

# Bone tissue metabolism in psoriatic arthritis patients

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## Abstract

The chronic inflammatory joint process creates a significant threat to appropriate bone metabolism. In psoriatic arthritis, the loss of bone mass is of a complex nature. The inflammatory cytokines such as interleukin-1, interleukin-6 and tumour necrosis factor  $\alpha$  are the major factors causing bone tissue degradation. The circulating precursor cells of osteoclasts also seem to play an important role. The studies on bone tissue metabolism conducted so far in patients from that group, however, are not unequivocal. Regardless of the causes of local and generalised bone destruction, recognition of osteoporosis in psoriatic arthritis is insufficient. Modern arthritis treatment methods developed during the recent decades have a significant influence on bone mass loss inhibiting.

**Key words:** psoriatic arthritis, bone tissue metabolism.

## Bone tissue metabolism

Chronic arthritis is accompanied by bone remodeling disorders. There are numerous causes of bone tissue metabolism in psoriatic arthritis. Local destructive lesions, involutinal forms of osteoporosis as well as secondary osteoporosis may occur. The domination of resorption processes over osteogenesis is the cause of bone mass loss regardless of the etiology. Numerous factors participate in bone tissue remodeling process regulation (Table I).

In the case of bone tissue metabolism disorders during chronic arthritis, including the psoriatic arthritis, the major role is attributed to active cytokines. Interleukin 1 (IL-1), interleukin 6 (IL-6), and tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) act through osteoclastogenesis and stimulation of mature osteoclasts. Significant progress in bone biology understanding has been made in recent years. This was due to discovery of molecules belonging to the TNF family: the receptor activator of nuclear factor- $\kappa$ B ( $\kappa$ B-RANK), its ligand – receptor activator of nuclear factor- $\kappa$ B ligand (RANKL) and osteoprotegerin (OPG) [1, 2]. RANK is the functional receptor of RANKL, belonging to the family of TNF receptors. RANK expression occurs first of all on the cells of monocyte-macrophage line, pre-osteoclast cells, osteoclasts, T and B lymphocytes, vascular endothelium cells, dendritic cells, chondrocytes and fibro-

blasts. The factors increasing RANK expression are, *inter alia*, vitamin D<sub>3</sub>, IL-1, interferon  $\gamma$  (INF- $\gamma$ ). RANKL is defined under a number of names such as: the osteoclast differentiation factor (ODF), receptor activator of nuclear factor- $\kappa$ B ligand (RANKL) and the ligand for osteoprotegerin (OPGL). Binding with its functional receptor, RANK is a powerful activator of bone resorption. RANKL may be present in the form bound to the cellular membrane of the osteoblast precursor cells, pre-osteoblasts and osteoblasts (RANKL1, RANKL2) and in the soluble form (soluble RANKL, sRANKL). RANKL1 and RANKL2 appear, *inter alia*, on activated lymphocytes T (CD4+ and CD8+), immature lymphocytes B, osteoblasts, osteoclasts, bone marrow stromal cells, fibroblasts, epithelial cells and vascular endothelium. sRANKL is primarily produced by activated lymphocytes T. RANKL expression is increased by IL-1 $\beta$ , IL-6, IL-8, IL-11, IL-17, INF- $\gamma$ , TNF, IGF-1, glucocorticoids, parathormone, prostaglandin E<sub>2</sub>, vitamin 1,25(OH)D<sub>3</sub> [3, 4]. RANKL together with M-CSF induces osteoclastogenesis and inhibits apoptosis of osteoclasts binding with RANK on pre-osteoclasts and mature osteoclasts. Osteoprotegerin is a natural RANKL antagonist. RANKL binding and neutralisation is the main role of osteoprotegerin. It can also bind TRAIL (TNF-related apoptosis inducing ligand), inhibiting apoptosis of cells [5]. This contributes to inhibiting osteoclastogenesis and osteo-

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clasts' activity. Excretion of OPG is intensified by  $17\beta$  estradiol, GH, IL-13, IL-18, PDGF, IFN- $\gamma$ , and TGF- $\beta$ . PGE<sub>2</sub>, glucocorticoids, PTH, IGF-1, IL-17, IL-1, IL-6 and IL-11 inhibit osteoprotegerin production [6]. Under physiological conditions, the bone as highly-specialised tissue is rebuilt continually. Cells synthesizing the bone (osteoblasts) and resorbing the bone (osteoclasts) participate in that reconstruction. Osteoclasts develop from mesenchymal stem cells and gradually transform into osteocytes. Osteoclasts are developed from hematopoietic bone marrow cells of monocyte-macrophage line. The RANK/RANKL/OPG system and M-CSF (macrophage colony-stimulating factor) play a major role in the osteoclast diversification process. Osteoclastogenesis is induced by osteoblasts excreted M-CSF causing development of pre-osteoclasts. RANKL binds to RANK present in precursors of osteoclasts stimulating their maturing [7].

