Pyridinoline in Evaluation of Subchondral Remodeling and Cartilaginous Tissue Metabolism in Patients With Early Signs of Knee Osteoarthrosis

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Research Article

Keywords: osteoarthrosis, pyridinoline, osteocalcin, cartilage oligomeric matrix protein, cartilage glycoprotein

Posted Date: July 27th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1892536/v1

PYRIDINOLINE IN EVALUATION OF SUBCHONDRAL REMODELING AND CARTILAGINOUS TISSUE METABOLISM IN PATIENTS WITH EARLY SIGNS OF KNEE OSTEOARTHROSIS

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Osteoarthrosis is a polyetiological disease affecting 15 to 85 percent of people over 40 years of age. It makes as much as 50 percent of all articular pathology cases, so the interest of the scientific community in this problem keeps growing.

One of the key patterns of osteoarthrosis progressing is the disorder of metabolic processes in articular connective tissue and, in particular, the disorder of collagen synthesis and disorganization of the spatial orientation of collagen molecules. Pyridinoline (PYD) is the integral indicator of this disorganization; it ensures the stability of collagen matrix due to the formation of pyridine crosslinks. Some research claim the predictive value of PYD determining in patients with rheumatoid arthritis and other connective tissue pathologies in joints.

Our study involved 42 patients aged 36-50 years with early signs of knee osteoarthrosis and 19 virtually healthy individuals without articular pathologies. All patients underwent standard radiography of their knee joints in the anterior (maximally extended position of the knee joint) and lateral (joint flexion up to 15º) projections in the supine position. Bone formation was assessed by osteocalcin (OC) content and bone resorption by CrossLaps and PYD levels while cartilage matrix destruction by cartilage oligomeric matrix protein (COMP) and cartilage glycoprotein (YKL-40) serum concentrations with enzyme immunoassay (ELISA) method.

Our findings showed that the disorders of bone formation (increased OC level) and bone resorption (increased CrossLaps and PYD levels) as well as the rearrangement of the cartilage matrix structure featured by the increased COMP and YKL-40 contents were specific for patients with early signs of knee osteoarthrosis lacking evident clinical and radiological manifestations of the disease. Interestingly, the significant ($p<0.05$) increase in pyridinoline serum concentration possibly resulted from the intermolecular disbanding in collagen polypeptide chains as a structure-forming component of the extracellular matrix in connective tissue. The sensitivity and specificity assessment of changes in PYD serum concentrations reneders the use of this indicator in the comprehensive evaluation of the condition of patients with early signs of knee osteoarthrosis aimed at increasing the effectiveness of diagnostic approaches to early osteoarthrosis detection and the designning pathogenetic therapy to be a promising trend for further research.

Key words: osteoarthrosis, pyridinoline, osteocalcin, cartilage oligomeric matrix protein, cartilage glycoprotein

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Relevance

Osteoarthrosis is a polyetiological disease affecting 15 to 85 percent of people over 40 years of age. It makes as much as 50 percent of all articular pathology cases [1], so the interest of the scientific community in this problem keeps growing.

One of the key patterns of osteoarthrosis progressing is the disorder of metabolic processes in articular connective tissue and, in particular, the disorder of collagen synthesis and disorganization of the spatial orientation of collagen molecules, pyridinoline (PYD) being the integral indicator of this disorganization. The functional value of PYD is to ensure the stability of cross-links in collagen fibers and elastin forming from hydroxylysyl and lysyl residues and catalyzed by lysyl oxidase [2]. PYD was first isolated from bovine achilles tendon and described by D. Fujimotto, et al. (1977) [3], it is comprised in collagen fibers of bone and cartilage tissues while never found in skin collagen [4].

Some research claim the predictive value of PYD determining in patients with rheumatoid arthritis and other connective tissue pathologies in joints [5-7].

This research was aimed at assessing the role of PYD in subchondral remodeling and cartilage metabolism in patients with early signs of knee osteoarthrosis.

Material and Methods

This study involved 42 patients aged 36-50 years (17 men and 25 women) with early signs of knee osteoarthrosis and 19 virtually healthy individuals without articular pathologies. The patients signed their voluntary informed consents for participation in the research designed under the Declaration of Helsinki as amended in 2013. The research protocol was approved by the Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education V.I. Razumovsky Saratov State Medical University of the Russian Federation Healthcare Ministry, Protocol #2 of Feb. 02, 2022.

The research exclusion criteria were:

- a history of oncology or infectious diseases as well as a concomitant somatic pathology able to affect the analyzed parameters
- a course of NSAID medication as well as the systemic or intraarticular use of cartilage protectors over the course of the past three months
- osteopeny or osteoporosis
- a history of traumas to capsular ligamentous apparatus in joints
- severe pain syndrome in knee joint
- menopause or hormone replacement therapy in women

The research employed instrumental, clinical, laboratory and statistical methods. Instrumental examination involved radiography of the knee joints in frontal and lateral projections in the supine position of the patient. Clinical research methods included history taking, complaints logging, and orthopedic status determining. Laboratory methods consisted of determining markers of cartilage tissue destruction – oligomeric matrix cartilage protein (COMP) and cartilage glycoprotein (YKL-40). Bone metabolism was assessed by measuring bone formation indicator osteocalcin (OC), as well as bone resorption indicator C-terminal type I collagen telopeptides (CrossLaps) and pyridinoline (PYD). All analyzed markers were detected in blood serum by enzyme-linked immunosorbent assay (ELISA). Statistical processing was carried out using Statistica 6.0 software using the nonparametric Mann-Whitney U-test. The results were considered significant at $p<0.05$.

