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ARTHROSONOGRAPHY AND THE BIOMARKER CARTILAGE OLIGOMERIC MATRIX PROTEIN IN THE DETECTION OF KNEE OSTEOARTHROSIS EFFUSION

ARTROSONOGRAFIJA I BIOMARKER OLIGOMERNI PROTEIN MATRIKSA HRSKAVICE U DETEKCIJI EFUZIJE KOD OSTEOARTROZE KOLENA

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Summary: Osteoarthrosis of the knee is a degenerative disease with inflammatory episodes objectively shown by arthrosonography. Cartilage Oligomeric Matrix Protein – COMP is a useful biomarker for early cartilage destruction. The aim of this paper is a comparative analysis of the clinical, arthrosonographic findings and the COMP concentration in the sera of patients for the detection of joint inflammation. The analysis included 88 patients with knee OA. Clinical examination determined the outflow, arthrosonography the size of synovitis and effusion, and serum analysis the COMP concentration (ng/ml). Minimum outflow had 34.1% of patients, moderate 22.7%, and significant 4.5%. Sensitivity of the clinical diagnosis of outflow is 73%, and specificity 73% (p=0.000). Seventy five percent of patients had effusion; 28.4% of patients in the suprapatellar recessus (SR), 27.3% in the medial (MR), and 62.5% in the lateral (LR). In SR, effusion was 10.13±4.35 mm, MR 8.53±2.27 mm, LR 11.38±4.44 mm. Synovitis was found in 67% of patients, in SR the size of 4.84±3.57 mm, in MR 3.15±1.86 mm, in LR 6.09±2.80 mm. The average value of the size of effusion in patients with significant outflow in SR was 13.85 (10.36–17.43) mm (p=0.000), MR 4.9 (0–10.22) mm (p=0.008), LR 12.0 (11.34–14.50) mm (p=0.000), in LR with moderate outflow 6.94 (1.16–8.13) mm and minimum outflow 4.9 (0–7.25) mm. There is a significant correlation between the size of synovitis and effusion in the SR, MR and LR (p=0.000). The average value of the concentration of COMP in patients without effusion was 54 (44.5–58) ng/ml, with effusion 57 (48.75–64.25) ng/ml (p=0.030). Arthrosonography and the determination of the COMP concentration are sensitive methods for diagnosing joint effusion.

Keywords: osteoarthrosis of the knee, arthrosonography, effusion, synovitis, cartilage oligomeric matrix protein

Kratak sadržaj: Osteoartroza (OA) kolena je degenerativna bolest sa inflamatornim epizodama koje artrosonografija objektivno prikazuje. Oligomerni protein matriksa hrskavice – COMP je korisan marker za ranu destrukciju hrskavice. Cilj rada je uporedna analiza kliničkog, artrosonografskog pregleda i koncentracije COMP u serumu bolesnika radi detekcije zglobne inflamacije. Analizom je obuhvaćeno 88 bolesnika sa OA kolena. Kliničkim pregledom je utvrđen izliv, artrosonografskim veličina sinovitisa i efuzije, analizom seruma koncentracija COMP (ng/ml). Minimalan izliv je imalo 34,1% bolesnika, umeren 22,7%, značajan 4,5%. Senzitivnost kliničke dijagnoze izliva je 73%, a specifičnost 73% (p=0,000). Efuziju je imalo 75% bolesnika, u suprapatelarnom recesusu (SR) efuziju je imalo 28,4% bolesnika, medijalnom (MR) 27,3%, lateralnom (LR) 62,5%. U SR efuzija je bila 10,13±4,35 mm, MR 8,53±2,27 mm, LR 11,38±4,44 mm. Sinovitis je nađen kod 67% bolesnika, u SR veličine 4,84±3,57 mm, MR 3,15±1,86 mm, LR 6,09±2,80 mm. Srednja vrednost veličine efuzije kod bolesnika sa značajnim izlivom u SR je bila 13,85 (10,36–17,43) mm (p=0,000), MR 4,9 (0–10,22) mm (p=0,008), LR 12,0 (11,34–14,50) mm (p=0,000), samo u LR sa umerenim izlivom 6,94 (1,16–8,13) mm i minimalnim izlivom 4,9 (0–7,25) mm. Postoji značajna povezanost veličine sinovitisa i efuzije u SR, MR i LR (p=0,000). Srednja vrednost koncentracije COMP kod bolesnika bez efuzije je bila 54 (44,5–58) ng/mL, sa efuzijom 57 (48,75–64,25) ng/mL (p=0,030). Artrosonografija i određivanje koncentracija COMP predstavljaju senzitivne metode u dijagnostikovanju zglobne efuzije.

