

Osteoporosis in Rheumatoid Arthritis

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1. Introduction

Rheumatoid arthritis (RA) is the most common form of inflammatory arthritis in adults and is characterized by chronic, progressive, systemic inflammation leading to substantial pain, disability, and other morbidities¹. Osteoporosis (OP) is more frequent in patients with RA than in the general population due to active systemic inflammation as well as the use of corticosteroids and immobility. OP is characterized by low bone mass, and microarchitectural deterioration of bony tissue, with a consequent increase in bone fragility and susceptibility to fractures. According to the WHO criteria (Tab. 1), osteoporosis can also be defined as a value of bone mineral density (BMD) more than - 2.5 standard deviations below the young normal mean. Subsequent disability may lead to loss of independence and quality of life. Underlining the clinical significance of BMD in RA, the risk of hip² and vertebral fractures³ and the associated morbidity, mortality and healthcare costs are increased in patients with RA (Fig.1).

T - Score	Diagnosis
0 to > -1	Normal bone density
-1 to >-2,5	Osteopenia
< -2,5	Osteoporosis
< -2,5 with fracture	Severe osteoporosis

Table 1. WHO T-score criteria for Bone Mineral Density

Localized bone loss in the form of bone erosions and periarticular osteopenia constitutes an important radiographic criterion for the diagnosis of RA. In addition, generalized bone loss has been demonstrated in RA, systemic lupus erythematosus, and ankylosing spondylitis in several observational and some longitudinal studies using markers of bone turnover, bone histomorphometry, and bone densitometry⁴.

¹ Pattison DJ, Harrison RA, Symmons DP. The role of diet in susceptibility to rheumatoid arthritis: a systematic review. *J Rheumatol*. 2004;31(7):1310-9.

² Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy and hip fracture. *Ann Rheum Dis* 1995;54:49-52.

³ Arai, T. & Kragic, D. Van Staa TP, Geusens P, Bijlsma JWJ, Leufkens HGM, Cooper C. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. *Arthritis Rheum* 2006;54:3104-12.

⁴ Eggelmeijer F, Papapoulos SE, Westedt ML, Van Paassen HC, Dijkmans BA, Breedveld FC: Bone metabolism in rheumatoid arthritis; relation to disease activity. *Br J Rheumatol* 1993, 32: 387-391.

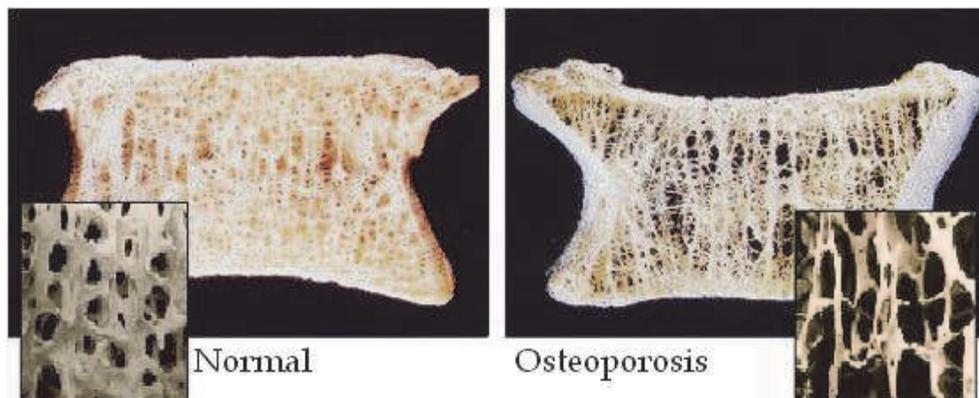


Fig. 1. In osteoporosis, the cortex becomes thinner and more brittle, while the inner trabecular bone develops larger holes

OP occurs in two forms during the course of the AR⁵:

1. periarticular osteopenia in close proximity to inflamed joints, which is a typical phenomenon in early and prolonged rheumatoid disease;
2. generalized osteoporosis, which affects the axial and appendicular bones. Inflammation has the effect of provoking more severe and accelerated bone loss in the hand as compared with hip and spine.

In all inflammatory diseases, use of glucocorticoids (GC) is a common therapy. There is no doubt about the deleterious effect of GC in bone metabolism, suppressing bone formation and enhancing bone resorption. The addition of GC to osteoprogenitor cells *in vitro* actually increases their bone-forming capacity but it also increases apoptosis of mature osteoblasts and osteocytes and therefore affects capacity of bone formation. This potent anti-inflammatory drug reduces production of pro-inflammatory cytokines (IL-1, IL-6, and TNF- α), but provokes bone resorption by increasing the synthesis of RANKL and inhibiting OPG production with consequent induction of osteoclastogenesis⁶.

Systemic inflammation and GC use accelerates bone loss independent of other risk factors⁷ but other factors must be valorized. Immobilization due to pain from inflamed joints, impairment of physical activity, reduced calcium intake, and poor nutrition associated with enhanced basal energy expenditure are also risk factors related to low BMD, common in this population. In children, delayed puberty and stunted growth can adversely affect bone remodeling⁸.

⁵ Sambrook PN: The skeleton in rheumatoid arthritis: common mechanism for bone erosion and osteoporosis? *J Rheumatol* 2000, 27:2541-2542. Gregório LH, Lacativa PG, Melazzi AC, Russo LA.

⁶ Glucocorticoid-induced osteoporosis. *Arq Bras Endocrinol Metab.* 2006;50(4):793-801.

⁷ Roldán JF, Del Rincón I, Escalante A. Loss of cortical bone from the metacarpal diaphysis in patients with rheumatoid arthritis: independent effects of systemic inflammation and glucocorticoids. *J Rheumatol.* 2006;33(3):508-16.

⁸ Viswanathan A, Sylvester FA. Chronic pediatric inflammatory diseases: effects on bone. *Rev Endocr Metab Disord.* 2008;9(2):107-22.

Consequently, increase in bone resorption, both focal and systemic, are common in patients with RA. In patients with active RA compared to matched controls and patients with inactive RA serum osteocalcin which reflects bone formation was found to be significantly lower and crosslinked N-telopeptidases of type 1 collagen (NTX) and deoxypyridinoline (DPD) which reflect bone resorption, were significantly higher. There were positive correlations between these bone markers and disease activity⁹.