Research Results

It is currently accepted that one of the main pathogenetic mechanisms of osteoarthrosis progressing is an inflammatory and degenerative processes in articular system that involves cartilage matrix.

In our study, the evidence of articular cartilage disorganization was a significant ($p<0.05$) increase in the content of cartilage glycoprotein YKL-40, a protein component featuring the level of inflammatory activity and the state of chondrocytes [8] as well as an increased level of oligomeric matrix cartilage protein (COMP) that belongs to an extracellular protein of the thrombospondin-5 family, which binds polymeric collagen fibers in the extracellular matrix of articular cartilage [9], as compared with the data obtained in the controls group (Fig. 1).

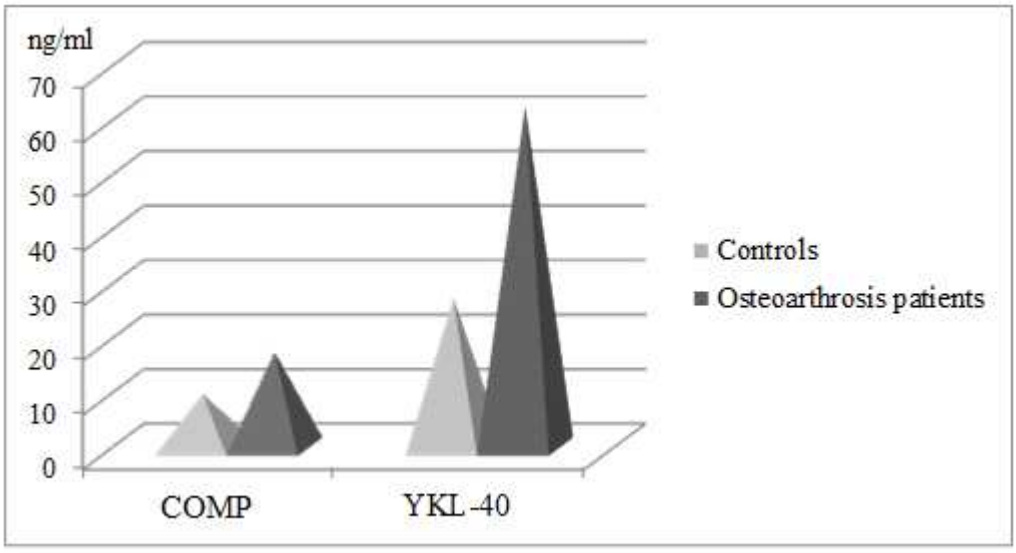

Figure 1. Concentrations of cartilage metabolism markers

Bone tissue is known to be dynamic in its metabolic aspect, bone formation and resorption constantly follow each other [10]. In our study, when determining the content of osteocalcin (OC) bone formation marker, a glutamine vitamin-K-dependent non-collagen protein that features the rate of new bone tissue formation, a significant ($p<0.01$) increase of it was found in patients with early osteoarthrosis signs as compared to the controls (Fig. 2). The findings are evidence of the increasing synthetic osteoblast activity.

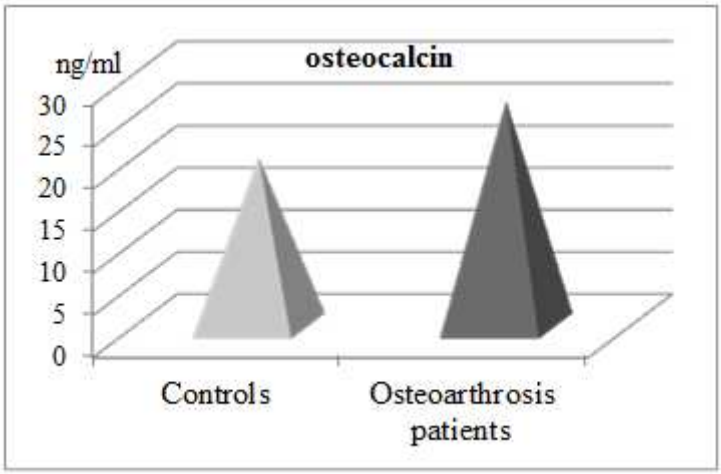

Figure 2. The serum content of bone formation osteocalcin marker

It is known that bone tissue organic matrix is predominantly formed by type I collagen molecules; therefore, its individual fragments are most often studied for diagnostic purposes. Our findings revealed an increase in resorption markers levels. Thus, the content of CrossLaps, a C-terminal telopeptide resulting from type I collagen degradation in bone tissue resorption, significantly ($p<0.05$) exceeded the corresponding values in the controls. However, in patients with early osteoarthrosis signs an excessive serum PYD concentration was observed compared to that in the controls (Fig. 3).