Ritchlin *et al.* [8] showed that in the psoriatic arthritis, the quantities of osteoclasts precursors (OCP) in peripheral blood and the RANKL/OPG ratio were higher than in the case of the rheumatoid arthritis. At the same time, administration of TNF- $\alpha$  inhibitors decreased the quantities of circulating osteoclast precursors. Also Xing *et al.* [9] detected the OCP quantities significantly higher than in the rheumatoid arthritis and suggested using that test as an indicator for high risk of bone destruction. In other studies, increased vascularisation and characteristically winding, glomic course of the vessels in the synovial membrane was found [10]. On that basis, a bone tissue metabolism disorder model was proposed. It was assumed that TNF- $\alpha$  is responsible for increasing the quantities of circulating OCPs, that enter intensely vascularised synovial membrane containing winding blood vessels. The osteoclast precursor cells stick to endothelium cells activated by inflammatory cytokines and next migrate into the environment. Simultaneously, the increased OPG level may inhibit osteoclastogenesis, allowing undiversified OCP migration within the bone tissue. In the presence of TNF- $\alpha$  and M-CSF, OCP binds with RANKL on the synoviocyte surface initiating osteoclastogenesis. In patients with the psoriatic arthritis, a significant concentration increase of TNF- $\alpha$ , IL-2, IL-10, IL-1 $\beta$  and IFN- $\gamma$  was found [11, 12]. Partsch *et al.* observed an increased level of TNF- $\alpha$  receptors and high concentrations of TNF- $\alpha$ , IL-1, IL-6, and IL-8 in the synovial membrane of the patients [13]. In the isolated fresh peripheral blood monocytes, Nishibu *et al.* [14] showed the increase of IL-1 $\beta$ , IL-6, IL-8 in patients with psoriasis and psoriatic arthritis, significantly higher in persons with arthritis, without any relation to the psoriasis area and severity index (PASI). Elkayam *et al.* [15] recorded the increase of IL-6 and IL-10, the soluble receptor IL-2 (sIL-2R) and the IL-1 receptor antagonist (IL-1ra) in the serum of the examined patients. The levels of IL-6 and IL-10 in the same study showed no correlation to the clinical severity parameters of arthritis and skin lesions while the IL-1ra level was correlated to the

**Table 1.** Regulating factors of the bone tissue reconstruction

Bone regeneration stimulators	Bone resorption stimulators
Estrogens	Parathyroid hormone
Androgens	1,25(OH) <sub>2</sub> D <sub>3</sub>
Calcitonin	Thyroid hormones
Insulin-like growth factors I and II (IGF)	Glucocorticoids
Transforming growth factor $\beta$ (TGF- $\beta$ )	Oxygen free radicals
Mechanical load	Tumor necrosis factor $\alpha$ (TNF- $\alpha$ )
	Transforming growth factor $\alpha$ (TGF- $\alpha$ )
	Interleukins (IL-1, IL-6)
	Interferon $\gamma$ (INF- $\gamma$ )
	Lack of mechanical loads

number of painful and swollen joints while the sIL-2R was correlated with skin lesions.

A prolonged inflammatory process, in addition to local destruction within the joints, creates conditions for generalised osteoporosis. Osteoporosis is a systemic disease of the osseous system. It is characterised by low bone mass combined with abnormal bone tissue structure. Excessive bone fragility and increased susceptibility to fractures are the consequences of those disorders. Pathogenesis of osteoporosis in the psoriatic arthritis has not been fully explained. The frequency of osteoporosis accompanying the psoriatic arthritis is influenced, in addition to the inflammatory process, by decreased mobility and decrease of physiological mechanical loads. Medical drug intake is one of the possible factors contributing to decreasing the density of bones. Non-steroid anti-inflammatory drugs, by their undesired influences, lead to impairment of liver and kidney functions disrupting vitamin D metabolism. They also cause gastrointestinal disorders resulting in limitations on the diet and intake of further medical drugs including preparations containing aluminium [16]. The methotrexate (MTX) therapy, particularly in the case of high doses, may lead to osteopathy development manifesting through bone pain, osteopenia and the distal section fractures [17]. Bone resorption is caused by increasing the activation of osteoclasts. In *in vitro* studies, the effect dependent on the MTX dose was observed [18], but at the same time cases of severe osteoporosis were observed even if low doses of that drug were applied [6].