2. Epidemiology and prevalence

Rheumatoid arthritis is a chronic inflammatory and destructive joint disease that affects 0.5-1% of the world's population and commonly leads to significant disability and consequent impairment of quality of life¹⁰. It is two or three times more frequent in women than in men and can start at any age, with its peak incidence between the fourth and sixth decades of life¹¹. Generalized osteoporosis is an extra-articular complication of rheumatoid arthritis that results in increased risk of fractures and associated morbidity, mortality, and healthcare costs. The incidence of osteoporosis among patients with rheumatoid arthritis is 15-20% at the hip and spine¹². Haugeberg elegantly showed a twofold increase in osteoporosis in women with RA and a twofold increase of reduced bone mass in men with RA, compared with patients without RA in a population based study¹³. Italian research, performed with patients with established RA, reported disease-related factors, such as long disease duration, high disease activity, joint damage, functional disability and corticosteroid use, as determinants of osteoporosis or reduced BMD¹⁴. Hence, patients with long-standing RA with destructive disease, functional disability or immobilisation, or who are on longterm corticosteroid treatment are at high risk for osteoporosis¹⁵. This could be explained by the fact that generalised osteoporosis is more associated with long-standing, destructive and disabling RA, whereas early RA is associated with periarticular osteoporosis. This is further supported by the fact that longer symptom duration is independently associated with more generalised osteoporosis in studies.

⁹ Seriola B, Ferretti V, Sulli A, Caratto E, Fasciolo D, Cutolo M. Serum osteocalcin levels in premenopausal rheumatoid arthritis patients. *Ann N Y Acad Sci.* 2002;966:502-7.

¹⁰ Brandão L, Ferraz MB, Zerbini CAF. Avaliação da qualidade de vida na artrite reumatóide: revisão atualizada [Evaluation of quality of life in rheumatoid arthritis]. *Rev Bras Reumatol.* 1997;37(5):275-81.

¹¹ Gabriel SE. The epidemiology of rheumatoid arthritis. *Rheum Dis Clin North Am.* 2001;27(2):269-81. Martin JC, Munro R, Campbell MK, Reid DM. Effects of disease and corticosteroids on appendicular bone mass in postmenopausal women with rheumatoid arthritis: comparison with axial measurements. *Br J Rheumatol.* 1999;36(1):43-9.

¹² Lodder MC, Haugeberg G, Lems WF, et al. Radiographic damage associated with low bone mineral density and vertebral deformities in rheumatoid arthritis: the Oslo-Truro-Amsterdam (OSTRA) collaborative study. *Arthritis Rheum.* 2003;49(2):209-15.

¹³ Haugeberg G, Uhlig T, Falch JA, Halse JI, Kvien TK. Reduced bone mineral density in male rheumatoid arthritis patients: frequencies and associations with demographic and disease variables in ninety-four patients in the Oslo County Rheumatoid Arthritis Register. *Arthritis Rheum* 2000;43:2776-84.

¹⁴ Sinigaglia L, Nervetti A, Mela Q, Bianchi G, Del Puente A, Di Munno O, et al. A multicenter cross sectional study on bone mineral density in rheumatoid arthritis. Italian Study Group on Bone Mass in Rheumatoid Arthritis. *J Rheumatol* 2000;27:2582-9.

¹⁵ Lems WF, Dijkman BAC. Should we look for osteoporosis in patients with rheumatoid arthritis? *Ann Rheum Dis* 1998;57:325-7.

Numerous studies have investigated the relation between demographic and disease related variables on the one hand, and bone mass on the other, in patients with RA. These studies tried to identify patients at high risk of osteoporosis¹⁶. Studies investigating the variables associated with BMD¹⁷ showed some inconsistencies, which might be caused by differences in methodological aspects, such as sample size and patient selection. Moreover, the complex interaction between inflammation, immobility, and corticosteroid use may contribute to the lack of unanimous results.

Only a few studies focusing on BMD in patients with early RA have been performed; however the disease duration in some was up to 5 years¹⁸. Very little is known about the extent of osteoporosis and the influence of disease-associated factors on BMD in patients with recently diagnosed RA¹⁹. These data are required in order to unravel the common mechanisms between generalised osteoporosis and RA.

Symptom duration and the presence of RF were the only RAspecific markers for osteoporosis and reduced BMD in this study. It is known that seropositive RA is associated with more aggressive joint disease and is more commonly complicated by extra-articular manifestations than is seronegative RA^{20 21}. Previous studies showed an independent association between the presence of RF and osteoporosis or reduced BMD in established and recent onset RA.

3. Etiology and pathophysiology

3.1 Bone remodeling

Throughout life, normal skeletal maintenance occurs by a tightly coupled process of bone remodeling. It consists of a sequential process of bone resorption by osteoclasts followed by deposition of new bone by osteoblasts. Osteoblasts are derived from precursor cells that can also be stimulated to become muscle, fat or cartilage; however, under the right conditions these cells change (or differentiate) to form new bone, producing the collagen that forms the scaffolding or bone matrix. This calcium- and phosphate-rich mineral is added to the matrix to form the hard, yet resilient, tissue that is healthy bone. The osteoclasts remove bone by dissolving the mineral and breaking down the matrix in a process that is called bone resorption. The osteoclasts come from the same precursor cells in the bone marrow that

¹⁶ Martin JC, Munro R, Campbell MK, Reid DM. Effects of disease and corticosteroids on appendicular bone mass in postmenopausal women with rheumatoid arthritis: comparison with axial measurements. *Br J Rheumatol* 1997;36:43–9.

¹⁷ Kroot EJ, Nieuwenhuizen MG, Waal Malefijt MC, van Riel PL, Pasker-de Jong PC, Laan RF. Change in bone mineral density in patients with rheumatoid arthritis during the first decade of the disease. *Arthritis Rheum* 2001;44:1254–60.

¹⁸ Shenstone BD, Mahmoud A, Woodward R, Elvins D, Palmer R, Ring F, et al. Bone mineral density in nonsteroid treated early rheumatoid arthritis. *Ann Rheum Dis* 1994;53:681–4.

¹⁹ Keller C, Hafstrom I, Svensson B. Bone mineral density in women and men with early rheumatoid arthritis. *Scand J Rheumatol* 2001;30:213–20.

²⁰ Egeland T, Munthe E. The role of the laboratory in rheumatology. Rheumatoid factors. *Clin Rheum Dis* 1983;9:135–60. 22.

²¹ Van Zeben D, Hazes JM, Zwinderman AH, Cats A, van der Voort EA, Breedveld FC. Clinical significance of rheumatoid factors in early rheumatoid arthritis: results of a follow up study. *Ann Rheum Dis* 1992;9:1029–35.

produce white blood cells. These precursor cells can also circulate in the blood and be available at different sites in need of bone breakdown. Osteoclasts are formed by fusion of small precursor cells into large, highly active cells with many nuclei. Removal and replacement of bone in the remodeling cycle is controlled by local and systemic factors that regulate bone remodeling to fulfill both its structural and metabolic functions. The activation of this process involves an interaction between cells of the osteoblastic lineage and the precursors that will become osteoclasts. The differentiation of myeloid progenitor cells into committed osteoclast lineage is characterized by the appearance of the mRNA and protein for vitronectin receptor, cathepsin K, tartrate-resistant acid phosphatase, and calcitonin receptor²²⁻²³. This process of osteoclastogenesis requires the presence of receptor activator of nuclear factor- κ B ligand (RANKL; also known as OPGL, TRANCE, ODF, and SOFA) and the permissive factor, macrophage colony stimulating factor (M-CSF) secreted by the local osteoblast/stromal cells. RANKL binds to its receptor RANK expressed on the surface of osteoclast precursor cells and stimulates their differentiation into mature osteoclasts²⁴. The osteoblast/stromal cells also secrete osteoprotegerin (OPG; also known as OCIF, TR-1, FDCR-1, and TNFRSF-11B), a soluble decoy receptor protein that binds to RANKL and prevents its binding to RANK on the preosteoclast cells. The biologic effects of OPG are, therefore, the opposite of those of RANKL, i.e. OPG inhibits osteoclastogenesis and osteoclast function and promotes osteoclast apoptosis²⁵. The production and activity of both RANKL and OPG are influenced by several cytokines, inflammatory mediators, and calcitropic hormones that 'converge' onto these proteins. The net RANKL/OPG balance determines the differentiation, activation, and survival of osteoclasts, which in turn determine bone loss²⁶.

