Bone loss in osteoporosis and arthritis
Pathogenesis and therapeutic strategies

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ABSTRACT

Bone makes up a framework that provides protection for internal body organs. The homeostasis of bone is maintained by balanced old bone resorption and new bone formation. However, this balance can be altered such as in postmenopausal women, patients with some cancers, and patients with chronic inflammatory conditions such as rheumatoid arthritis. In recent years, the management of chronic inflammatory conditions was revolutionized by the use of biologic therapies that target key pro-inflammatory proteins and/or pathways. However, whilst the anti-inflammatory effect of these biologic agents is well-established, their effect on bone loss is just emerging. The use of these agents highlights the relationship between the pathogenesis of chronic inflammation and bone loss. Here, we provide an overview of advances in understanding this relationship in patients with rheumatoid arthritis.

The structure and organization of bone. Bone is composed of a mineralized matrix with inorganic and organic components. The inorganic component is mainly crystalline mineral salts and calcium phosphate in the form of hydroxyapatite, Ca_{10}(PO_{4})_{6}(OH)_{6} on which bone hardness depends. The organic part is primarily type I collagen, which forms more than 25% of bone, and is in a fiber form with a triple helical structure that provides bone’s flexibility. Bone acts as a framework for the muscular system to provide protection for internal organs and as a mineral reservoir. There are 2 main types of bone, cortical, which makes up to 80% of bone and trabecular, which makes up to 20%. Cortical bone is dense and compact and forms the protective exterior shell of long bones and vertebrae and helps resist the stress of weight. Trabecular bone is spongy-like and comprises a network of fine and interlacing partitions, the trabeculae, and forms the main part of the vertebral body and the epiphyses of long bones. Bone loss initially affects areas composed, primarily, of trabecular bone due to its higher rate of turnover (~8 times higher) than cortical bone. Bone homeostasis. Bone homeostasis is tightly regulated by remodeling, in which old bone is removed (resorption) and replaced by new bone. These processes involve osteoblasts, osteocytes, and osteoclasts. Osteoblasts are responsible for bone formation. They
are relatively immature cells, which line the bone and produce hormones, such as prostaglandins, enzymes such as alkaline phosphatase, and matrix proteins such as glycosaminoglycans, osteocalcin, osteonectin, and bone sialoproteins.3 Osteocytes are generated from osteoblasts that migrate into the bone matrix from the surface of narrow regions of newly-formed organic matrix. They act as mechano-sensory receptors to regulate bone's response to stress and mediate bone formation, matrix maintenance, and calcium homeostasis.4

Osteoclasts are multinucleated cells of monocyte origin that cause resorption. They differentiate from monocytes with macrophage-colony-stimulating factor (M-CSF), receptor activator for nuclear factor κB (RANK), RANK-ligand (RANK-L), and osteoprotegerin (OPG). The engagement of RANK by RANK-L triggers signaling that leads to bone resorption. Receptor activator for nuclear factor κB -L is a member of the tumor necrosis factors (TNF) super family of ligands and receptors and a key osteoclastogenic cytokine that exists in soluble and tissue-bound forms. It is inhibited by its natural decoy receptor, OPG, which is soluble and non-signaling.2,5 Genetic deletion of OPG in mouse and human leads to profound osteoporosis while overexpression leads to osteopetrosis secondary to a near-total lack of osteoclasts. Pro-inflammatory cytokines suppress OPG production and enhance RANK-L expression, thus, promoting osteoclast formation and function.5

Changes in bone metabolism. Bone metabolism undergoes physiological as well as pathological changes. Such changes are measured using clinical and laboratory tests. Bone mineral density (BMD) is a measure of the amount of bone minerals per square centimeter of bone tissue in g/cm² determined using a number of protocols. Laboratory tests include serum levels of bone-specific alkaline phosphatase, osteocalcin, deoxypyridinoline, and others.6-8

Reduction in BMD in any individual relative to the normal value in a population is characteristic of osteoporosis, a condition common in postmenopausal women, with one in 3 over the age of 50 years worldwide.6 Osteoporosis starts when the regular processes of bone formation and resorption become unbalanced leading to net loss and fractures, mostly of vertebra, hip, and wrists. In addition to osteoporosis, bone loss is also seen in patients with chronic inflammatory diseases, such as RA, cancer, endogenous and exogenous thyroxin excess, patients with diseases affecting the gastrointestinal tract, and patients with long-term treatment with corticosteroids.5,6-10