Ključne reči: osteoartroza kolena, artrosonografija, efuzija, sinovitis, oligomerni protein matriksa hrskavice

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Introduction

Osteoarthrosis (OA) is an inflammatory disease of the synovial joints that occurs in episodes, and is characterized by focal deterioration and articular cartilage abrasion, with sclerosis and cystic formations beneath the bone surface, as well as osteophyte formation on the joint surface (1). Thickening of the joint capsule and chronic synovitis are common secondary symptoms (2, 3), but may occur at an early stage of the disease and advance progressively with the deterioration of chondropathy. Radiological diagnosis can be made in cases of significant joint destruction (4). Conventional radiography and computerized tomography are methods which do not allow direct visualization of early changes in the joint cartilage. Joint space narrowing is merely an indirect sign of joint destruction, and soft tissue changes are not detected (5). Nuclear magnetic resonance, still a very expensive method, provides a much more objective insight into the inflammatory events in arthrosis, along with arthroscopy and arthrography which are invasive techniques (6). Arthrosonography, an ultrasonic review, is a cheaper, more accessible and non-invasive diagnostic technique, suitable for detecting changes in soft tissue structures and on the surface of bone (5–8).

Inflammation in OA is usually mild and insufficient to cause an increase in the traditional laboratory parameters of inflammation, but can be proved by use of synovial markers indicating synovial activity, such as COMP (Cartilage Oligomeric Matrix Protein) (9, 10). COMP is a noncollagen protein of the articular cartilage matrix (11). It is synthesized by chondrocytes and synovial cells upon activation by proinflammatory cytokines. This protein enters the type II collagen matrices, stimulates and regulates fibrillogenesis and stabilizes the collagen matrix in cartilaginous tissue (12, 13). It is useful as a marker of early cartilage destruction, because it is released first during decomposition of the collagen matrix, resulting in cartilage deterioration (14).

The aim of this work is a comparative analysis of the clinical and arthrosonographic (US) findings, as well as the COMP biomarker concentration in the sera of patients for the detection of joint inflammation in patients with OA of the knee.

Material and Methods

The analysis involved 88 patients diagnosed with primary osteoarthrosis of the knee, according to ACR criteria (American College of Rheumatology), who had shown first symptoms of the disease at least six months before the beginning of study.

Patients fulfilling the following criteria were excluded from the research: patients with stage 4 according to Steinbrocker's functional classes; patients with knee injuries dating more than six months before the beginning of research; patients with total of partial endoprosthesis or knee joint osteotomy; those who have undergone knee joint arthroscopy in the last year; patients who had received intraarticularly corticosteroid or chondroprotective injections in the last four weeks or radionuclide in the last three months before being considered for this research.

Clinical and ultrasonic reviews of the knee were made. The clinical review determined the outflow and the size of synovitis and effusion was established by arthrosonography in B mode on an SDU-1200 system using a 10 MHz linear probe. The front longitudinal approach determined the presence or absence of signs of synovial inflammation: effusion, defined as outflow size larger than 4 mm in suprapatellar, lateral and/or medial knee recess; synovitis, defined as synovial membrane thickening larger than 4 mm. The maximum depth of outflow and the thickness of synovial tissue were measured and expressed as mm. Outflow is morphologically marked as present or absent, and as minimal, moderate and significant; synovitis is marked as present or absent (nodular, diffuse or nodular-diffuse).