3.2 Focal bone erosion in rheumatoid arthritis: The role of the rank/rankl/OPG system and the TNF- α

Although the mechanisms of cartilage destruction in rheumatoid arthritis (RA) are well described, the mechanisms responsible for bone erosion in this disease have only recently been studied. The role of osteoclasts in bone erosion in RA has been suspected for many years on the basis of indirect evidence, including the identification of multinucleated cells with phenotypic features of osteoclasts at sites of erosion in human RA²⁷⁻²⁸.

²² Lee SK, Goldring SR, Lorenzo JA: Expression of the calcitonin receptor in bone marrow cell cultures and in bone: a specific marker of the differentiated osteoclast that is regulated by calcitonin. *Endocrinology* 1995, 136:4572-4581.

²³ Faust J, Lacey DL, Hunt P, Burgess TL, Scully S, Van G, Eli A, Qian Y, Shalhoub V: Osteoclast markers accumulate on cells developing from human peripheral blood mononuclear precursors. *J Cell Biochem* 1999, 72:67-80.

²⁴ Lacey DL, Timms E, Tan HL, Kelley MJ, Dunstan CR. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell* 1998, 93:165-176.

²⁵ Simonet WS, Lacey DL, Dunstan CR, Kelley M, Chang MS. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. *Cell* 1997, 89:309-319.

²⁶ Suda T, Takahashi N, Martin TJ: Modulation of osteoclast differentiation. *Endocr Rev* 1992, 13:66-80.

²⁷ Gravallesse EM, Harada Y, Wang JT, Gorn AH, Thornhill TS, Goldring SR. Identification of cell types responsible for bone resorption in rheumatoid arthritis and juvenile rheumatoid arthritis. *Am J Pathol* 1998;152:943-51.

Inflammation modulates bone resorption mainly by two mechanisms. Firstly, pro-inflammatory cytokines have a final common mediator of osteoclast function: receptor activator of nuclear factor- κ B (RANK) and its functional ligand (RANKL), also known as TRANCE (TNF-related activation induced cytokine)^{29 30}. Secondly, osteoclastogenesis can be regulated through the modulation of macrophage colony stimulating factor (M-CSF).

RANKL is a membrane-bound tumor necrosis factor (TNF) receptor expressed on osteoblast precursor cells that recognize RANK on the osteoclast surface through a direct cell-cell interaction. This process is essential for osteoclast differentiation, activation and survival. RANKL is considered the key osteoclastogenic cytokine as the RANKL-RANK interaction stimulates several transcription factors and all three families of MAP kinases³¹. The osteoblast/stromal cells also secrete osteoprotegerin (OPG), a soluble decoy receptor protein that binds to RANKL and prevents its binding to RANK on the preosteoclast cells. The biologic effects of OPG are, therefore, the opposite of those of RANKL; in fact, it inhibits osteoclastogenesis and osteoclast function and promotes osteoclast apoptosis³². The net RANKL/OPG balance determines the differentiation, activation, and survival of osteoclasts, which in turn determine bone loss³³. Synovial tissues provide a source of RANKL that could influence osteoclastogenesis. Synovial fibroblasts from patients with RA produce mRNA and protein for RANKL. RANKL is also expressed by T lymphocytes from RA synovial tissues³⁴. Adjuvant-induced arthritis (AIA) is an animal model of T lymphocyte mediated inflammatory arthritis characterized by destruction of bone and cartilage similar to that in RA. In this model, activated T cells express RANKL protein on their surface, and through binding of RANKL to RANK on preosteoclasts, these cells promote osteoclastogenesis and subsequent bone loss. Co-culture experiments using RA synovial fibroblasts and peripheral blood mononuclear cells as a source of osteoclast precursors demonstrate that osteoclast-like cells are generated, and the generation of these cells is inhibited by the addition of OPG (Fig.2) Similarly, activated T cells expressing RANKL induce osteoclasts from autologous peripheral blood monocytes, a process that is also inhibited by OPG³⁵.

²⁸ Suzuki Y, Nishikaku F, Nakatuka M, Koga Y. Osteoclast-like cells in murine collagen induced arthritis. *J Rheumatol* 1998;25:1154-60.

²⁹ Romas E, Bakharevski O, Hards DK, Kartsogiannis V, Quinn JMW, Ryan PFJ, et al. Expression of osteoclast differentiation factor at sites of bone erosion in collagen-induced arthritis. *Arthritis Rheum* 2000;43:821-6.

³⁰ Leisen JCC, Duncan H, Riddle JM, Pitchford WC. The erosive front: a topographic study of the junction between the pannus and the subchondral plate in the macerated rheumatoid metacarpal head. *J Rheumatol* 1988;15:17-22.

³¹ Mundy GR. Osteoporosis and inflammation. *Nutr Rev.* 2007;65(12 Pt 2):S147-51

³² Teitelbaum SL. Osteoclasts: what do they do and how do they do it? *Am J Pathol.* 2007;170(2):427-35.

³³ Takayanagi H, Iizuka H, Juji T, Nakagawa T, Yamamoto A. Involvement of receptor activator of nuclear factor κ B ligand/osteoclast differentiation factor in osteoclastogenesis from synoviocytes in rheumatoid arthritis. *Arthritis Rheum* 2000;43:259-69.

³⁴ Kong YY, Feige U, Sarosi I, Bolon B, Tafuri A. Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand. *Nature* 1999;402:304-9.

³⁵ Suzuki Y, Tsutsumi Y, Nakagawa M, Suzuki H, Matsushita K, Beppu MI. Osteoclast-like cells in an in vitro model of bone destruction by rheumatoid synovium. *Rheumatology (Oxford)* 2001;40:673-82.

