (bone mineral density, BMD) as measured by dual-energy X-ray absorptiometry (DXA). Over the years, however, BMD proved to be a less than ideal tool for diagnosing postmenopausal osteoporosis [1,2]. Furthermore, recent data also challenge the usefulness of BMD for diagnosing

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glucocorticoid-induced osteoporosis [3] and male osteoporosis [4]. Thus, the 1993 criteria for diagnosis and treatment guidance developed by the World Health Organization (WHO) [5] need to be revised in order to introduce clinical risk factors and biophysical parameters related to other properties of bone tissue. Trabecular microarchitecture was considered a key factor in the original WHO definition of postmenopausal osteoporosis [5]. A revised definition developed in 2001 by a consensus panel at the National Institutes for Health [6] states that, in addition to complementary quantitative parameters, qualitative parameters play a role. This new definition emphasizes that microarchitecture is not the only qualitative feature related to bone strength. Several reviews on this point have been published [7–10]. There is general agreement that bone turnover orchestrates the qualitative and quantitative changes in bone tissue [7–10] (Fig. 1). Qualitative bone properties can be considered at various levels, from bone shape and size to bone tissue molecular composition (Table 1)

Although the limitations of BMD measurements as a diagnostic tool have been emphasized for many years, this parameter remains a key determinant of bone strength that can be used to define the fracture risk [11]. In contrast, BMD is clearly inadequate for characterizing the effects of bone resorption inhibitors in patients with osteoporosis [12]. Thus, there is a need for new methods.

2. Available medications for postmenopausal osteoporosis

Medications for postmenopausal osteoporosis include bone resorption inhibitors and bone formation enhancers.

2.1. Bone resorption inhibitors

Hormone replacement therapy (HRT) counters the bone turnover acceleration that occurs after the menopause.

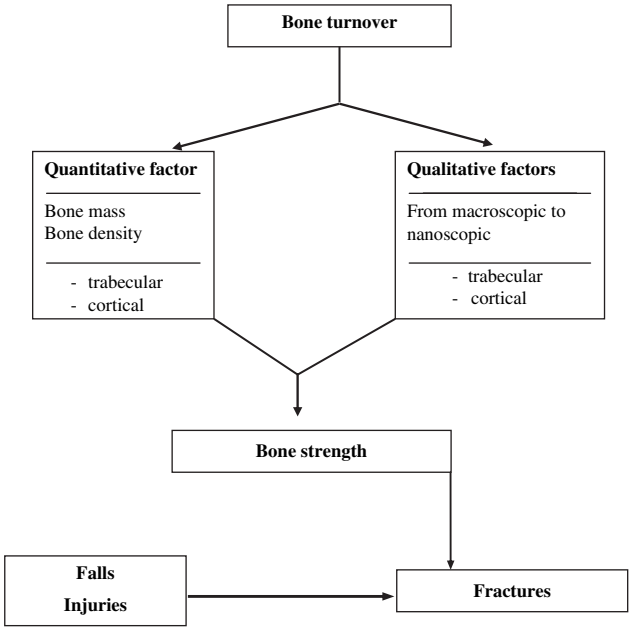

Fig. 1. Factors involved in osteoporotic fractures.

Table 1
Factors that determine bone quality [8]: a multiscale concept

Bone geometry	Bone size (vertebrae, femur…)
Geometric variables	Bone shape
	Femoral neck length
	Cortical thickness
	Corticomedullary ratio
	Fracture-related vertebral deformity
	Coxa vara/coxa valga
Microarchitecture	
Trabecular	Connections among trabeculae
Cortical	Perforations–disconnections
	Plate-rod distribution
	Anisotropy
	Microcracks
	Mineral content within trabeculae
Nanoscopic level	Collagen:
and molecular level	Type
	Linking peptides
	Aging
	Homogeneity
	Bone crystal:
	Mineral composition
	Orientation
	Homogeneity
	Size
	Aging

However, the use of HRT for preventing osteoporosis is declining. Bisphosphonates are the most potent bone resorption inhibitors. Among them, etidronate is gradually being superseded by risedronate and alendronate; all three drugs are used orally. Ibandronate has been licensed for use in France and will be available soon. Injectable bisphosphonates such as zoledronate are being developed. A single selective estrogen receptor modulator (SERM), called raloxifene, is available to date, although other SERMs are being developed. Lastly, other drug classes such as RANK-ligand inhibitors are under investigation.

Calcium and vitamin D supplementation seeks chiefly to correct nutritional deficiencies. Bone resorption inhibition mediates the effects of supplementation, most notably in older individuals. However, calcium and vitamin D supplementation is not usually classified among the bone resorption inhibitors.

2.2. Bone formation enhancers (anabolic agents)

Teriparatide, which is the 1–34 segment of parathyroid hormone, is the only bone formation enhancer available to date. Teriparatide exerts potent anabolic effects on bone. It is reserved for patients who have severe postmenopausal osteoporosis with at least two vertebral fractures.

2.3. Bone resorption inhibition plus bone formation enhancement

Strontium ranelate is a recently marketed agent that may be capable of both inhibiting bone resorption and enhancing bone