In contrast to osteoporosis, patients with the rare condition of osteopetrosis have an increase in BMD. Osteopetrosis, also known as marble bone disease, is an inherited but extremely rare condition in which bone hardens and becomes denser. In addition, some patients can suffer from the softening of the bones due to defective bone mineralization as a result of inadequate amounts of available phosphorus and calcium.5

Regulation of bone metabolism. Bone is continuously remodeled to maintain optimal mass and repair any damages such as fractures. A number of factors affect bone remodeling including aging, menopausal status, chronic inflammation, diet, drugs, lack of exercise, hormones, stress, and injuries.11 In menopausal women, estrogen levels play the key role in the remodeling process through their ability to stimulate osteoblasts. Estrogen is produced by the ovaries before menopause. After menopause, the ovaries stop producing estrogen but the adrenal gland secretes small amounts of androgens and these are converted to estrogen by the enzyme aromatase. Reduced estrogen levels in postmenopausal women results in reduced osteoblasts activity and bone mass.9 Bone mass is also influenced by ethnicity, genetics, and lifestyle. For example, African-American females achieve higher peak bone mass than Caucasian females. Indeed, there is evidence that vertebral fractures are less common in black than white and Japanese women.12,13 The risk of bone loss is enhanced by excessive consumption of alcohol and smoking.11

Measurement of changes in bone metabolism. A range of clinical and laboratory protocols are used to monitor changes in bone metabolism. In most clinical settings, BMD and bone mineral content (BMC) are used as standard units to determine changes in bone metabolism. Bone mineral density signifies total bone mineral mass, whereas BMC represents total bone mineral mass in a specific region. Measurement of BMD at any skeletal site provides a predictive value of fracture incidence. Moreover, in order to predict osteoporotic fractures, assessment of the axial skeletal sites of the spine and femur has proved to be useful.6-8 Protocols in general use for assessing changes in bone density and metabolism are summarized below.

A) Radiographic protocols. 1) Dual energy x-ray absorptiometry (DEXA). Dual energy x-ray absorptiometry is the most widely used protocol for its precision, accuracy, and low radiation dose. The World Health Organization (WHO) standards for the diagnosis of osteoporosis are based on DEXA.7,8 Dual energy x-ray absorptiometry involves 2 different energy x-ray beams that are absorbed differently by
bone mineral and soft tissues and assessment depends on measurement of the transmission of x-rays with high and low energies. Results of DEXA represent a composite measure of both cortical and trabecular bones in gram/square centimeter.14-16

2) Peripheral dual energy x-ray absorptiometry (pDEXA). This technique measures bone density at peripheral sites, such as the wrist and calcaneus, using dual energy x-ray. However, variations between the peripheral and central sites are common and may underestimate fracture risks. Nevertheless, pDEXA is appropriate for older patients because bone loss in the peripheral skeleton of elderly patients would have reached that of central skeletal sites.16,17

3) Single x-ray absorptiometry (SXA). Single x-ray absorptiometry uses the same principles as DEXA, but it does not allow for adjustment for soft tissue as it utilizes only a single energy beam. Therefore, the use of SXA is limited to distal appendicular skeletal structures that have little interfering soft tissue. The most common sites are the calcaneus, the distal radius and ulna. The protocol is an inexpensive predictor of fracture risks in older women.11,16

4) Quantitative ultrasound (QUS). Quantitative ultrasound uses non-ionizing radiation, hence, has the potential of becoming a low-cost alternative to DEXA. Several prospective studies indicate that the predictive capability of QUS for hip fracture is as good as DEXA and that QUS and DEXA both predict hip fractures better than DEXA alone of the lumbar spine. Because the results of most trials depend on DEXA, many believe that more information is needed before QUS is widely used.16,17