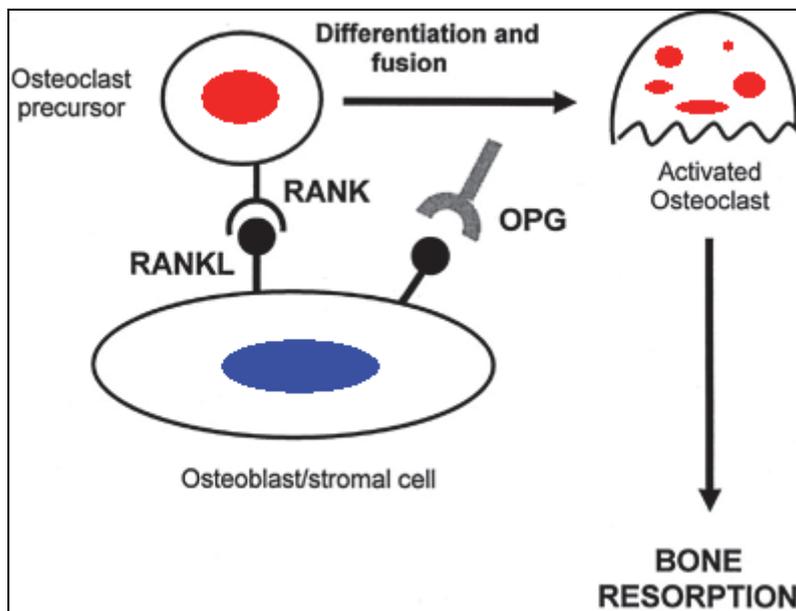


Fig. 2. A schematic overview of the RANK/RANKL/OPG system

Synovial tissues may also provide a source of osteoclast precursor cells, as macrophages isolated from RA synovial tissues differentiate into osteoclasts in the presence of M-CSF plus RANKL. More recent studies have extended these findings. Cells digested from RA synovial tissue samples generate TRAP positive multinucleated cells that form resorption pits on dentine slices³⁶ a definitive demonstration that these cells are osteoclasts. Synovial fibroblasts in rheumatoid synovium may also contribute significantly to localized bone loss. These cells produce chemokines such as macrophage inflammatory peptide 1, regulated-upon-activation normal T cell expressed and secreted, IL-8, and IL-16, which promote lymphocyte infiltration and support lymphoproliferation via secretion of various colony-stimulating factors³⁷. This results in a large pool of RANKL-expressing lymphocytes supporting osteoclastogenesis and local bone loss. Furthermore, synovial fibroblasts may directly contribute to local bone destruction by expressing RANKL on their surface³⁸ and by secreting cathepsins. Elevated levels of tumor necrosis factor (TNF)- α have been demonstrated by immunoassays in several inflammatory arthritides. TNF- α promotes expression of adhesion molecules, activation of leukocytes, recruitment of leukocytes, and production of proinflammatory cytokines (e.g. IL-1, IL-6, and IL-8) in RA. There are two mechanisms by which TNF- α acts in osteoclasts, both marrow stromal cells and osteoclast

³⁶ Kontoyiannis D, Kollias G: Fibroblast biology: synovial fibroblasts in rheumatoid arthritis: leading role or chorus line? *Arthritis Res* 2000, 2:342-343.

³⁷ Ross FP, Chappel J, Alvarez JL, Sander D, Butler WT, Farach-Carson MC. Interactions between the bone matrix proteins osteopontin and bone sialoprotein and the osteoclast integrin α v β 3 potentiate bone resorption: *J Biol Chem* 1993, 268:9901-9907.

³⁸ Teitelbaum SL. Osteoclasts: what do they do and how do they do it? *Am J Pathol.* 2007;170(2):427-35.

precursors express TNF- α receptors. The main process occurs when stromal cells are exposed to TNF- α and produce RANKL, M-CSF, and IL-1, which promote osteoclast formation and activation. TNF- α and RANKL are synergistic, and minimal levels of one markedly enhances the osteoclastogenic capacity of the other³⁹ (Fig. 3).

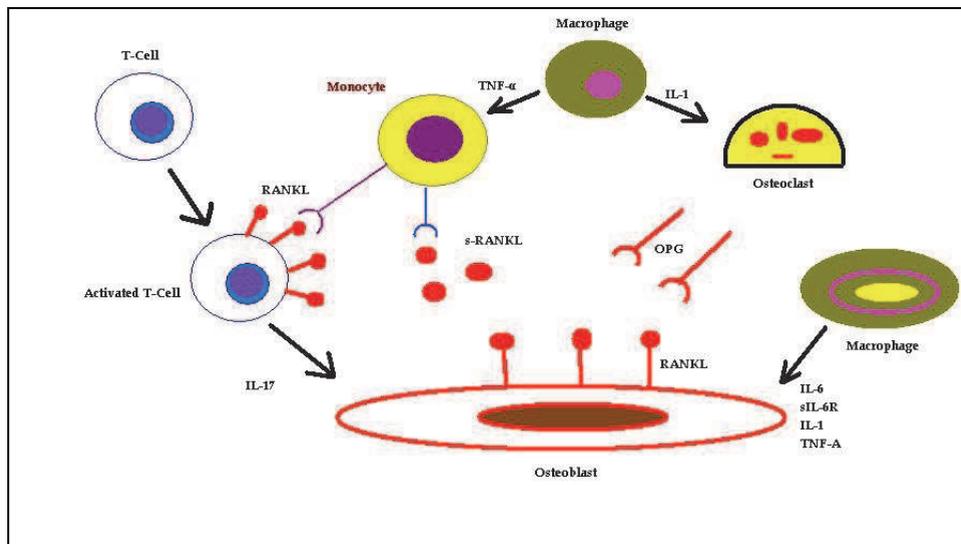


Fig. 3. Activated human T cells induce osteoclastogenesis from human monocytes

TNF- α also has potent antiapoptotic effects on osteoclasts, prolonging their lifespan⁴⁰. The second mechanism occurs when the inflammatory process becomes more aggressive and TNF- α may promote osteoclast formation by directly stimulating its precursors in the absence of stromal cells responsive to the cytokine, perhaps through activation of transforming growth factor (TGF)- β .

3.3 Focal bone erosion in rheumatoid arthritis: The role of the glucocorticoid use

In all inflammatory diseases, use of glucocorticoids (GC) is a common therapy. The use of GC, however, is associated with a variety of adverse effects,¹ including the development of osteoporosis and fractures. In patients who have received GCs for longer than six months, the estimated glucocorticoid-induced osteoporosis (GIO) frequency is 50%⁴¹. The pathogenesis of GIO is multifaceted. Glucocorticoids have indirect effects on osteoporosis by inhibiting calcium absorption from the gastrointestinal track and decreasing the renal tubular reabsorption of calcium and consequently secondary hyperparathyroidism. GCs

³⁹ Weitzmann MN, Pacifici R. The role of T lymphocytes in bone metabolism. *Immunol Rev.* 2005;208:154-68.

⁴⁰ Van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid induced osteoporosis: a meta-analysis. *Osteoporos Int.* 2002;13:777- 87.

