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KINGA LIS

Department of Laboratory Medicine Collegium Medicum, Nicolaus Copernicus University,
M. Skłodowskiej-Curie 9, 85-094 Bydgoszcz, Poland
e-mail: kzlis@gazeta.pl

Bone sialoprotein as a biochemical marker of subchondral bone turnover

Sialoproteina kostna jako wskaźnik biochemiczny przemiany metabolicznej kości podchrzęstnej

SUMMMARY

Osteoarthritis is one of the most common types of degenerative joint diseases. Osteoarthritis is characterized by degradation and loss of articular cartilage and subchondral bone remodeling. Inflammation of the synovial membrane is typical of the clinical stages of this disease. The subchondral bone is not an innocent bystander but is the site of several dynamic morphological changes that appear during osteoarthritis. The loss of articular cartilage and structural changes of subchondral bone during joint destruction is irreversible. Because of this it seems necessary to find a sensitive and specific biochemical marker which would reflect cartilage destruction and subchondral bone metabolism.

The bone sialoprotein is synthesized mostly in the osseous tissue being directly found under the surface of joint cartilage. Therefore it is often perceived as a valuable marker of the metabolism of the subchondral layer of the bone. Bone sialoprotein seems to be of use as the marker in the estimation of subchondral bone turnover.

STRESZCZENIE

Choroba zwyrodnieniowa stawów jest jedną z najczęściej rozpoznawanych chorób układu stawowego. Zmiany zwyrodnieniowe w stawach obejmują zarówno chrząstkę stawową, jak i kość podchrzęstną oraz otaczające tkanki miękkie. W późnym etapie choroby rozwija się także zapalenie błony maziowej. Zarówno utrata chrząstki stawowej, jak i przebudowa strukturalna kości podchrzestnej są nieodwracalne. Dlatego tak ważne jest wczesne rozpoznanie choroby zwyrodnieniowej. Do diagnostyki wczesnych zmian zwyrodnieniowych niezwykle przydatne są wskaźniki biochemiczne charakterystyczne dla poszczególnych struktur stawowych.

Sialoproteina kostna jest specyficzną glikoproteiną syntetyzowaną głównie w tej warstwie kości, która zlokalizowana jest bezpośrednio pod powierzchnią chrząstki stawowej. Dlatego też jest najbardziej czułym wskaźnikiem przemian metabolicznych kości podchrząstnej. Oznaczanie stężenia sialoproteiny kostnej w surowicy może być więc niezwykle przydatne do oceny szybkości degradacji tej warstwy kości.

K e y w o r d s: subchondral bone, bone sialoprotein, osteoarthritis

BONE SIALOPROTEIN (BSP)

Bone sialoprotein is glycoprotein with molecular weight 57 kDa, that is almost 10% of noncollagenic proteins of bone matrix. It belongs to the same group of compounds as osteonectin and osteopontin. It was isolated for the first time in 1985 by Heinegard and colleagues [19, 38, 51]. There was a notice that the structure of a bone sialoprotein molecule in mammals is very stable [10].

Bone sialoprotein is a factor controlling the bone resorption process and new bone tissue creation. It has the ability to fix with osteoclasts by alfa-beta 3 integrine [37]. BSP plays an essential role in processes initiating crystallization of hydroxyapatites in bone matrix and is responsible for interactions between bone molecules and bone mineral. It is being suggested that bone sialoprotein and antiintegrine antibodies inhibit bone resorption by blocking integrine playing an essential part in osteoclast function control [37]. BSP strongly fixes hydroxyapatite in bone matrix monitoring in that way bone mineralization [9, 18, 23, 25]. Expression BSP by osteoblasts is intensified by factors stimulating bone tissue synthesis and inhibiting processes by cytokines and hormones limiting new bone formation [21].

OSTEOARTHRITIS (OA)

Osteoarthritis is not only of articular cartilage disease but it is a complex illness of the joint tissues. The degenerative process may include bones building the joint connection, joint capsule, soft tissues, articular cartilage, synovial membrane and periarticular muscles. In tissues affected by osteoarthritis there are morphological changes noticed such as: irregular distribution, laceration and loss of articular cartilage, sclerosis and cyst creation in the subchondral bone, osteophyte formation and synovitis. Synovial membrane inflammation in osteoarthritis is not the primary cause of disease but it plays an important role in the progression of joint tissues lesions [5, 20, 26].

