

REVIEW

Cortical remodeling during menopause, rheumatoid arthritis, glucocorticoid and bisphosphonate therapy

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Abstract

Bone mass, bone geometry and its changes are based on trabecular and cortical bone remodeling. Whereas the effects of estrogen loss, rheumatoid arthritis (RA), glucocorticoid (GC) and bisphosphonate (BP) on trabecular bone remodeling have been well described, the effects of these conditions on the cortical bone geometry are less known. The present review will report current knowledge on the effects of RA, GC and BP on cortical bone geometry and its clinical relevance. Estrogen deficiency, RA and systemic GC lead to enhanced endosteal bone resorption. While in estrogen deficiency and under GC therapy endosteal resorption is insufficiently compensated by periosteal apposition, RA is associated with some periosteal bone apposition resulting in a maintained load-bearing capacity and stiffness. In contrast, BP treatment leads to filling of endosteal bone cavities at the epiphysis; however, periosteal apposition at the bone shaft seems to be suppressed. In summary, estrogen loss, RA and GC show similar effects on endosteal bone remodeling with an increase in bone resorption, whereas their effect on periosteal bone remodeling may differ. Despite over 50 years of GC therapy and over 25 years of BP therapy, there is still need for better understanding of the skeletal effects of these drugs as well as of inflammatory disease such as RA on cortical bone remodeling.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease characterized by destruction of periarticular bone and cartilage and soft-tissue damage, leading to

impaired joint function [1]. Bone erosion, periarticular osteopenia and systemic bone loss, are central features of RA [2]. In a recent cross-sectional study we found that RA patients had thinner cortices at the shafts of the tibia, radius and metacarpal bone, and that the outer diameter of the metacarpal bone was increased. Disease severity, measured by the extent of erosions and the cumulative dose of glucocorticoids (GCs), correlated negatively with shaft cortical thickness [3]. However, despite increased outer circumference and thinner cortical shaft, the calculated load-bearing capacity (strength strain index) of long bone shafts was not impaired in RA patients and adaptation to muscular strength remained unchanged [4].

In the last years, several case studies have linked RA with increased risk of bone shaft fractures at the metatarsal, tibial and femoral bones [5-7]. Since these fractures occur without previous trauma, and are not at typical locations for osteoporosis-associated fractures, they are called insufficiency or atypical fractures. The reasons for these fractures are not yet known, but associated factors are estrogen deficiency, RA, diabetes, GC therapy and treatment with anti-resorptive drugs, such as bisphosphonates (BPs). In a recent report of summarized clinical data on cases with shaft fractures associated with BP, the task force of the American Society for Bone Mineral Research [6] found that patients with atypical fractures of the femur had a higher number of comorbid conditions such as RA (odds ratio = 16.5) and underwent therapy with GC (odds ratio = 5.2) [8].

Findings of a potential association of BP with insufficiency fractures are in strong contrast to the actual therapy concept and impede the clinician's decision-making in treating RA patients on GCs with BP therapy. Hence, there is a need to elucidate the effect of RA, BP and GC (and their combination) on long-term adaptation of bone geometry and bone mineral density.

Physiology of adaptation of bone geometry

Bone adapts its shape in response to prevailing loads by bone modeling and remodeling at the outer and inner envelopes of the cortical shaft. During bone modeling

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(construction, growth) bone is deposited at the periosteal surface without prior resorption on the endosteal surface, leading to an increase in cortical diameter (Figure 1a) [9]. During bone remodeling (reconstruction, lifetime adaptation to load and age), osteoclasts resorb a small volume of bone at a distinct location at the inner site of the cortex adjacent to the marrow (Figure 1b) [10]. If periosteal apposition increases (as an adaptive response) to compensate for the loss of strength (caused by endosteal bone loss), there will be no loss in bone strength (Figure 1c) [11-13]. Alternatively, if periosteal apposition is impaired, endosteal resorption will produce cortical thinning and loss of bone mass and strength, predisposing to fractures.

Various factors influence adaptation of bone geometry. These factors include the menopause, GC therapy and treatment with anti-resorptive drugs, as well as diseases such as RA, hyperparathyroidism, diabetes mellitus, hypophosphatasia and vitamin D deficiency and mechanical factors such as weight. In the following paragraphs, current knowledge on the main factors causing bone loss and potentially leading to fractures in patients with RA will be summarized and resulting research questions highlighted.