⁴¹ Pereira RM, Delany AM, Canalis E. Cortisol inhibits the differentiation and apoptosis of osteoblasts in culture. *Bone* 2001;28:484-90.

reduce growth hormone (GH) secretion and may alter the GH/insulin-like growth factor (IGF)-I axis. An important role may be played by skeletal IGF-I because GCs inhibit IGF-I transcription in osteoblasts. Glucocorticoids have direct effects on bone cells. GCs reduce the replication, differentiation and function of osteoblasts⁴² and increase the apoptosis rates of mature cells, thereby depleting the osteoblastic cell population and inhibiting the function of mature cells. Furthermore, in the presence of GCs, bone marrow stromal cells do not differentiate into osteoblasts; instead, these cells differentiate toward an adipocyte cell lineage. Moreover, GCs induce apoptosis in osteocytes and affect the functioning of these cells. GCs increase the expression of M-CSF and receptor activator of RANK-L. In addition, GCs decrease the expression of osteoprotegerin in stromal and osteoblastic cells. Through these mechanisms, GCs can induce the formation of osteoclasts and favor bone resorption. GCs also reduce the rate of apoptosis among mature osteoclasts.

4. Diagnosis

The initial evaluation of secondary osteoporosis should include a detailed history of clinical risk factors for fractures and the underlying medical conditions and medications that cause bone loss, a thorough physical. Patients with decreased bone density usually have no specific abnormal physical findings. Those with vertebral compression fractures will have kyphosis, protruding abdomen and height loss. Back tenderness is usually only present after an acute fracture. Gait speed and grip strength are often reduced in patients who have or are about to have a hip fracture. Visual acuity should be checked in geriatric patients because it is a risk factor for falling.

Based on these initial findings and the clinical index of suspicion, further laboratory and imaging studies as well as invasive tests are required. examination and laboratory. Optimal evaluation consists of establishing the diagnosis of osteoporosis on the basis of bone mass assessment (BMD), establishing the fracture risk, and determining the need for therapy. Dual-energy x-ray absorptiometry (DXA) is the preferred technique to measure BMD, and is the technique used at most centers⁴³. The hip and the spine are the preferred site for BMD measurement due to the high predictive value of hip BMD for fracture risk. The World Health Organization (WHO) has established the following operational definition for osteoporosis based on BMD as measured by DXA (Fig. 4), commonly expressed as a T-score.

The World Health Organization (WHO) has established criteria for making the diagnosis of osteoporosis, as well as determining levels that predict higher chances of fractures. These criteria are based on comparing the BMD of the patient with that of a typical healthy, young female's. BMD values that fall well below the average for the healthy, young female's (stated statistically as 2.5 standard deviations below the average) are diagnosed as osteoporotic. If a patient has a BMD value less than the healthy, young female, but not 2.5 standard deviations below the average, the bone is osteopenic. Osteopenic means decreased bone mineral density, but it's not as severe as osteoporosis.

⁴² Khan AA, Hanley DA, Bilezikian JP, Binkley N, Brown JP. Standards for performing DXA in individuals with secondary causes of osteoporosis. *Journal of Clinical Densitometry* 2006 9 47-57.

⁴³ Heaney RP. Thinking straight about calcium. *N Engl J Med* 1993; 328:503-505.



Fig. 4. A scanner used to measure bone density with Dual Energy X-ray absorptiometry.

Although these criteria are widely used, they were based on a Caucasian female, so there will be some differences when these levels are applied to non-Caucasian females or to males in general. Despite this flaw, BMD measurement is a common method that's helpful in all groups. Laboratory evaluation for secondary causes of osteoporosis should be considered when osteoporosis is diagnosed. Serum calcium, phosphorus, alkaline phosphatase, creatinine, vitamin D, complete blood count and thyroid stimulating hormone (TSH) levels are usually sufficient baseline tests. Further laboratory tests can be done as clinically appropriate, such as parathyroid hormone level, urine free cortisol, liver function tests, or serum immune electrophoresis. Biochemical indices of skeletal turnover could potentially be helpful in the diagnosis and monitoring of therapy.

5. Treatment

The treatment of inflammatory bone loss can be aimed at attempts to suppress bone resorption and to increase bone formation.

5.1 Calcium and vitamin D

Both alfacalcidol (25 OH vitamin D₃) and calcitriol (1,25 (OH)₂ Vitamin D₃) are used by some for the treatment of osteoporosis⁴⁴. An adequate intake of calcium and Vitamin D supplementation are recommended as vitamin D. Serum and urinary calcium, serum 25OHD, and PTH concentrations should be used to evaluate hypovitaminosis D, secondary hyperparathyroidism and low net calcium balance. In randomized trials, the use of calcium and vitamin D alone had no significant benefit in bone density. However, these disturbances usually found in inflammatory diseases should be corrected to avoid the interference with anti-osteoporotic treatment efficacy. Calcium intake (from diet, added to supplementation) must be at least 1,200 mg/d, and vitamin D supplementation should be at least 800 UI/d if any of those disturbances are found. In addition, the efficacy of anti-osteoporotic drugs has only been demonstrated in the presence of vitamin D and calcium supplementation. Therapy should be titrated with doses that result in normocalcemia and serum 25-hydroxyvitamin D concentrations of at least 30 ng/ml. In patients with normal renal function, a decrease in serum PTH levels from elevated to normal levels indicates that 25-hydroxyvitamin D deficiency has been corrected. Some anti-epileptic drugs, e.g. phenytoin, phenobarbitone, primidone, and carbamazepine, increase hepatic metabolism of vitamin D, requiring higher vitamin D doses.

5.2 Bisphosphonates

Bisphosphonates have a strong affinity for bone apatite, which is the basis for their clinical use. They are potent inhibitors of bone resorption and produce their effect by reducing the recruitment and activity of osteoclasts and increasing their apoptosis. In general, alendronate (70 mg/week) and risedronate (35 mg/week) are reasonable antiosteoporotic drugs for secondary osteoporosis. However, many patients with osteoporosis secondary to gastrointestinal diseases or concurrent medications not tolerating, or adhering to, oral bisphosphonates and those in whom oral bisphosphonates are contraindicated may benefit from treatment with i.v. ibandronate or zoledronic acid. Many studies have shown that Alendronate and Zoledronate are able to reduce joint swelling and blood inflammatory tests (IL-1, IL-6, TNF- α , b2-microglobulin and erythrocyte sedimentation rate and C-reactive protein values) in various experimental arthritis animal models and in human studies. These medications reduce the macrophage production of TNF- α , IL-1 and nitric oxide (NO) and induce apoptosis of monocyte-macrophage-derived cell lines. These effects are in part dependent on RANKL inhibition and in part dependent on cytoplasmic events which involve protein-kinase C and iron ions. All these effects explain why, although bisphosphonates enhance proliferation of T-lymphocytes, they have been successfully used to treat bone loss secondary to RA⁴⁵. The overall safety profile of bisphosphonates is favorable. Oral bisphosphonates are associated with mild gastrointestinal disturbances, and rarely cause esophagitis and ulcer. A recent study also showed an increase in esophageal cancer among chronic users. Intravenous zoledronate can induce a transient acute phase

⁴⁴ Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med.* 2001;344:1434-4.

