



- **FACT SHEET No. 3**

Joint Biochemical Markers for Cartilage, Bone, Cartilage Degradation, Bone Remodeling, and Inflammation

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The joint is composed of three major compartments: bone, articular cartilage, and synovium. All three can be affected in rheumatic diseases such as osteoarthritis or rheumatoid arthritis. Osteoarthritis is a disease of the whole joint characterized by osteophyte formation, subchondral sclerosis, articular cartilage breakdown, and alterations of the synovium (inflammation, proliferation, and synovial thickening).

Cytokines, enzymes, and extracellular matrix constituents, such as precursors or degradation products of collagen and proteoglycan, are potential biochemical markers of these tissues available in research use. Their concentrations are linked to tissue metabolism and can be measured in blood, urine, or synovial fluid. In clinical practice, markers of inflammation are usually considered well correlated with synovitis. Markers of cartilage degradation have a moderate to good relation with clinical and radiological variables in osteoarthritis, and markers of bone metabolism are less effective in joint diseases than in osteoporosis, probably because of the size of the bone compartment[1-3].

Cartilage

Cartilage is a non-vascularized tissue consisting of chondrocytes and extracellular matrix (ECM). This latter is composed primarily of collagen (mainly Type II collagen), small non-collagen proteins (aggrecan, a high molecular weight proteoglycan, and cartilage oligomeric matrix protein (COMP). This composition is strictly regulated by chondrocytes in response to changes in their chemical and mechanical environment. The turnover of cartilage is maintained by a balance between catabolic and anabolic



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processes, except in pathological status in which the degradation exceeds the formation, resulting in a loss of cartilage matrix.

Some markers coming from cartilage matrix can be quantified: enzyme immunoassay for secreted markers, polymerase chain reaction (PCR) for DNA expression[4]

- ECM components:
 - increase of Type II collagen in serum and in urine and Type IIA procollagen amino terminal propeptide (PIIANP) in serum for cartilage synthesis
 - C-telopeptide of Type II collagen (CTX-II) in urine, N-terminal propeptide of Type II collagen (PIINP), cartilage oligomeric matrix protein (COMP) link protein in serum and aggrecan fragments for cartilage degradation
- Matrix-degrading enzymes:
 - proteolytic enzymes: metalloproteinases (MMPs) such as MMP-3, MMP-9 and MMP-13
 - aggrecanases such as a disintegrin and metalloproteinase with thrombospondin-like motifs (ADAMTS): ADAMTS-4 or ADAMTS-5

Bone

Bone is a tissue mainly composed of osteoblasts (bone-forming cells), osteoclasts (bone-degrading cells), and resident cells named osteocytes. These cells are embedded into a mineralized organic matrix composed of collagen (mainly Type I collagen), proteoglycans such as hyaluronic acid and chondroitin sulfate, and inorganic components such as hydroxyapatite. Bone remodeling is permanent with a balance between formation and degradation. Bone in contact with cartilage (subchondral bone) is altered in osteoarthritis featuring subchondral bone sclerosis and osteophytes.

- Markers of bone formation are osteocalcin in serum, bone alkaline phosphates in serum, and the propeptides of Type I collagen (N-terminal propeptide of Type I procollagen (PINP) and C-terminal propeptide of Type I procollagen (PICP))
- Degradation markers are primarily various fragments of Type I collagen (CTX-I) in urine and in serum, N-telopeptide of Type I collagen (NTX-I) and C-terminal propeptide of Type I procollagen (ICTP)[3]

Inflammation

Synovitis is a common feature of osteoarthritis. It is a proliferation of synoviocytes and tissue hypertrophy. Synoviocytes release inflammatory mediators and matrix-degrading enzymes into the joint cavity. Their activation is secondary to inflammatory mediators and cartilage matrix molecules, after which synovial tissue drives progressive joint degeneration in a feedback cycle.[1]

The biochemical inflammatory markers are:



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- Proteins of acute phase: Serum C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR)
- Inflammatory mediators: prostanoid cyclooxygenase (COX) enzyme, Prostaglandin E2 (PGE2), PGD2, PGF2a, thromboxane, and PGI2[2]
- Circulating or local cytokines: interleukin-1 (IL-1), IL-6, IL-17, IL-18, Tumor Necrosis Factor-alpha (TNF- α), and chemokines such as CC-chemokine ligand (CCL5) and IL-8[5]
- Nitric oxide[6]
- Synovium degradation products: hyaluronan or hyaluronic acid (HA)

Although numerous joint biomarkers have been listed as potential early diagnostic and/or prognostic tools in arthritis, their use in clinical practice remains challenging today and most of them are devoted to research use only.

References

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