Menopause

Estrogen loss during the menopause is the most common cause of fractures in older people. Trabecular bone loss occurs years before the menopause; at the onset of estrogen decline, a phase of rapid bone loss starts, leading to loss of an approximate mean of 10% of bone at the spine and about 5% at the hip over a period of 5 years [14,15]. This phase is characterized by bone resorption, leading to trabecular thinning and perforation, resulting in a loss of connectivity [16]. This initial acute phase – the high-turnover phase – is followed by a long-lasting period of slower bone loss where the dominant micro-architecture change is trabecular thinning and increased cortical porosity [17].

On a cellular level, the high-turnover phase is caused by an increased activity of osteoclasts, driven by the increased production of receptor activator of NF- κ B ligand [18-20]. The second phase is caused by impaired osteoblastic activity due to increased osteoblast death and decreased function [21]. Estrogen therapy blunts bone resorption and stimulates bone formation. The dominant effect of estrogen is the inhibition of osteoclast differentiation and activation, and, to a lesser extent, impairment of apoptosis of the osteoblasts [19,20,22]. Studies on bone geometry and strength of the one-third distal radius in perimenopausal and postmenopausal women showed an accelerated endosteal resorption and decreased periosteal apposition at the radius shaft. This endosteal resorption during the postmenopausal years leads to cortical thinning – and because the outward

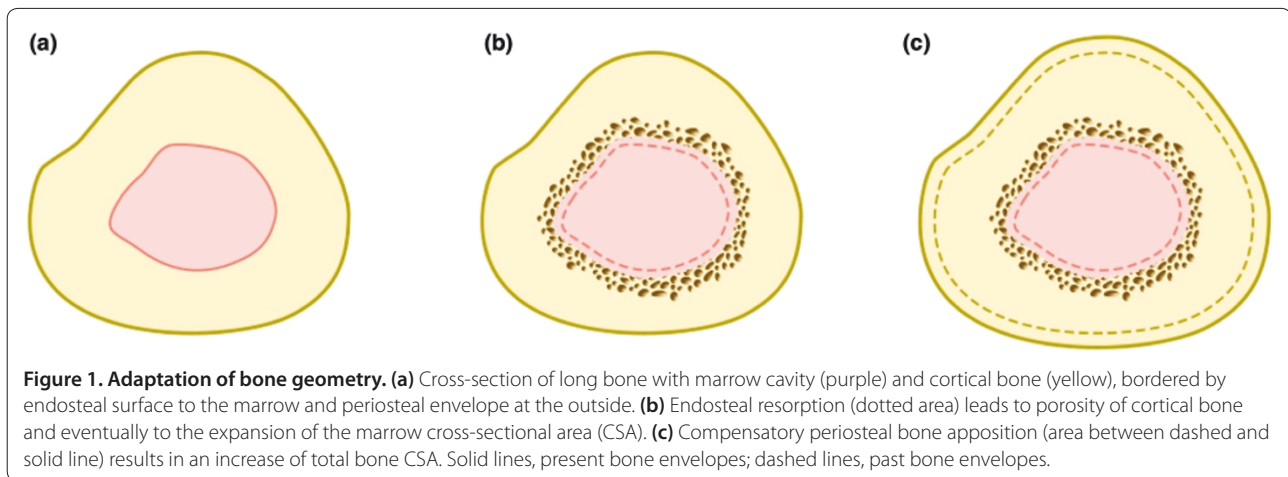
apposition of bone is minimal, the cortical cross-sectional area and bending strength decrease (Figure 2a) [23].

Thinning of the cortical shaft thickness of the radius and tibia is associated with an increased fracture risk [24]. In estrogen-treated women, loss of bone strength was partially prevented [24] and the risk of vertebral and hip fracture incidence in postmenopausal women declined [25]. In summary, estrogen deficiency leads to thinning and loss of bony trabeculae as well as increased endosteal resorption and impaired periosteal bone apposition, resulting in a net loss of bone with diminished strength to compression and bending.