⁴⁵ Ahrader SP, Raggi KR. Parathyroid hormone (1-84) and treatment of osteoporosis. *Ann Pharmacother.* 2005;39:1511-6.

reaction with fever, bone and muscle pain that ameliorates or disappears after subsequent courses. Osteonecrosis of the jaw has been described in cancer patients receiving high doses of intravenous pamidronate or zoledronate. Atrial fibrillation was noted to occur in a higher frequency after intravenous zoledronate, but a cause-effect relationship was not established and it was not seen in another study.

5.3 Teriparatide

Intermittent administration of PTH (for example, with daily subcutaneous injections) results in an increase of the number and activity of osteoblasts, leading to an increase in bone mass and in an improvement in skeletal architecture at both cancellous and cortical skeletal sites. The 1-34 N-terminal fragment (teriparatide) is used for the management of osteoporosis. Treatment with teriparatide has been shown to reduce significantly the risk of vertebral fractures and to reduce non-vertebral but not hip fractures⁴⁶. The recommended dose is 20 µg of teriparatide daily, given as a subcutaneous injection. The effect was initially seen in patients with severe osteoporosis and established vertebral fractures. Efficacy was later shown with osteoporosis even without fractures⁴⁷.

5.4 Strontium ranelate

Strontium ranelate is a recently approved agent in Europe, for the treatment of postmenopausal osteoporosis, to reduce the risk of vertebral and hip fractures (49). There is some evidence that strontium ranelate both inhibits bone resorption and stimulates bone formation, suggesting that the agent may uncouple the bone remodelling process. The recommended daily dose is a one 2-gram sachet once daily by mouth. The absorption of strontium ranelate is reduced by food, milk and its derivative products and the drug should be administered, therefore, between meals. Ideally, it should be taken at bedtime, preferably two hours after eating. Strontium ranelate is not recommended for patients with severe renal impairment (creatinine clearance below 30 mL/min).

5.5 Denosumab

Denosumab, a new drug under evaluation, acts as an anti-RANKL blocking osteoblast differentiation and slowing bone resorption similar to the OPG. Denosumab is a fully human monoclonal antibody that mimics the activity of osteoprotegerin. It binds to RANKL, thereby preventing RANKL from interacting with RANK and reducing its bone resorption.

5.6 Raloxifene

Raloxifene is part of Selective Estrogen Receptor Modulators (SERMs). They are a class of medications that act on the estrogen receptors throughout the body in a selective manner.

⁴⁶ Reginster JY, Felsenberg D, Boonen S, Diez-Perez A, Rizzoli R. Effects of long term strontium ranelate treatment on the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis, results of five year, randomizes, placebo-controlled trial. *Arthritis and Rheumatism*. 2008;58:1687-95.

⁴⁷ Gillespie MT. Impact of cytokines and T lymphocytes upon osteoclast differentiation and function. *Arthritis Res Ther*. 2007;9:103.

Normally, bone mineral density (BMD) is tightly regulated by a balance between osteoblast and osteoclast activity in the trabecular bone. Estrogen has a major role in regulation of the bone formation-resorption equilibrium, as it stimulates osteoblast activity⁴⁸. Some SERMs such as raloxifene, act on the bone by slowing bone resorption by the osteoclasts. Raloxifene has the added advantage of reducing the risk of invasive breast cancer.

6. Therapy in glucocorticoid treatment

There are a number of guidelines regarding the management of GIO in patients who are receiving glucocorticoid treatment or that will be starting this therapy. We have analyzed the guidelines established by the American College of Rheumatology (ACR)⁴⁹, and the Dutch Society of Rheumatology (DSR)⁵⁰. A Cochrane Database Meta-Analysis concluded that calcium and vitamin D supplementation should be started in all patients who are administered glucocorticoids because of their low toxicity, low cost and the possible benefit in terms of fracture risk⁵¹. Vitamin D is a hormone that increases intestinal calcium absorption and increases its reabsorption in distal renal tubules. Serum levels of at least 30 ng/mL (82 nmol/L), and optimally of 40–60 ng/mL, of 25-hydroxyvitamin D should be the target treatment regimen for GIO management. To achieve these levels, 1,000 to 2,000 IU of oral vitamin D daily may be necessary⁵². Bisphosphonates are indicated for the prevention and treatment of GIO and most guidelines recommend the use of these drugs. The prevention and treatment goals of bisphosphonate use are stabilized or increased bone mineral density, as well as reduced frequency of fractures. A study using risedronate showed a decrease in vertebral fractures after one year of treatment⁵³. Currently, alendronate (70 mg/ week or 10 mg/ day) and risedronate (35 mg/week or 5 mg/ day) are the only oral antiresorptive drugs that are recommended in GIO. Recently, zoledronic acid was approved for the prevention and treatment of GIO. In a multicenter, double-blind, double-dummy, randomized controlled trial that included 833 patients, a single 5 mg intravenous infusion of zoledronic acid caused a greater increase in bone mineral density than oral risedronate at 5 mg daily⁵⁴. Bisphosphonate treatment is recommended while patients

⁴⁸ Meunier PJ, Vignot E, Garnero P. "Treatment of postmenopausal women with osteoporosis or low bone density with raloxifene. Raloxifene Study Group". *Osteoporos Int* 1999;10 (4): 330–36.

⁴⁹ American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. *Arthritis Rheum.* 2001;44:1496–503.

⁵⁰ Geusens PP, de Nijs RN, Lems WF, Laan RF, Struijs A, van Staa TP, et al. Prevention of glucocorticoid osteoporosis: a consensus document of the Dutch Society for Rheumatology. *Ann Rheum Dis.* 2004; 63:324–5.

⁵¹ Berris KK, Repp AL, Kleerekoper M. Glucocorticoid-induced osteoporosis. *Curr Opin Endocrinol Diabetes Obes.* 2007;14:446–50.

⁵² Heaney RP. The vitamin D requirement in health and disease. *J Steroid Biochem Mol Biol.* 2005;97:13–9, doi: 10.1016/j.jsbmb.2005.06.020.

⁵³ Wallach S, Cohen S, Reid DM, Hughes RA, Hosking DJ, Laan RF, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. *Calcif Tissue Int.* 2000;67:277–85.

⁵⁴ Reid DM, Devogelaer JP, Saag K, Roux C, Lau CS, Reginster JY, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet.* 2009;373:1253–63,

are on glucocorticoids; however, in subjects with significant bone loss, therapy may need to be continued following the discontinuation of glucocorticoids. Caution needs to be exercised when considering the use of bisphosphonates in women of childbearing age with GIO,^{55 56} given that bisphosphonates have an extended half-life and may cross the placenta with potentially unfavorable effects on fetal skeletal development. A recent review of 51 human cases examining exposure to bisphosphonates before or during pregnancy did not demonstrate skeletal abnormalities or other congenital malformations in the infants. Similarly, a related case-controlled study suggested that preconceptional and first-trimester use of bisphosphonates may pose limited fetal risk⁵⁷. Saag et al., published a randomized multicenter trial to compare use of oral alendronate (10 mg/day) and subcutaneous teriparatide (20 mg/day) over 18 months in patients with established GIO. The study showed that among patients with osteoporosis with a high risk for fracture, the bone mineral density increase in patients receiving teriparatide was greater than in those receiving alendronate⁵⁸.