For the determination of human COMP (Cartilage Oligomeric Matrix Protein) in serum the commercial enzyme immunoassay »Weislab hCOMP Quantitative Kit« was used, manufactured by Euro-Diagnostica, Arnhem, the Netherlands.

The assay uses a 96-well microplate coated with natural human COMP and rabbit polyclonal antiserum against human COMP. This is a standard ELISA inhibition test with overnight preincubation of serum and primary antiserum. After overnight incubation, the serum is moved into a microplate coated with COMP. The bound antibody is detected by using anti-rabbit IgG conjugate marked with alkaline phosphatase.

The testing procedure lasts two days. On the first day serum samples are diluted using dilution buffer (1/50). After that, 75 μL of each calibrator, C10, C20, C30, C40, C60, C80, as well as controls C1 and C2, is dropped into the preincubation microplate using a hand pipette, followed by all samples of the diluted serum of patients, according to the pattern prescribed by the assay manufacturer. Subsequently, 75 μL of anti-COMP reagent is dropped by a hand pipette into each of the wells of preincubation microplate and agitated on a shaker for five minutes. The microplate is then left for overnight incubation (12–18 hours) at 4 °C (refrigerator).

On the next day, 100 μL from each well of the preincubation microplate are moved into the antigen coated microplate. The microplate is incubated at room temperature for 60 minutes. The microplate is then washed three times on a semiautomatic »Behring«

analyzer for microplate washing, using commercial washing dilution (approximately 300 μL/well), with consecutive filling and emptying of the wells. After the final wash, all the wells are completely emptied by turning the microplate upside down and blotting in on absorbent paper. On the same analyzer 100 μL of conjugate is then added into each well and the microplate is incubated at room temperature for 60 minutes. The next step is washing the microplate again as described above, after which 100 μL of pNPP dilution substrate is added into each well and the microplate is incubated at room temperature for 60 minutes. The results of absorbance are read on a semiautomatic reader at 405 nm. On the basis of calibrator values and minding the serum dilutions, the value of COMP in the examined samples is calculated by using the appropriate software.

The following descriptive statistics were used in this study: arithmetic mean, standard deviation, median, quartiles. Kolmogorov-Smirnov and Shapiro-Wilk tests were used for determining normality distribution of the markings. Comparison of mean values of the two populations was done using independent t-test and Mann-Whitney test. The dependence of category variables was established by Chi-square test. The dependence of constant variables was examined using Spearman's correlation coefficient. Linear regression was used to determine the dependency of a constant variable upon other variables. Backward method was also used in regression.

Results

The research included 88 patients, 20 (22.7%) males and 68 (77.3%) females with primary OA of the knee. Mean age of the subjects was 69.97±9.37, and disease duration 6.46 ± 6.73 years.

The clinical review determined minimal outflow in 34.1% of patients, moderate in 22.7%, and significant in 4.5% of patients, while 38.6% had no outflow.

Effusion was present in 75% of patients, established by arthrosonography.

There is a significant difference between the frequency of clinical finding of outflow and the presence of effusion during arthrosonography (p=0.000) in patients with OA of the knee (*Table I*). Sixteen pa-

Table I The frequency of clinical findings of outflow and ultrasonic findings of effusion in patients with knee OA.

Outflow	Effusion					
	Absent		Present		Total	
	Number of patients	Percentage of patients	Number of patients	Percentage of patients	Number of patients	Percentage of patients
Absent	16	47.05	18	52.94	34	100
Present	6	11.11	48	88.88	54	100
Total	22	25.0	66	75.0	88	100
						p = 0.000

Table II Average value of ultrasound parameters: size (mm) effusion in suprapatellar recess (SR), medial (MR), lateral (LR) and synovitis in suprapatellar recess (SR), medial (MR), lateral (LR) in patients with knee osteoarthrosis.