Rheumatoid arthritis

RA is a chronic inflammatory joint disease characterized by destruction of periarticular bone and cartilage and soft-tissue damage, leading to impaired joint function [1]. The general consensus is that the pathogenic process of bone loss in RA patients is due to the abundance of osteoclasts [26]. Bone erosion, periarticular osteopenia and systemic bone loss are central features of RA [2]. Chronic inflammatory diseases such as RA cause skeletal breakdown and enhance the risk of nontraumatic fractures [27,28]. Approximately 25% of patients with early RA show an osteopenic bone mineral density at the spine or hip before the onset of therapy, and 10% have osteoporosis [29-32]. A large case-control study based on the British General Practice Research Database has shown that RA doubles the risk of hip and vertebral fractures, supporting the concept that the effect of RA is independent and additive to GC [33].

With a newly established protocol using peripheral quantitative computed tomography (QCT) we investigated the differences in volumetric bone mineral density (BMD) and bone geometry at the metacarpal bone, tibia and radius in 50 female RA patients and compared it with 100 healthy female controls [3]. We found that RA patients had significantly lower trabecular volumetric BMD at the distal epiphyses of the radius (-19%), tibia (-14%) and metacarpal bone (-12%). At the shafts of these bones RA patients had thinner cortices (-7% to -16%), and at the metacarpal shaft the outer diameter was increased by 5% (Figure 2b). The extent of bone erosions and the cumulative dose of GCs correlated negatively with trabecular and total volumetric BMD as well as with shaft cortical thickness [3]. In a subsequent study with 64 RA patients and 128 healthy controls, we assessed factors associated with differences in bone geometry between RA patients and healthy controls. Based on linear models with explanatory variables (muscle cross-sectional area, age, RA status and sex), we found that patients with RA showed a greater age-related decrease in cortical thickness with a concomitant increase



in outer bone circumference consistent with an enhanced aging pattern [4].

These observations suggest that the biological changes of endosteal resorption and periosteal bone apposition found in healthy populations [11,23,34] are accelerated in patients with RA. Possible explanations for this process may be inflammation-driven endosteal resorption, which was also found in human juvenile idiopathic arthritis [35], experimentally induced inflammatory knee arthritis or adjuvant-induced arthritis [36-38]. Similarly, inhibition of bone resorption by the anti-receptor activator of NF- κ B ligand antibody denosumab prevented metacarpal shaft bone loss in patients with RA [39]. Periosteal bone formation has been found in human studies [35] and in animal studies [36-38], with one of these studies observing that periosteal bone formation occurred after the endosteal resorption, when inflammation had already subsided [38]. This observation suggests that periosteal bone formation may be a compensatory mechanism to restore bone strength. In other words, the calculated load-bearing capacity of RA patients was not impaired and adaptation to muscular strength remained unchanged [4].

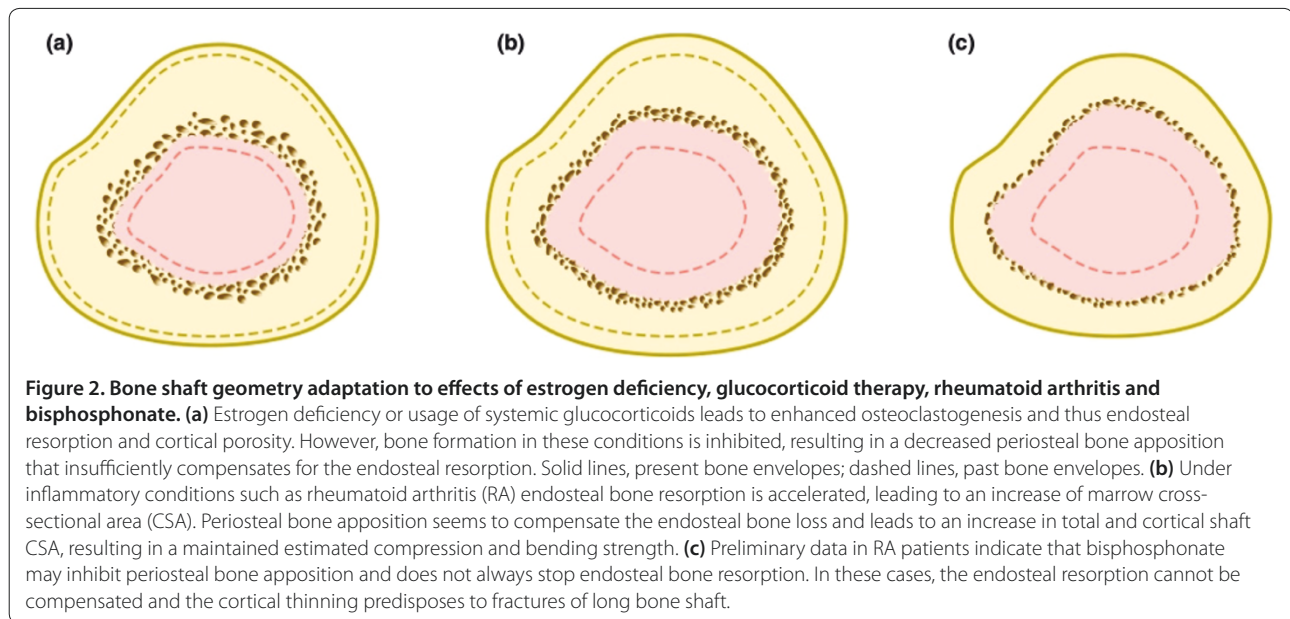
In summary, RA is associated with an increased endosteal bone resorption and compensatory periosteal bone formation of the affected shafts leading to a change in geometry with maintained strength. Longitudinal data for the effects of inflammation on bone geometry and volumetric BMD in patients with RA have not yet been published.