7. Conclusion

Localized bone loss in RA results from the activation of an inflammatory immune response, which increases both the number and the activity of osteoclasts.

Osteoporosis in patients with rheumatoid arthritis is a silent disease that evolves in parallel with the underlying disease and gives a sign to exist only after the fracture. Patients with rheumatoid arthritis are subject to chronic systemic inflammation and a chronic intake of corticosteroids. These elements form the basis of the osteoclastic process. The diagnosis and prevention becomes necessary to understand in all its aspects, the patient rheumatic disease and to avoid untoward developments. Therapy to prevent or reverse this bone loss should be directed at the suppression of inflammation, direct inhibition of osteoclast-mediated bone resorption, or stimulation of osteoblastic bone formation.

The challenge now is to determine if altering this inflammatory induced bone loss in RA will translate into reduced functional disability. The future is promising in this scientific arena.

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9. References

Ahrader SP, Raggucci KR. Parathyroid hormone (1-84) and treatment of osteoporosis. *Ann Pharmacother.* 2005;39:1511-6.

⁵⁵ Franchimont N, Canalis E. Management of glucocorticoid induced osteoporosis in premenopausal women with autoimmune disease. *Autoimmun Rev.* 2003;2:224-8.

⁵⁶ Djokanovic N, Klieger-Grossmann C, Koren G. Does treatment with bisphosphonates endanger the human pregnancy? *J Obstet Gynaecol Can.* 2008;30:1146-8.

⁵⁷ Levy S, Favez I, Taguchi N, Han JY, Aiello J, Matsui D, et al. Pregnancy outcome following in utero exposure to bisphosphonates. *Bone.* 2009;44:428-30.

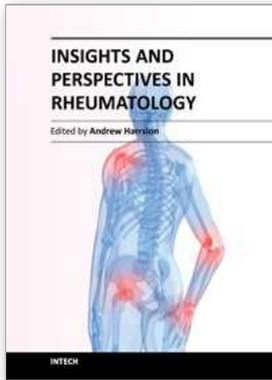
⁵⁸ Saag KG, Shane E, Boonen S, Mari'n F, Donley DW, Taylor KA, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med.* 2007;357:2028-39.

- American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. *Arthritis Rheum.* 2001;44:1496-503.
- Arai, T. & Kragic, D. Van Staa TP, Geusens P, Bijlsma JWJ, Leufkens HGM, Cooper C. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. *Arthritis Rheum* 2006;54:3104-12.
- Berris KK, Repp AL, Kleerekoper M. Glucocorticoid-induced osteoporosis. *Curr Opin Endocrinol Diabetes Obes.* 2007;14:446-50.
- Brandão L, Ferraz MB, Zerbini CAF. Avaliação da qualidade de vida na artrite reumatóide: revisão atualizada [Evaluation of quality of life in rheumatoid arthritis]. *Rev Bras Reumatol.* 1997;37(5):275-81.
- Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy and hip fracture. *Ann Rheum Dis* 1995;54:49-52.
- Djokanovic N, Klieger-Grossmann C, Koren G. Does treatment with bisphosphonates endanger the human pregnancy? *J Obstet Gynaecol Can.* 2008;30:1146-8.
- Egeland T, Munthe E. The role of the laboratory in rheumatology. Rheumatoid factors. *Clin Rheum Dis* 1983;9:135-60. 22.
- Eggelmeijer F, Papapoulos SE, Westedt ML, Van Paassen HC, Dijkmans BA, Breedveld FC: Bone metabolism in rheumatoid arthritis; relation to disease activity. *Br J Rheumatol* 1993, 32: 387-391.
- Faust J, Lacey DL, Hunt P, Burgess TL, Scully S, Van G, Eli A, Qian Y, Shalhoub V: Osteoclast markers accumulate on cells developing from human peripheral blood mononuclear precursors. *J Cell Biochem* 1999, 72:67-80.
- Franchimont N, Canalís E. Management of glucocorticoid induced osteoporosis in premenopausal women with autoimmune disease. *Autoimmun Rev.* 2003;2:224-8.
- Gabriel SE. The epidemiology of rheumatoid arthritis. *Rheum Dis Clin North Am.* 2001;27(2):269-81. Martin JC, Munro R, Campbell MK, Reid DM. Effects of disease and corticosteroids on appendicular bone mass in postmenopausal women with rheumatoid arthritis: comparison with axial measurements. *Br J Rheumatol.* 1999;36(1):43-9.
- Geusens PP, de Nijs RN, Lems WF, Laan RF, Struijs A, van Staa TP, et al. Prevention of glucocorticoid osteoporosis: a consensus document of the Dutch Society for Rheumatology. *Ann Rheum Dis.* 2004; 63:324-5.
- Gillespie MT. Impact of cytokines and T lymphocytes upon osteoclast differentiation and function. *Arthritis Res Ther.* 2007;9:103.
- Glucocorticoid-induced osteoporosis. *Arq Bras Endocrinol Metab.* 2006;50(4):793-801.
- Gravallese EM, Harada Y, Wang JT, Gorn AH, Thornhill TS, Goldring SR. Identification of cell types responsible for bone resorption in rheumatoid arthritis and juvenile rheumatoid arthritis. *Am J Pathol* 1998;152:943-51.
- Haugeberg G, Uhlig T, Falch JA, Halse JI, Kvien TK. Reduced bone mineral density in male rheumatoid arthritis patients: frequencies and associations with demographic and disease variables in ninety-four patients in the Oslo County Rheumatoid Arthritis Register. *Arthritis Rheum* 2000;43:2776-84.
- Heaney RP. Thinking straight about calcium. *N Engl J Med* 1993; 328:503-505.