Ultrasound parameters	Arithmetic mean	SD	Minimum	Maximum	25-th	Median	75-th percentile
Size (mm)							
Effusion in SR	10.13	4.35	5.64	16.34	6.07	10.03	14.23
Effusion in MR	8.53	2.27	5.60	10.36	6.08	9.80	10.34
Effusion in LR	11.38	4.44	4.97	15.50	7.06	11.97	15.41
Synovitis in SR	4.84	3.57	1.99	10.87	2.50	3.04	8.09
Synovitis in MR	3.15	1.86	1.56	6.33	1.88	2.53	4.73
Synovitis in LR	6.09	2.80	1.90	9.56	3.60	6.57	8.34

Table III Comparison of high value (median) size effusion (mm) in suprapatellar (SR), medial (MR) and lateral recesses (LR) between patients with absent, minimal, moderate or significant outflow.

Effusion in SR (mm)	Outflow			
		25th per.	Mediana	75th per.
	Absent	0	0	0
	Minimal	0	0	5.66
	Moderate	0	0	9.22
	Important	10.36	13.85	17.43
				p = 0.000
Effusion in MR (mm)	Absent	0	0	0
	Minimal.	0	0	5.10
	Moderate	0	0	5.71
	Important	0	4.90	10.22
				p = 0.008
Effusion in LR (mm)	Absent	0	0	4.35
	Minimal.	0	4.90	7.25
	Moderate	1.16	6.94	8.13
	Important	11.34	12.00	14.50
				p = 0.000

tients (47.05% of all patients without clinical outflow) had neither clinical outflow nor effusion, six (11.11% of all patients with clinical outflow) had clinical outflow, but not effusion. Eighteen patients (52.94% of all patients without clinical outflow) had no clinical outflow, but did have effusion, and 48 (88.8% of all patients with clinical outflow) had both clinical outflow and effusion.

The sensitivity of the clinical diagnosis of outflow was 73% (percentage of accurate diagnosis of outflow by clinical review in the group with outflow/effusion confirmed by ultrasonic review).

The specificity of the clinical diagnosis of outflow was 73% (percentage of outflow diagnosis by clinical review in the group without outflow/effusion confirmed by an ultrasonic review).

In 28.4% of patients effusion in the suprapatellar recess (SR) of the knee joint was observed, 27.3% had effusion in the medial recess (MR), and 62.5% in the lateral (LR).

The mean values of the size of effusion and synovial membrane proliferation (synovitis) found in the subjects are presented in *Table II*. The mean values of the size of effusion in the suprapatellar recess were 10.3±4.35 mm, 8.53±2.27 mm in the medial, and 11.38±4.44 mm in the lateral.

Synovitis was established in 67% of patients. The mean values of the proliferated synovial membrane thickness were in the suprapatellar recess 4.84±3.57 mm, in the medial 3.15±1.86 mm, and 6.09±2.80 mm in the lateral recess.

Table IV Comparison of high value (median) concentration of COMP biomarker between patients with present or absent effusion regardless of position or size.

Effusion	Number of patients	Percentage of patients	Concentration of COMP (ng/mL)		
			25-th perc.	mediana	75-th perc.
Absent	22	25.0	44.50	54.00	58.00
Present	66	75.0	48.75	57.00	64.25
					p = 0.030

A significant difference was found between the mean values of the size of effusion in the suprapatellar (p=0.000), medial (p=0.008) and lateral recess (p=0.000) in patients with absent, minimal, moderate and significant outflow (*Table III*). The mean value of the size of effusion in the suprapatellar recess in patients with significant outflow was 13.85 (10.36–17.43) mm, in the medial recess 4.9 (0–10.22) mm, and in the lateral recess 12.0 (11.34–14.50) mm. When there is moderate or minimal outflow, effusion appears only in the lateral recess, in patients with moderate outflow the size of 6.94 (1.16–8.13) mm, and in patients with minimal outflow 4.9 (0–7.25) mm.