Glucocorticoids

GC use, quantified either by daily or cumulative dosage, is strongly related to an increased fracture risk [40,41]. Prednisone equivalent >5 mg daily is associated with vertebral fractures in postmenopausal women within the first 6 months of treatment [42]. The relative risk for

fractures in GC users in a general practice research database is 2.86 (95% confidence interval = 2.31 to 3.16) for the spine and 2.01 (95% confidence interval = 1.47 to 2.29) for the hip compared with subjects not using GCs [42]. The areal BMD at the lumbar spine and hip showed an up to 12% increased bone loss in GC users compared with nonusers of similar age and sex [42]. A meta-analysis of the relationship between areal BMD changes and fractures showed that low areal BMD was associated with a relative risk of 1.48 for vertebral fractures and 1.41 for hip fractures [43]. Further, it has been shown that fractures occurred at a younger age in male GC users compared with nonusers at comparable areal BMD [44]. This finding indicates that GCs not only lead to decreased areal BMD, but fractures occur at an even higher rate than that expected based on areal BMD. One can therefore speculate that there is not only a loss in bone mass but also in bone quality in GC users. The effects of GC on bone cells include early and quick induction of osteoclastogenesis leading to increased bone resorption as well as apoptosis of osteoblasts and osteocytes [45].

Histomorphometric analyses showed trabecular thinning and reduced osteoid thickness, a marker for osteoblastic activity in GC users [46,47]. At the iliac crest, cortical porosity and Haversian canal density were higher in patients treated with GCs [48]. Using QCT of the spine, rapid decline of vertebral trabecular volumetric BMD was found upon GC treatment with subsequent recovery following discontinuation [49]. Thinning of the cortical shell at the distal radius was found by peripheral QCT [50,51] and at the proximal femur by QCT [52]. Consistent with these results, GC administration to ovariectomized sheep showed that the cortical width and cortical bone area were reduced by 7 to 8% and the marrow area increased by 8% in GC-treated animals compared with controls (Figure 2a) [53]. Trabecular bone formation in the GC-treated animals decreased by 68%



after 2 months and by 90% after 4 months. The apparent trabecular BMD and compressive stiffness were reduced by 34% and 55%, respectively. The results are consistent with a substantially reduced bone formation in the cortical and trabecular bone and reduced cortical width due to increased endosteal resorption. Impaired cortical bone remodeling together with increased cortical porosity bears the potential for increased fracture risk at appendicular bone sites such as the femur and tibia [48,53].

In summary, BMD and bone quality are reduced upon GC treatment due to increased endosteal resorption, cortical porosity and impaired periosteal apposition. Longitudinal data on bone shaft geometry changes in GC-treated patients, however, are as yet absent.

Bisphosphonates

BP therapy is the strategy of choice for prevention and treatment of bone loss and fractures associated with osteoporosis. Current clinical practice treats patients on high-dose long-term GC therapy with BP to prevent bone loss. BP therapy has been shown to reduce the relative risk for new vertebral and hip fractures in postmenopausal women by 70% and 50%, respectively, over 3 years [54]. Indications for treatment with BPs are a quantitative estimate of the 10-year probability of a major osteoporotic fracture (clinical spine, hip, forearm or shoulder) exceeding 15 to 30% [55-57], inadequate vertebral fracture or GC therapy depending on the risk category [58].