5) Quantitative computed tomography (QCT). Quantitative computed tomography is an x-ray absorptiometric protocol that uses a computed tomography scanner to determine volumetric density (mg/cm³) of trabecular or cortical bone in 3 dimensions (3D). It calculates BMD at selected regions of interest by the mean Hounsfield number. The ability of QCT to selectively-assess the metabolically-active and structurally-important trabecular bone in the vertebral body results in an excellent differentiation of vertebral fracture from healthy vertebrae. Currently, QCT is used to assess BMD only in the spine. Generally, it has better sensitivity than DEXA, but is costly and has high radiation levels.16

6) Radiographic absorptiometry. This protocol is used for bone mass measurement at peripheral sites, most commonly the hand or heel. It relies on taking 2 x-rays at slightly different angles and images are analyzed for the average density of the middle phalanx of the middle 3 fingers, which is reported in absorptiometry units. However, the usefulness of the protocol to predict site-specific fracture risk remains to be established.16

B) Laboratory measurements of bone metabolism. Changes in bone metabolism can be assessed by measuring biomarkers of bone formation and resorption. Bone formation is generally assessed by measuring blood levels of osteocalcin, alkaline phosphatases, and pro-collagen peptides. In contrast, bone resorption is assessed by products of collagen breakdown such as C- and N-telopeptide cross-links of collagen and their adjacent peptides in blood and/or urine. These measurements are widely used to confirm the pathological bone loss and response to therapy as changes in bone resorption markers precede bone formation as detected by the established radiographic protocols.17 Our own studies indicate that the combination of DEXA scan and blood levels of RANK-L and OPG are best at revealing changes in bone metabolism in patients.

Pathological changes in bone metabolism.
A) Primary osteoporosis. Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone resulting in fragility and fractures, as commonly seen in postmenopausal women. The condition is categorized into primary and secondary. Reduction in bone mass, which is unrelated to chronic illnesses or medication and is a consequence of aging and decreased gonadal function constitutes primary osteoporosis. In women, reduction of estrogen in premenopausal or early menopausal stages increases the risk of osteoporosis. Low levels of testosterone and/or estrogen in men can also result in osteoporosis. Deficient intakes of calcium and vitamin D, sedentary lifestyle, smoking, and excessive alcohol drinking may also accelerate this condition.

Secondary osteoporosis occurs in chronic diseases such as endocrine disturbances, cancer, gastrointestinal diseases, renal failure, and inflammation. The condition could also be induced with long-term treatment with glucocorticoids.11

Treatment of osteoporosis. The ultimate objective of treating osteoporosis patients is to prevent bone fractures. There are a range of drugs in use for treating patients with osteoporosis. 1) Hormone replacement therapy (HRT) is effective in preventing osteoporosis and fractures, and is widely used in postmenopausal women. However, HRT can increase the risk of breast cancer, thromboembolism, and cardiovascular disease.18-21 To achieve the greatest beneficial effects, treatment must
Bisphosphonates are synthetic analogues of cellular inorganic pyrophosphonates that reduce the number of osteoclasts by inducing apoptosis. They also inhibit farnesyl diphosphate synthase, which is part of the mevalonate pathway of cholesterol synthesis and also inhibit glucocorticoid-induced RANK-L expression. Bisphosphonates are used for the treatment of postmenopausal patients and patients with metastatic bone disease secondary to breast cancer. Bisphosphonates, however, have serious side-effects, such as effects on the gastrointestinal tract and osteonecrosis of the jaw.

Selective estrogen receptor modulators (SERMs) bind estrogen receptors and act as estrogen-agonists or antagonists depending on the target tissue and hormonal status. The first generation includes tamoxifen, for which estrogen-like agonist activity on bone occurs at the same time with estrogen antagonist activity on the breast. Second-generation SERMs include raloxifene, which has estrogen-like actions on bone, lipids, and the coagulation system and estrogen antagonist effects on the breast and uterus. Raloxifene can be used as an alternative to HRT without deleterious effects on the endometrium while showing a significant increase in BMD at the lumbar spine, hip, and whole body and a decrease in total cholesterol and LDL levels. Calcitonin (CT) is an endogenous polypeptide hormone that suppresses bone resorption by acting similarly to estrogens. Nasal application of CT for treatment, which started more than 50 years ago has almost stopped and replaced by a newly developed oral formulation, which has increased efficacy in phase II and III clinical trials. The introduction of this new formulation is likely to enhance patient compliance as it has fewer side effects. Teriparatide (Forsteo) is a recombinant form of parathyroid hormone (PTH) and the first anabolic agent with proven anti-fracture effects and good safety profile. Unlike anti-resorption agents, teriparatide increases bone formation, cortical thickness, and trabecular bone connectivity. However, due to excessive new bone formation and osteosarcoma in rats, this treatment has been limited to a maximum of 24 months. Biological agents, the development and clinical application of biological therapies have revolutionized medicine. This class of therapeutics includes recombinant proteins, monoclonal antibodies (mAbs), and soluble receptors that selectively target key disease-promoting proteins and/or pathways. Denosumab is one such agent approved by the US Food and Drug Administration (FDA) in 2010. It is a fully human mAb that inhibits RANK-L binding to RANK. The agent is used for treating postmenopausal patients and patients treated for cancer or for RA. There is evidence that the increase in BMD with denosumab is greater than the bisphosphonate agent alendronate and that it decreases the risk of fracture.