The frequency of bone transformation disorders in psoriatic arthritis has not been determined precisely. The dual-energy X-ray absorptiometry (DEXA) still is the "golden standard" among the image-based methods of bone density examination. The generally accepted T-score stan-

dards for osteopenia are  $-1$  to  $-2.5$ , for osteoporosis – under  $-2.5$ . The current literature provides data offering more than one, frequently contradictory, interpretations. In his work, using the fan-beam densitometric technique, Frediani *et al.* [19] observed a significant decrease in the bone mineral density (BMD) in patients with psoriatic arthritis (within the lumbar spine 1.112 vs. 1.326; within the femoral neck 0.870 vs. 1.006). In combination with ultrasonographic densitometric measurement of the calcaneus he assessed the frequency of mineralisation disorders in at least one of the osseous system regions in 67% of women before menopause, 100% – in the period after menopause and 80% of men. Borman *et al.* [20], among the patients with the psoriatic arthritis (excluding women in post-menopause period), identified osteoporosis in 5% of the cases and osteopenia in 50% (in the control group osteopenia was found in 27.5% of the cases). He also established a correlation between the demineralisation intensity and the duration of joints disease without correlation with the inflammation markers levels. Similar results were obtained by Dheda *et al.* [21], namely an evident BMD decrease was observed in patients with arthritis duration exceeding 9 years (in the lumbar spine 0.93 vs. 1.028, in femoral neck 0.837 vs. 0.939); an evident correlation with the number of joints involved. According to some researchers, osteoporosis in the psoriatic arthritis is more frequent in men than women (10% vs. 1.75%) and applies even to patients aged around 30 years [22]. This may be caused by a higher OPG level in women with the psoriatic arthritis related to the level of estrogens. Grisar *et al.* [23] found correct DEXA measurement results with the increased inflammation markers levels. On the other hand, the studies by Hofbauer *et al.* [22] did not confirm the correlations between the ESR and CRP levels and the BMD although they showed a correlation with the TRAIL and OPG levels. The TRAIL level was increased significantly and was correlated with the CRP, while the OPG level did not differ from the control group but was correlated with the ESR.

Some authors suggest, however, lack of correlation between the generalised bone loss and psoriatic arthritis. Reid *et al.* and Nolla *et al.* [24, 25] did not find significant differences in bone density between the patients with arthritis of peripheral joints and the control group selected by gender, age and menopausal status. Those studies prove the need for conducting further work on bone transformations in the psoriatic arthritis.

Biochemical markers of bone turnover became useful in bone metabolism monitoring. They are protein fragments of bone structure components as well as proteins and enzymes released by active osteoblasts and osteoclasts. In practical terms, they offer a rapid method for assessment of bone tissue metabolism reflecting the intensity of all reconstruction processes within the osseous system. The bone alkaline phosphatase (b-ALP) isoenzyme, osteocalcin (OC) and propeptide procollagen

type I: N-terminal propeptide procollagen type I (PINP), C-terminal propeptide procollagen type I (PICP) are the bone formation markers. Their concentration correlates with osteoblasts' activity. The collagen degeneration products highly specific of bone tissue metabolism: pyridinoline (PYD), deoxypyridinoline (DPD), collagen type 1 cross-linked N-telopeptide (NTX), collagen type 1 cross-linked C-telopeptide (CTX) are bone resorption markers while isoenzyme 5b – tartrate-resistant acid phosphatase (TRAP), synthesized by osteoclasts indirectly indicates the quantity of active cells [26, 27]. Data from studies carried at different centres are not clear. Borman *et al.* [20] did not observe a significant difference in the levels of CTX, ALP, calcium, phosphorus in the serum of patients with psoriatic arthritis and psoriasis although CTX increase depending on the duration of arthritis was determined. In their works, Franck *et al.* [28] found a significant increase in the osteocalcin level in patients with high CRP values. That correlation was also indicated by the alkaline phosphatase levels. Slightly different, interesting results were obtained by Grisar *et al.* [23]. In this study, the osteocalcin concentration did not exceed the reference values (the increased level was observed in the ankylosing spondylitis) while the b-ALP increase was found (in ankylosing spondylitis and reactive arthritis, no changes were observed). They showed the evident correlation between the increased deoxypyridinoline level in urine, NTX and CTX with the disease activity (OB, CRP). The significantly increased OPG level was also determined. In the study by Hofbauer *et al.* [22], no correlation was found between inflammatory state indicators (OB, CRP) and bone turnover markers. No correlation between the TRAIL and OPG levels with the bone metabolism markers was detected either.

## Conclusions

Bone tissue metabolism disorders in the psoriatic arthritis are relatively poorly known and the results of research conducted at different centres frequently differ significantly. The simultaneous presence of bone resorption and bone formation is characteristic of the psoriatic arthritis. It can be assumed that high levels of osteoclast precursors circulating may in the future represent a prognostic factor for development of arthritis in the progress of psoriasis. The current pharmacological treatment of the psoriatic arthritis based on non-steroidal anti-inflammatory drugs (NSAIDs) and traditional disease-modifying drugs (DMARDs) did not inhibit loss of bone mass during the progress of inflammation. It seems that high hopes can be linked to the currently available TNF inhibitors: etanercept, infliximab and adalimumab, which, by acting against the causative factor of the inflammation contribute to improving the bone tissue metabolism. In treatment of osteoporosis during the progress of chronic arthritis, common principles assumed for the other forms of the disease are applicable.

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