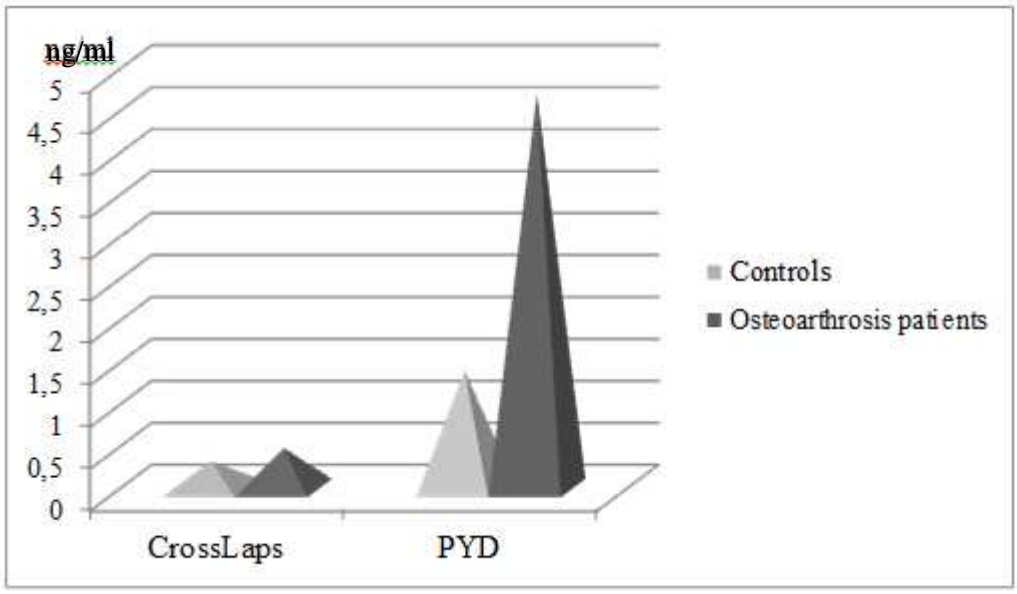

Figure 3. The serum content of bone resorption markers

PYD is a trifunctional pyridine cross-link that forms between specific hydroxylysine residues in the area of a single collagen molecule telopeptide and helical region of neighboring collagen molecule (Fig. 4). As Figure 3 shows, the serum PYD concentration in osteoarthrotis patients is 3.4 times higher than that in the controls, while the CrossLaps content in osteoarthrotis patients was increased by only 1.5 times as compared to the controls. This presents an opportunity of using this indicator as a reliable marker of bone tissue collagen resorption in patients with early osteoarthrosis signs.

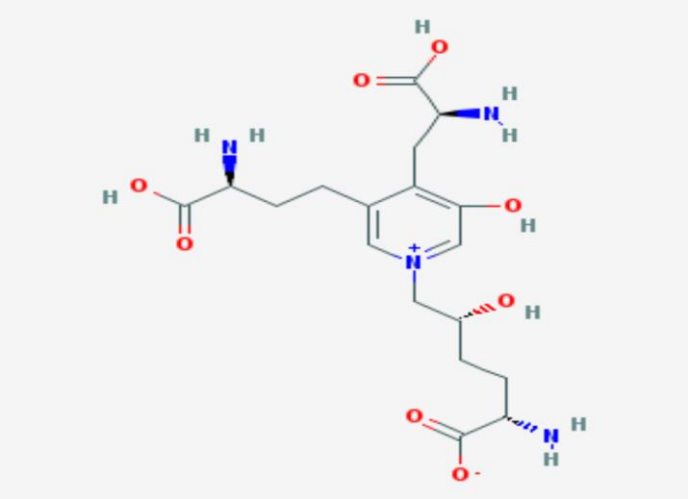

Figure 4. Pyridinoline formula

Conclusion

Our findings show that in patients with early knee osteoarthrosis lacking any clinical and radiological manifestations the disorder of bone formation (increased OC level) along with the intensified bone resorption (increased CrossLaps and PYD concentrations) was observed. Subchondral remodeling was accompanied by rearranging of cartilage matrix structure evidenced by significantly increased COMP and YKL-40. An indirect stability assessment of the collagen network that forms the extracellular framework of supporting connective tissues revealed a significant increase in PYD serum concentration in osteoarthrosis suggesting intermolecular bond disorder. Concluding and evaluating significant changes in PYD content, it makes sense to use this marker for comprehensive assessment of patients with early signs of knee osteoarthrosis as well as designing diagnostic and therapeutic strategies.

This research was performed as a part of the project *Development of a digital personalized intellectual system for objectifying subchondral remodeling for the diagnosis of early osteoarthritis based on a mathematical model for predicting the progression of inflammatory and degenerative changes in supporting connective tissues*, state registration number NIOKTR 122022700115-5. It received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors. The authors have ***no conflicts of interest*** to declare.

All authors give their consents to distribute the full text of this paper to Ulyanov V.Yu., MD, DSc, Associate Professor.

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