Secondary osteoporosis. In addition to primary osteoporosis, patients with a range of chronic inflammatory diseases, cancer, and patients with endogenous and exogenous thyroxin excess develop osteoporosis secondary to their primary pathology. In RA, the production of autoantibodies and pro-inflammatory cytokines such as tumor necrosis factors-alpha (TNF-α) causes chronic inflammation, which leads to joint damage, but generalized bone damage is also a feature of the disease. Bone damage in RA occurs very early in the course of the disease, progresses rapidly, and is not repaired as it would be under physiological conditions. The detrimental effect of chronic inflammation on bone is evident in the increase in fracture risk in RA; the more inflammation that is present, the greater the risk of fracture. Indeed, decreases of 2.5 in vertebral and 5% in femoral neck BMD, are apparent just in the first year of RA, and such loss doubles in the second year if disease activity remains uncontrolled.

With regards to mechanisms of bone loss in RA, the available evidence indicates that pro-inflammatory mediators, including TNF-α, promote osteoclastogenesis. Although the perception has been that bone loss in RA due to pro-inflammatory mediators is most likely to be confined to the periarticular region of affected joints, emerging evidence from the use of biological anti-inflammatory agents provide compelling evidence for their involvement in generalized osteoporosis too. This evidence highlights the overlap between inflammatory pathways in RA and mechanisms of bone resorption including direct and indirect effects on osteoclastogenesis. Thus, mice engineered to lack osteoclasts do not develop bone erosion in arthritis induced by TNF-α. Further, this appears to occur through the ability of TNF-α to induce RANK-L expression of T-lymphocytes and osteoclasts. Indeed, when RANK-L is inhibited, the formation of osteoclasts in arthritic joints is inhibited. Interestingly, however, inhibition of RANK-L does not appear to have any impact on the inflammation. Further, a phase 2 clinical trial of denosumab in RA showed that the agent reduced bone erosion, but had no effect on disease activity. This data indicates that interfering with the RANK/RANK-L/OPG pathways have few detrimental effects on the immune system. In contrast, data on the effect of biologic inhibitors of inflammation suggests that the inflammatory response
in RA promotes RANK-L expression and bone resorption not only in the periarticular region, but also results in generalized bone loss. Support for this notion is provided by observations in which treatment with biologic anti-inflammatory agents including anti-TNF-α agents reduced RANK-L expression and increased OPG production. Furthermore, treatment of psoriatic arthritis patients with biologic anti-TNF-α agents reduced the number of peripheral osteoclast precursors.

This association between chronic inflammation and bone loss in RA is clouded by the fact that a significant proportion of RA patients are treated with glucocorticoids. Glucocorticoids are used for their anti-inflammatory efficacy, but their long-term use leads to bone loss. Therefore, it has been difficult to discern exactly how much each of these 2 events play in bone loss in RA. In this respect, it is interesting to note that a recent study revealed that osteoclasts induction in RA is inhibited with a compound modulator of the monomer glucocorticoid receptor. This compound does not induce glucocorticoid receptor dimerization, but suppresses the production of pro-inflammatory cytokines in fibroblast-like synovial cells from patients with RA and in osteoblasts. This observation further highlights the direct relationship between chronic inflammation and bone loss in RA.