- Heaney RP. The vitamin D requirement in health and disease. *J Steroid Biochem Mol Biol.* 2005;97:13-9.
- Keller C, Hafstrom I, Svensson B. Bone mineral density in women and men with early rheumatoid arthritis. *Scand J Rheumatol* 2001;30:213-20.
- Khan AA, Hanley DA, Bilezikian JP, Binkley N, Brown JP. Standards for performing DXA in individuals with secondary causes of osteoporosis. *Journal of Clinical Densitometry* 2006 9 47-57.
- Kong YY, Feige U, Sarosi I, Bolon B, Tafuri A. Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand. *Nature* 1999;402:304-9.
- Kontoyiannis D, Kollias G: Fibroblast biology: synovial fibroblasts in rheumatoid arthritis: leading role or chorus line? *Arthritis Res* 2000, 2:342-343
- Kroot EJ, Nieuwenhuizen MG, Waal Malefijt MC, van Riel PL, Pasker-de Jong PC, Laan RF. Change in bone mineral density in patients with rheumatoid arthritis during the first decade of the disease. *Arthritis Rheum* 2001;44:1254-60.
- Lacey DL, Timms E, Tan HL, Kelley MJ, Dunstan CR. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell* 1998, 93:165-176.
- Lee SK, Goldring SR, Lorenzo JA: Expression of the calcitonin receptor in bone marrow cell cultures and in bone: a specific marker of the differentiated osteoclast that is regulated by calcitonin. *Endocrinology* 1995, 136:4572-4581.
- Leisen JCC, Duncan H, Riddle JM, Pitchford WC. The erosive front: a topographic study of the junction between the pannus and the subchondral plate in the macerated rheumatoid metacarpal head. *J Rheumatol* 1988;15:17-22.
- Lems WF, Dijkmans BAC. Should we look for osteoporosis in patients with rheumatoid arthritis? *Ann Rheum Dis* 1998;57:325-7.
- Levy S, Fayed I, Taguchi N, Han JY, Aiello J, Matsui D, et al. Pregnancy outcome following in utero exposure to bisphosphonates. *Bone.* 2009;44:428-30.
- Lodder MC, Haugeberg G, Lems WF, et al. Radiographic damage associated with low bone mineral density and vertebral deformities in rheumatoid arthritis: the Oslo-Truro-Amsterdam (OSTRA) collaborative study. *Arthritis Rheum.* 2003;49(2):209-15.
- Martin JC, Munro R, Campbell MK, Reid DM. Effects of disease and corticosteroids on appendicular bone mass in postmenopausal women with rheumatoid arthritis: comparison with axial measurements. *Br J Rheumatol* 1997;36:43-9.
- Meunier PJ, Vignot E, Garnero P. "Treatment of postmenopausal women with osteoporosis or low bone density with raloxifene. Raloxifene Study Group". *Osteoporos Int* 1999;10 (4): 330-36.
- Mundy GR. Osteoporosis and inflammation. *Nutr Rev.* 2007;65(12 Pt 2):S147-51.
- Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med.* 2001;344:1434-4.
- Pattison DJ, Harrison RA, Symmons DP. The role of diet in susceptibility to rheumatoid arthritis: a systematic review. *J Rheumatol.* 2004;31(7):1310-9.
- Pereira RM, Delany AM, Canalis E. Cortisol inhibits the differentiation and apoptosis of osteoblasts in culture. *Bone* 2001;28:484-90.
- Reginster JY, Felsenberg D, Boonen S, Diez-Perez A, Rizzoli R. Effects of long term strontium ranelate treatment on the risk of nonvertebral and vertebral fractures in

- postmenopausal osteoporosis, results of five year, randomizes, placebo-controlled trial. *Arthritis and Rheumatism*. 2008;58:1687-95.
- Reid DM, Devogelaer JP, Saag K, Roux C, Lau CS, Reginster JY, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, doubleblind, double-dummy, randomised controlled trial. *Lancet*. 2009;373:1253-63,
- Roldán JF, Del Rincón I, Escalante A. Loss of cortical bone from the metacarpal diaphysis in patients with rheumatoid arthritis: independent effects of systemic inflammation and glucocorticoids. *J Rheumatol*. 2006;33(3):508-16.
- Romas E, Bakharevski O, Hards DK, Kartsogiannis V, Quinn JMW, Ryan PFJ, et al. Expression of osteoclast differentiation factor at sites of bone erosion in collagen-induced arthritis. *Arthritis Rheum* 2000;43:821-6.
- Ross FP, Chappel J, Alvarez JI, Sander D, Butler WT, Farach-Carson MC. Interactions between the bone matrix proteins osteopontin and bone sialoprotein and the osteoclast integrin alpha v beta 3 potentiate bone resorption: *J Biol Chem* 1993, 268:9901-9907.
- Sambrook PN: The skeleton in rheumatoid arthritis: common mechanism for bone erosion and osteoporosis? *J Rheumatol* 2000, 27:2541-2542. Gregório LH, Lacativa PG, Melazzi AC, Russo LA.
- Saag KG, Shane E, Boonen S, Marín F, Donley DW, Taylor KA, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med*. 2007;357:2028-39,
- Seriolo B, Ferretti V, Sulli A, Caratto E, Fasciolo D, Cutolo M. Serum osteocalcin levels in premenopausal rheumatoid arthritis patients. *Ann N Y Acad Sci*. 2002;966:502-7.
- Shenstone BD, Mahmoud A, Woodward R, Elvins D, Palmer R, Ring F, et al. Bone mineral density in nonsteroid treated early rheumatoid arthritis. *Ann Rheum Dis* 1994;53:681-4.
- Simonet WS, Lacey DL, Dunstan CR, Kelley M, Chang MS. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. *Cell* 1997, 89:309-319.
- Sinigaglia L, Nervetti A, Mela Q, Bianchi G, Del Puente A, Di Munno O, et al. A multicenter cross sectional study on bone mineral density in rheumatoid arthritis. Italian Study Group on Bone Mass in Rheumatoid Arthritis. *J Rheumatol* 2000;27:2582-9.
- Suda T, Takahashi N, Martin TJ: Modulation of osteoclast differentiation. *Endocr Rev* 1992, 13:66-80.
- Suzuki Y, Nishikaku F, Nakatuka M, Koga Y. Osteoclast-like cells in murine collagen induced arthritis. *J Rheumatol* 1998;25:1154-60.
- Suzuki Y, Tsutsumi Y, Nakagawa M, Suzuki H, Matsushita K, Beppu MI. Osteoclast-like cells in an in vitro model of bone destruction by rheumatoid synovium. *Rheumatology (Oxford)* 2001;40:673-82.
- Takayanagi H, Iizuka H, Juji T, Nakagawa T, Yamamoto A. Involvement of receptor activator of nuclear factor kappa-B ligand/osteoclast differentiation factor in osteoclastogenesis from synoviocytes in rheumatoid arthritis. *Arthritis Rheum* 2000;43:259-69.
- Teitelbaum SL. Osteoclasts: what do they do and how do they do it? *Am J Pathol*. 2007;170(2):427-35.
- Van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid induced osteoporosis: a meta-analysis. *Osteoporos Int*. 2002;13:777- 87.

- Van Zeben D, Hazes JM, Zwinderman AH, Cats A, van der Voort EA, Breedveld FC. Clinical significance of rheumatoid factors in early rheumatoid arthritis: results of a follow up study. *Ann Rheum Dis* 1992;9:1029-35.
- Viswanathan A, Sylvester FA. Chronic pediatric inflammatory diseases: effects on bone. *Rev Endocr Metab Disord*. 2008;9(2):107-22.
- Wallach S, Cohen S, Reid DM, Hughes RA, Hosking DJ, Laan RF, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. *Calcif Tissue Int*. 2000;67:277-85.
- Weitzmann MN, Pacifici R. The role of T lymphocytes in bone metabolism. *Immunol Rev*. 2005;208:154-68.



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