Aggrecan and Cartilage Oligomeric Matrix Protein in Serum and Synovial Fluid of Patients with Knee Osteoarthritis

Mohammed M. El-Arman · Ghada El-Fayoumi · ElWaleid El-Shal · Ibrahim El-Boghdady · Atef El-Ghaweet

Received: 11 October 2009/Accepted: 29 January 2010/Published online: 2 March 2010
© Hospital for Special Surgery 2010

Abstract Aggrecan and cartilage oligomeric matrix protein (COMP) which are important degradation products of articular cartilage may be promising diagnostic markers in serum and/or synovial fluid for diagnosis of knee osteoarthritis (OA). Our objective was to measure serum and synovial fluid levels of aggrecan and COMP in patients with OA of the knee joint to find out if they could be of diagnostic value in OA and if their levels correlate with the clinical and radiological manifestations of the disease. Sixty-six patients suffering from primary knee OA with effusion (26 males and 40 females) were studied. Twenty individuals (six males and 14 females) with recent traumatic

knee effusion matched for age and sex were chosen to serve as a control group. All subjects had thorough clinical and radiological (X-ray and MRI) evaluation. Aggrecan and COMP in serum and synovial fluid were measured by ELISA. Serum and synovial fluid aggrecan and COMP levels were significantly higher than the control. Serum and synovial fluid aggrecan and COMP levels were positively correlated with age, body mass index, disease duration, plain X-ray and MRI scores. In OA, serum and synovial fluid aggrecan and COMP levels are elevated and represent useful markers in the diagnosis. Moreover, these elevated levels positively correlated with radiological joint damage but not with clinical disease parameters. These markers have the potential to be used for monitoring articular cartilage destruction and response to different therapeutic modalities.

Author contributions: Mohammed El-Arman designed the research and analyzed the data. G. El-Fayoumi, E. El-Shal, A. El-Ghaweet and Ibrahim El-Boghdady provided the samples and clinical data. Mohammed El-Arman prepared reagents/analytic tools and performed laboratory part and wrote the paper.

Each author certifies that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Each author certifies that his or her institution has approved the reporting of these cases, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participating in the study was obtained.

Level of Evidence: Level II Prognostic study. See levels of evidence for a complete description.

M. M. El-Arman (✉)
Department of Clinical Pathology,
Mansoura University,
Mansoura, 35111, Egypt
e-mail: moha_mm2001@yahoo.com

G. El-Fayoumi · E. El-Shal · I. El-Boghdady · A. El-Ghaweet
Department of Rheumatology and Rehabilitation,
Mansoura University,
Mansoura, Egypt

Keywords aggrecan · cartilage oligomeric matrix protein · osteoarthritis

Introduction

Osteoarthritis (OA) is a disease of complex etiology that occurs as a result of both mechanical and biological events. The most established method for assessing joint damage in OA is joint space width (JSW) measurement using plain X-rays [1, 2]. However, when radiological diagnosis is established, significant joint damage has often already occurred, as the arthrosis is initiated long before the radiographic diagnosis can be effected, and the diagnosis will only be made late in the disease [3]. Clearly, to identify patients with a high risk for destructive OA and to monitor drug efficacy, more sensitive techniques than plain X-ray are needed [4]. Magnetic resonance imaging (MRI) is currently being optimised for this purpose [5]. Alternatively, specific and sensitive biochemical markers (aggrecan and COMP) reflecting abnormalities of the turnover of bone, cartilage, and synovial tissues are increasingly used as

helpful tools in early diagnosis before irreversible damage has occurred [6].

The aim of the present study was to measure serum and synovial fluid levels of aggrecan and cartilage oligomeric matrix protein (COMP) in patients with OA of the knee joint to evaluate their potential utility as diagnostic biomarkers for knee OA and to correlate their levels with the clinical and radiological manifestations of the disease. Specifically, we aimed to compare the levels of aggrecan and COMP in the serum and synovial fluid of patients with osteoarthritic and post-traumatic knee effusions. In addition, we aimed to correlate the levels of aggrecan and COMP with patient age and BMI. Finally, we wished to assess if the level of aggrecan and COMP could be correlated to disease severity as assessed by radiographic and MRI assessment of disease severity.