**Progress in diagnosis and treatment of inflammation and their impact on osteoporosis in RA.** Early diagnosis of RA has become possible with the development of specific laboratory tests for anti-cyclic citrullinated peptides (anti-CCP) autoantibodies and sensitive imaging protocols. These advances have laid the foundation for early targeted treatment of inflammation and bone loss in RA.

**Anti-cyclic citrullinated peptides autoantibodies.** Anti-CCP autoantibodies are highly specific for RA (~96%), and when combined with positivity for the rheumatoid factors (RF), confirmed diagnosis of RA reaches ~100% in patients with early undifferentiated arthritis. Interestingly, recent studies indicate that anti-CCP autoantibodies are also good predictors of reduction in lower lumbar and femoral BMD and radiographic erosions.

**Ultrasound (US) and magnetic resonance imaging (MRI) in detecting early bone erosion in RA.** Conventional radiographic methods are not reliable in revealing early bone erosion in RA because such methods could only provide evidence of severe damage. However, the use of US and MRI has enabled in early diagnosis of RA. The ability of these protocols to reveal small erosions, early changes in bone, synovitis, tenosynovitis, and effusion is now widely used. However, whilst both protocols help evaluate early inflammatory changes in RA synovia it is likely that a combination of MRI and bone metabolism biomarkers, for example, measurement of RANK-L/OPG will better predict changes in BMD in early RA. Nevertheless, there are some disadvantages with the routine use of MRI including limited availability, long times for investigation and high costs. Ultrasound provides the benefit that it is more practical than MRI as it has a greater availability and lower cost.

**Biologic anti-inflammatory agents and their impact on osteoporosis in RA.** The discovery and application of biologic inhibitors of TNF-α have revolutionized the treatment of patients with RA. However, until recently the long-term effects of these agents, as well as other biologic anti-inflammatory agents, on osteoporosis in RA and their mechanisms of action were unclear. Tumor necrosis factors-alpha is a pleiotropic cytokine with effects on cells, tissues, and organs (Figure 1). In response to injury or infection, TNF-α is produced by macrophages. This induces the innate immune system to mount a range of responses resulting in acute inflammation. Tumor necrosis factor alpha achieves these effects by promoting lymphocyte and neutrophil adhesion, hematopoiesis, the production of collagenase and prostaglandin E2 (PGE2), and the induction of other pro-inflammatory cytokines. Tumor necrosis factor alpha also contributes to proteoglycan breakdown, acute tubular necrosis, and bone resorption.

**Mechanism of bone loss due by TNF-α.** Tumor necrosis factor-α promotes osteoclastogenesis by activating NF-κB transcription factor, which is also induced by RANK/RANK-L. Activation of NF-κB is a key target for TNF-α action through TNF receptor-1 (TNFR-1), which is expressed on macrophages. This promotes pro-osteoclasts maturation even in the absence of RANK/RANK-L signaling. Tumor necrosis factors-alpha also enhances osteoclast differentiation by increasing the expression of M-CSF and RANK-L in osteoblasts. Furthermore, TNF-α inhibits osteoclast apoptosis by activating the mammalian target of rapamycin/S6 kinase (mTOR). This enhances bone resorption by increasing the number of long-lived osteoclasts (Figure 2).

At the molecular level, TNF-α inhibits osteoblasts differentiation by inhibiting the transcriptional regulation of the osterix (Ox, Sp7) promoter, a key regulator of the initial stages of osteoblast differentiation. Further, TNF-α inhibits the Wnt-β-catenin pathway through up-regulating the inhibitor Dickkopf-related protein 1 (DKK1) (Figure 3).
Biologic anti-inflammatory agents and their role in limiting osteoporosis in RA. 1) Etanercept is one of the first agents used for the treatment of RA. It is a recombinant dimeric form of soluble TNF-α receptor II, which binds with high affinity to and inhibits TNF-α and lymphotoxin-alpha (LT-α). In 2004, the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) study established that the combination of methotrexate and etanercept improved radiographic changes in RA with 80% of patients having no progression in joint damage. Interestingly, only 37% of the patients had clinical remission as indicated by their disease activity score 28 (DAS28). 2) Infliximab is a chimeric mouse-human mAb that was first approved for treating patients with Crohn’s disease, but then used for treating RA in combination with methotrexate. Both etanercept and infliximab have been shown to reduce the risk of new fractures in patients with RA.