BPs accumulate in the bone's hydroxyapatite mineral phase, particularly at sites of active resorption [59,60] – where the nitrogen-containing BPs enter osteoclasts and reduce resorption by initiating early osteoclast death

[61]. Recent retrospective studies and case reports suggest that long-term BP therapy may result in the suppression of bone turnover and confer a predisposition to increased bone fragility, with an increased risk of atypical fractures [62]. The number of atypical fractures is low – corresponding to an incidence of subtrochanteric fractures of 3 per 10,000 person-years – compared with the overall incidence of hip fractures (103 per 10,000 person-years) [63]. Nevertheless, long-term BP use is more likely and the duration of BP use longer in patients with subtrochanteric and femoral shaft fractures compared with patients with typical osteoporotic hip fracture [63,64]. Hip fracture incidence declined by 12.8% from 1996 to 2007, since BPs were approved, whereas the number of subtrochanteric and femoral shaft fractures remained stable or even increased in the same period [65]. This coincidence made the US Food and Drug Administration issue an alert with a warning about the 'possible risk of rare atypical femur fractures associated with BP treatment in osteoporosis patients' [66].

A causal relationship between BP use and atypical femur fractures has not been established, but preclinical data evaluating the effects of BPs lend biologic plausibility to a potential association with long-term BP use. Of special interest was the finding that patients with femoral shaft fractures had a higher number of comorbid conditions – for example, diabetes mellitus, RA (odds ratio = 16.5) and concomitant use of additional anti-resorptive agent (such as estrogen, raloxifene or calcitonin) or systemic GCs (odds ratio = 5.2) – than those with typical hip fractures [8]. This association is striking since guidelines suggest treating patients with RA undergoing GC treatment with BPs, either preventative

to alleviate GC-induced osteoporosis or as therapy of already established osteoporosis [58]. In a recent longitudinal study using high-resolution computed tomography to measure the effect of alendronate treatment in postmenopausal women with low BMD, changes in trabecular and endosteal compartments at the epiphyses of tibia and radius were found [67]. Particularly at the weight-bearing tibia, a filling of endosteal bone cavities was found with a concomitant decrease in the medullary area [67]. At the tibia shaft, however, increased medullary area with unaltered periosteal circumference was seen in postmenopausal RA patients treated with alendronate [68] (Figure 2c).

In summary, the positive effects of BP therapy in reducing fracture risk are undoubted; in patients with comorbid conditions such as RA and GC use, however, BPs seem to be associated with atypical femoral fractures, for which the reason is not yet known. The recent reports of the potential association of BPs with atypical femur shaft fractures and the recommendations to treat RA patients on GCs with BP therapy are in stark contrast to the prevailing advice and therefore impede the clinician's decision-making in treating a large proportion of RA patients. Further research is needed to address these questions.

Conclusion

Current knowledge about the adaptation of bone shaft geometry to effects of estrogen deficiency, RA and systemic GC therapy suggests an enhanced endosteal bone resorption. While in estrogen deficiency and under GC therapy this endosteal resorption is insufficiently compensated by periosteal apposition (Figure 2a), in the RA it seems to be compensated by increased periosteal bone apposition (Figure 2b) resulting in a maintained load-bearing capacity and stiffness. BP therapy results in filling of endosteal bone cavities and hence reduction of the endosteal diameter at the epiphysis. However, periosteal apposition upon BP treatment in patients with osteoporosis has not yet been seen (Figure 2c). More so, studies elucidating the effect of BP treatment on the bone geometry of patients with RA are missing. Further, the effects of concomitant use of GCs and BPs on the bone shaft's inner and outer bone envelope are unexplored. There is a need for answering these questions, and studies that further clarify the effect of GCs and BPs (and their combination) on bone geometry and fragility will shed some light on these points.

Rheumatology key messages

- Estrogen loss, RA and GC show increased endosteal resorption of bone shaft.
- Periosteal bone remodeling of the bone shaft may be increased under inflammatory conditions.

- Studies are needed to elucidate the effect of BP on periosteal apposition under inflammatory conditions.

Abbreviations

BMD, bone mineral density; BP, bisphosphonate; GC, glucocorticoid; NF, nuclear factor; QCT, quantitative computed tomography; RA, rheumatoid arthritis.

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Competing interests

The authors declare that they have no competing interests.

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