A significant correlation was established between the mean values of the size of synovitis and effusion (*Figure 1*) in SR (r=0.966, p=0.000), MR (r=0.812, p=0.000) and LR (r=0.886, p=0.000).

There is a significant correlation between the mean values of synovitis in SR and effusion in MR (r=0.325, p=0.002), and LR (r=0.317, p=0.003); synovitis in MR and effusion in SR (r=0.275, p=0.009); synovitis in LR and effusion in SR (r=0.317, p=0.003).

No correlation was found between the mean values of the size of synovitis in MR and effusion in LR (r=0.180, p=0.093), or between the mean values of the size of synovitis in LR and effusion in MR (r=0.175, p=0.103).

A significant difference was found in the mean values of the biomarker COMP between patients with and without effusion regardless of the localization or size (p=0.030) (*Table IV*). The mean value of COMP concentration in 25% of patients with no established effusion was 54 (44.5–58) mg/mL, while in 75% of patients with effusion it was 57 (48.75–64.25) ng/ml.

No significant correlation was found between the mean values of COMP concentration and the size of effusion in SR (r=0.076, p=0.484), in MR (r=0.043, p=0.692), in LR (r=0.044, p=0.687) and synovitis in SR (r=0.086, p=0.428), in MR (r=0.026, p=0.809) and in LR (r=0.105, p=0.330).