Figure 1 - Tumor necrosis factor-alpha (TNF-α) has a wide range of biological effects. A cartoon summarizing the range of TNF-α effects on cells, organs, and tissues. The outcome of TNF-α binding to its receptors on its targets is indicated. MHC - major histocompatibility complex, IFN - interferon, PGE - prostaglandin, IL - interleukin, GM - Granulocyte-macrophage, CSF - colony-stimulating factor.

Figure 2 - Pathways of bone loss by tumor necrosis factor-alpha (TNF-α). Tumor necrosis factor-alpha directly activates macrophage differentiation, pre-osteoclast proliferation, mature osteoclasts activation, and inhibits their apoptosis. Tumor necrosis factor-alpha also promotes osteoporosis by inducing interleukin 6 (IL-6) and receptor activator of nuclear factor kappa B (RANK) production. Finally, TNF-α suppresses osteoblastogenesis by inhibiting the proliferation and differentiation of mesenchymal stem cell (MSCs) to osteoblasts.
Figure 3 - Tumor necrosis factor-alpha (TNF-α) promotes osteoporosis through impacting and activating a number of pathways and proteins. Tumor necrosis factor-alpha promotes bone resorption through enhancing osteoclastogenesis and receptor activator of nuclear factor kappa β (RANK) + osteoclast precursor cell proliferation. It also induces RANK-L production and inhibits osteoblast maturation and function, in part by increasing the expression of the Wnt antagonist Dickkopf-related protein 1 (DKK1) resulting in impaired bone formation. OPG - osteoprotegerin.

with methotrexate. Clinical evidence is consistent with a beneficial effect of infliximab on BMD. Some evidence indicates that infliximab preserved BMD in the lumbar spine and femoral neck after one year of treatment compared with bone loss of 3.9% and 2.5% at the same sites in a control group treated with methotrexate alone. 3) Adalimumab is a parenterally-administered fully human mAb to TNF-α. Consistent with the beneficial bone effects of the other biologic anti-TNF-α agents, adalimumab in combination with methotrexate significantly improved radiographic changes. 4) Rituximab is a chimeric, human-murine mAb that depletes B-cells by binding to CD20. It is highly effective in treating RA patients especially those who do not respond to biologic anti-TNF-α agents. Emerging evidence indicates that rituximab substantially reduces autoantibody levels and bone loss in RA. Mechanistically, treatment of patients with rituximab decreases synovial osteoclast precursors and RANK-L expression and increases OPG/RANKL ratio in blood. 5) Abatacept is a selective inhibitor of cognate T-lymphocyte interaction with antigen presenting cells. Clinical trials have shown that RA patients refractory to biologic anti-TNF-α agents respond well to abatacept and that the beneficial effects could be maintained for up to 3 years. Studies using dynamic contrast-enhanced (DCE) MRI and arthroscopy-acquired synovial biopsies show 15-40% improvement in MRI parameters together with increased plasma level of OPG with reduced RANK-L. 6) Tocilizumab is a mAb specific for IL-6 receptor (IL-6R) effective in RA patients refractory to biologic anti-TNF-α agents. Recent evidence indicates that tocilizumab induces repair in erosions, particularly in large lesions with sclerosis. 7) Anakinra is a recombinant human IL-1 receptor (IL-1R) antagonist licensed for the treatment of RA. In clinical trials, anakinra significantly reduced radiographic progression and protected bone and cartilage from progressive destruction.

In conclusion, significant advances have been made in recent years in understanding molecular mechanisms that underpin changes in bone homeostasis leading to osteoporosis. These advances have led to the discovery and successful application of targeted therapeutic strategies using biological agents in the clinic. These advances have had profound impact on the clinical management of primary osteoporosis and RA. As a by-product of the discovery and application of targeted biological therapies in RA, there is now compelling evidence for an overlap between chronic inflammation and osteoporosis in RA. This overlap is not confined to periarticular osteoporosis, but extends to generalized osteoporosis that is associated with the disease. This knowledge together with advances in early diagnosis of RA is making significant inroads into preventing bone loss, fractures, and disability in patients. These advances
could ultimately lead to progress in knowledge-based personalized treatment for patients in the future.

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