BONE SIALOPROTEIN AS A BIOCHEMICAL MARKER OF SUBCHONDRAL BONE TURNOVER DURING OSTEOARTHRITIS

Many different biochemical markers, characteristic of all joint structures is considered usefulness in laboratory diagnostics of osteoarthritis. We can measure synovial fluid, serum or urine concentration biochemical markers of articular cartilage and subchondral bone degradation (Table 1), articular cartilage matrix synthesis (Table 2) and joint inflammation process (Table 3) [2, 3, 7, 16, 22, 24, 29–32, 35, 39, 42, 44, 47–49, 52].

Physiologically, bone sialoprotein is secreted from bone matrix into joint fluid. Next through synovial membrane it goes to serum, where it reflects the metabolism of subchondral bone. Metabolic diseases of bones processing with intensification of resorption processes, such as osteoporosis or Paget's disease are connected with increased BSP concentration in blood serum. Increased concentration is stated also in diseases of kidneys, but it is not present in liver function

Table 1. Biochemical markers of articular cartilage and bone degradation

Joint structures degradation	Biochemical marker	Biological material for laboratory diagnostics
	CTx-II (type II collagen C-terminal telopeptide)	Urine
Cartilage collagen degradation (type II collage degradation)	C2C (C-terminus of the ¾ length type II collagen cleavage product long epitope, COL2-$^{3}/_{4}C_{Long}$)	Urine, serum, synovial fluid
	C1,C2 (C-terminus of the ¾ length type II collagen cleavage product short epitope, COL2-$^{3}/_{4}C_{Short}$)	Urine, serum, synovial fluid
	Helix-II (type II collagen helical peptide)	Urine
Articular cartilage matrix degradation	COMP (cartilage oligomeric matrix protein)	Serum, synovial fluid
	CILP (cartilage intermediate layer protein)	Serum, synovial fluid
	Keratan sulfate	Serum, synovial fluid
	GAGs (glycosaminoglycans)	Serum, synovial fluid
Cartilage degradation enzymes	Aggrekanases	Serum, synovial fluid
	MMPs (matrix metalloproteases)	Serum, synovial fluid
	Cats K (Cathepsin K)	Serum, synovial fluid
	TIMPs (tissue inhibitors of matrix metalloproteinases)	Serum, synovial fluid
	ADAMTSs (disintegrins and metalloproteinases with trombospondin motifs)	Serum, synovial fluid
Bone resorption	CTx-I (type I collagen C-terminal telopeptide)	Urine, serum, synovial fluid
	NTx (type I collagen N-terminal telopeptide)	Urine, serum, synovial fluid
	DPD (pyridinoline)	Urine
	PYD (deoxypyridinoline)	Urine
	TRAP 5b (band 5 tartrate resistant acid phosphatase)	Serum, synovial fluid
	RANK (osteoclastic receptor for sRANKL)	Serum, synovial fluid
	Cats K (Cathepsin K)	Serum, synovial fluid
	MMPs (matrix metalloproteases)	Serum, synovial fluid
Subchondral bone resorption	BSP (bone sialoprotein)	Serum, synovial fluid

Table 2. Biochemical markers of articular cartilage and bone synthesis

Joint structures synthesis	Biochemical marker	Biological material for laboratory diagnostics
Cartilage collagen synthesis	PIINP (epitope of type II N-terminal propeptide)	Serum, synovial fluid
	CPII (type II collagen C-terminal propeptide)	Serum, synovial fluid
Agreecan synthesis	CS-GAG (chondroitin sulfate glycosaminoglycans)	Serum, synovial fluid
	CS846 (chondroitin sulfate epitope of agreecan)	Serum, synovial fluid
Articular cartilage regeneration	IGF-1 (insuline-like growth factor 1)	Serum, synovial fluid
Bone synthesis	BASP (bone alkaline phosphatase)	Serum, synovial fluid
	OC (osteocalcin)	Serum, synovial fluid
	OPG (osteoprotegrin)	Serum, synovial fluid
	OPN (osteopontin)	Serum, synovial fluid
	ONC (osteonectin)	Serum, synovial fluid
	sRANKL (soluble receptor activator of nuclear factor (NF)-κB ligand)	Serum, synovial fluid
	PINP (epitope of N-terminal propeptide)	Serum, synovial fluid
	CICP/PICP (epitope of C-terminal propeptide)	Serum, synovial fluid