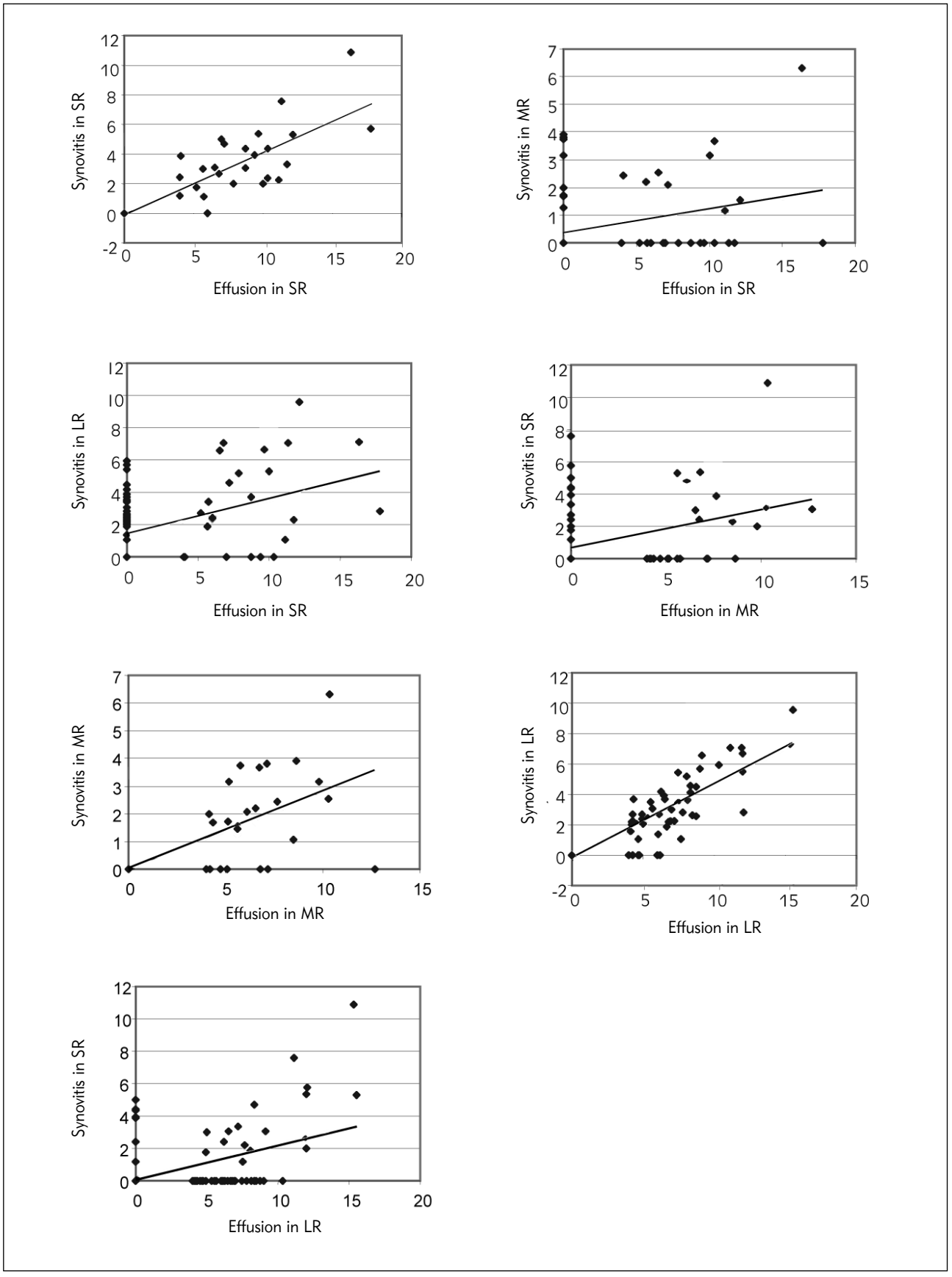

Figure 1 Connection between thickness of synovitis and size of effusion in suprapatellar, medial and lateral recesses.

Discussion

Osteoarthrosis of the knee is the most common osteoarthrosis of the peripheral joints that can be a cause of disability in the elderly population, and its prevalence increases with age (2). This research included 88 patients, 20 (22.7%) males and 68 (77.3%) females with primary OA of the knee. Mean age of the subjects was 69.97±9.37, and the average duration of disease was 6.46±6.73 years.

Clinical reviews determined minimal outflow in 34.1% of patients, moderate in 22.7%, significant in 4.5%, while 38.6% of patients had no outflow.

Arthrosonographic measurements and the methods used in our research were in accordance with the recommendations of the European Multicentre Studies – EULAR report, parts 1 (7) and 2 (8), that have dealt with synovial inflammations (synovial hypertrophy and effusion), as an important and significant cause of pain and progression of the knee joint osteoarthrosis.

Between the results obtained by a clinical review of the outflow and an arthrosonographic review of the effusion, a significant difference was established, namely, outflow was clinically diagnosed in 61.3% of patients, while effusion was seen using arthrosonography in 75% of patients (p=0.000). Similar results have been published in other studies, indicating the presence of inflammation in 51% (15), or as much as 79% of osteoarthrotic joints (16).

Sensitivity of the clinical diagnosis of outflow in our patients was determined to be 73% (percentage of accurate outflow diagnosis by clinical reviews in the group with outflow found by ultrasonic checkup), and specificity was 73% (percentage of outflow diagnosis by clinical review in the group with no outflow shown during ultrasonic checkup).

Many studies have proved ultrasound to be very useful in diagnosing and monitoring joint effusion and synovitis (17), especially in early osteoarthrosis (18), providing results comparable to MRI (19) and arthroscopy (20, 21). A radiographic finding is a standard addition to a clinical review. However, the discrepancy between a radiographic finding in osteoarthrosis and events in a painful knee in the general population (22) has been identified (23) and well documented (24, 25) long ago. According to recent research, agreement between ACR clinical criteria of arthrosis and radiographic findings of arthrosis is low, sensitivity is 41% and specificity 75% (26). Therefore, the ultrasonic technique of joint inspection (arthrosonography) is recommended as the gold standard in rheumatology, because it is much more precise than clinical reviews and radiographic findings (17).

By using arthrosonography, we can quickly and precisely detect joint effusion, as well as determine its localization, which clinical reviews rarely permit, especially in minor outflows. The largest number of our patients had effusion in the lateral recess (LR), 62.5%. In the suprapatellar recess (SR) of the knee joint effusion was seen in 28.4% of patients, and in 27.3% it was present in the medial recess (MR).