Table 3. Biochemical markers of joint inflammation

Joint inflammation	Biochemical marker	Biological material for laboratory diagnostics
Non-specific inflammation markers	OB (erythrocyte sedimentation rate)	Whole blood separated with natrium citrate
	IL-6 (interleukin 6)	Serum, synovial fluid
	CRP (C-reactive protein,)	Serum, synovial fluid
Specific joint inflammation markers	HA (hyaluronic amid)	Serum, synovial fluid
	YKL-40 (human cartilage glycoprotein-39 (HC gp39))	Serum, synovial fluid
	PIIINP (N-terminal peptide of type III procollagen)	Serum, synovial fluid

disorders [1, 15, 27, 45, 46, 50]. It is also considered as a sensitive factor of metabolic transformations of bone tissue in case of bones metastasis [6, 8, 13].

Bone sialoprotein shows essential positive correlation with commonly applied in evaluation of bone formation biochemical markers, osteoclacin (OC) and bone-specific alkaline phosphatase (BASP), whereas negative dependence connects sialoprotein concentration in blood serum with bone mineral density (BMD) [6, 46].

Changes of bone tissue structure, accompanying osteoarthritis are characterized by intensified resorption of subchondral layer with formation of free spaces in its matrix, which essentially decreases strength of bones building the joint and may be a cause of displacement of articular cartilage inside of subchondral bone [4, 17, 36]. Appearing changes manifest themselves in serum by increase of concentration of a marker characteristic of this layer of bone, that is bone sialoprotein [39, 41, 52].

Tests performed with the usage of animals let observe that in healthy animals, bone sialoprotein is localized mainly in a place of the point of junction of bone and articular cartilage. As degeneration changes develop essentially the concentration of this protein increases in the subchondral bone layer [12]. Moreover increase of BSP concentration during development of joint degeneration changes accompanies the increase of cartilage oligomeric matrix protein (COMP) in serum, considered as a sensitive and unique marker of degeneration disease progression [28, 40, 41]. Bone sialoprotein considered as a marker of intensified resorption of subchondral bone [14] also points to inverted dependence with development of exostosis, so called osteophyte, characteristic of degeneration changes in bones [11].

Osteoarthritis as a process locally appearing in joint cavity, can be diagnosed on the base of an analysis of the material taken directly from the place affected by disease. The good diagnostic material, in this case, seems to be joint fluid, whose compound, volume and biochemical and physical properties change in the joint affected by degeneration disease. Measurement of BSP concentration in joint fluid coming from knee joint people suffering from rheumatoid arthritis shows increased concentration of bone sialoprotein, increasing with disease progression [34, 43].

Bone sialoprotein can be also accepted as a good, long-lasting marker of damage of joint bone tissue [51]. Its diagnostic value is comparable with commonly applied biochemical markers, like osteocalcin or type I collagen C-terminal cross links telopeptide, but it is more constant than they are [51]. Bone sialoprotein appearing in large concentrations in joint fluid, as a result of joint mechanical damage, is characterized by essentially increased concentrations observed for at least one month after the initiation of damage [33].

CONCLUSIONS

Bone sialoprotein synthesized in subchondral bone seems to be a sensitive and unique marker of metabolic turnover of this bone layer. Many authors state that simultaneous biochemical markings characteristic of all joint structures affected by degeneration changes can be especially useful in modern diagnosis of osteoarthritis. Application of specific biochemical markers would accelerate recognition of disease as well as give facilities for monitoring its development and efficiency of medical treatment, which would beneficially affect the living comfort of patients [3, 24, 30, 31, 42, 44, 49, 52].

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