Arthrosonography can be used for the measurement and follow-up of the size of joint effusion and synovitis. The mean values of effusion size in our patients were the highest in the lateral recess, 11.38 ±4.44 mm. In the suprapatellar recess effusion was smaller – 10.13±4.35 mm, and the smallest in the medial recess, 3.15±1.86 mm.

The mean value of the size of effusion in the suprapatellar recess in patients with significant outflow was 13.85 (10.36–17.43) mm (p=0.000), in the medial recess 4.9 (0–10.22) mm (p=0.008), and in the lateral recess 12.0 (11.34–14.50) mm (p=0.000). In cases of moderate or minimal outflow, effusion appears only in the lateral recess, in patients with moderate outflow its size is 6.94 (1.16–8.13) mm, and in those with minimal outflow the size is 4.9 (0–7.25) mm.

During our research, we determined significant correlation between the mean values of the size of synovitis and effusion in SR, MR and LR, indicating that higher proliferation of the synovial membrane in a specific recess leads to a more pronounced effusion inside it. Also, significant correlation between the synovial membrane proliferation in SR and the size of effusion in MR and LR was established, as well as correlation between the synovial membrane proliferation in MR and LR with effusion in SR, indicating that synovitis in SR causes significant effusion in all three recesses of the knee joint, reflecting more intense inflammation of the knee joint, and also that synovitis in MR and LR can initiate inflammation and effusion in SR. If inflammation appears only in MR or LR, it generally develops in isolation and cannot cross from the medial into the lateral recess, or vice versa, without spreading onto the SR.

Biochemical markers (biomarkers) are molecules or fragments of the connective tissue matrix which are released into biological fluids during the process of tissue metabolism, and can be measured by immunoassay methods (27). Today, potentially specific biochemical markers are being developed, reflecting the quantitative and dynamic changes of degradation and reparation in remodeling joint tissue (28).

Cartilage oligomeric matrix protein, COMP, is a biomarker whose concentrations in serum highly correlate with the joint damage score obtained by magnetic resonance, as shown in the study by Bruyere et al. (19). Several studies have indicated that COMP levels in serum and urine are elevated in patients with osteoarthrosis in comparison with the control group (19, 29).

Significant difference was found in our research in the mean values of the COMP biomarker between patients with and without effusion, regardless of localization or size (p=0.030). The mean value of COMP concentration in patients with no effusion established by arthrosonography was 54 (44.5–58) ng/mL, while in patients with effusion it was 57 (48.75–64.25) ng/mL. The use of this biomarker allows us to determine if there is inflammation in the knee joint, but not to identify the recess. Namely, no significant correlation between the mean values of COMP concentration and the size of effusion in SR (r=0.076, p=0.484), MR (r=0.043, p=692), and LR (r=0.44, p=0.687) was found.

The study by Vilim et al. (30) has described COMP as a marker of disease progression, after a three-year follow-up of the COMP level in the sera of patients with knee osteoarthrosis. It has been concluded that in patients with radiographic changes there are high concentrations of COMP, and that they can serve as a prognostic marker for disease progression (30).

Conclusion

Arthrosonography is a more sensitive method for diagnosing and monitoring joint effusion and synovitis than the clinical review (sensitivity 73%, specificity 73%) (p=0.000) and should therefore become routine and fundamental in the work of rheumatologists. Patients with OA most often have effusion in the lateral recess. The size of effusion and synovitis differs significantly between patients with minimal, moderate and significant outflow (p=0.000). In cases of clinically determined significant outflow, arthrosonography reveals the largest effusion in the suprapatellar recess, whereas in cases of minimal and moderate outflow effusion only occurs in the lateral recess (p=0.000). Cartilage oligomeric matrix protein, COMP, is a biomarker whose elevated serum concentrations precisely indicate the presence of inflammation in the knee joint in OA, but fail to reveal in which recess tissue is inflamed.

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