Materials and methods

This prospective, controlled study was conducted on 66 consecutive patients with primary OA of the knee joint with effusion, who were attending the outpatient clinic of Rheumatology and Rehabilitation, Mansoura University Hospital, Egypt. The visits were prompted by the acute onset of pain and swelling and stiffness in the affected knees. There were 26 males and 40 females, and their ages ranged from 45 to 60 years. Disease duration ranged from 2 to 8 years. Patients were diagnosed according to the American College of Rheumatology criteria for diagnosis of primary knee OA [7]. Twenty individuals (six males and 14 females) with recent traumatic knee effusion were chosen from the Casualty Department, Mansoura University Hospital, to serve as a control group. All of these patients had suffered knee injury within 1 week of presentation but had no evidence of fracture or meniscal injury. They were matched for age and sex with the OA group. Their ages ranged from 40 to 55 years. Written consent was obtained from every subject in this study after IRB approval was obtained.

Patients were excluded if they presented with secondary OA, previous knee injury or intra-articular fracture, steroid

injection into the affected knee joint within 3 months of recruitment for the study, OA in joints other than the knee joint, osteoporosis and other rheumatic diseases. Also, we excluded patients with inflamed joints other than knee joint as this could affect serum levels of the biomarkers.

Each subject recruited into this study was evaluated with a thorough history and physical examination (Table 1). Height and weight were measured on the day of the visit to calculate the BMI. Pain severity was assessed using visual analogue scale ranging from a score of 1 representing mild pain to 10 representing extreme pain. The Vas line was 10 cm in length [8]. Tenderness was assessed on a rating scale of 0–3 [9]. The Quadriceps muscle was evaluated by thigh circumference measurement and quadriceps wasting was graded [10]. Joint effusion was graded on a scale of 0–3 [10]. Both active and passive ranges of motion (ROM) were tested, noting any pain elicited and loss of motion. Measurement was carried out using the standard full circle plastic goniometer. Maximum flexion and extension lag were graded [11]. Disease severity was assessed according to Lequesne et al. [12] with scoring range from 0–24. Functional assessment was done using the Western Ontario and McMaster (WOMAC) OA index that measure pain, joint stiffness and degree of difficulty to carry out daily life activity with scoring range from 0 to 96 [13]. Plain X-ray was done for the knees in anteroposterior (weight-bearing) and lateral views, and radiographs were scored from 0 to 4 depending upon X-ray findings [14]. MRI was performed for all cases [15] and the MRI was evaluated by a single observer blinded to the biomarker levels. MRI findings of interest included decrease of cartilage thickness, the presence of osteophytes, subchondral cysts and subchondral sclerosis.

Venous blood sample was withdrawn from each subject by sterile venipuncture during this office evaluation. The separated serum was kept frozen at -20°C till the time of estimation of aggrecan and COMP.

Aspiration of the knee joint fluid was done for the patients under complete aseptic conditions also during this office evaluation. About 10 mL of synovial fluid was collected from each knee collected into specimen tubes and

Table 1 Clinical and functional parameters of knee OA patients

Parameter		Mean $\pm$ SD
Disease duration (years)		5.15 $\pm$ 1.71
Side affected		
Right	28/66 (42.4%)	
Left	38/66 (57.6%)	
Duration of morning stiffness (minutes)		12 $\pm$ 5.40
Visual analogue scale for pain (cm)		3.97 $\pm$ 1.68
Periarticular tenderness grade		1.2 $\pm$ 0.40
Quadriceps wasting grade		1.22 $\pm$ 0.42
Effusion grade		2.15 $\pm$ 0.36
Crepitus		
Present	66/66 (100%)	
Maximum flexion grade		0.8 $\pm$ 0.68
Extension lag grade		1.12 $\pm$ 0.33
Disease severity (Lequesne index)		5.5 $\pm$ 0.67
WOMAC functional index		27.3 $\pm$ 6.70

Table 2 Serum and synovial aggrecan levels in OA patients versus controls

Parameter	Patients	Controls	<i>p</i>
Serum aggrecan level (μg/mL)			
Mean ± SD	6.96±3.55	3.63±1.88	<0.001
Synovial fluid aggrecan level (μg/mL)			
Mean ± SD	101.42±45.65	71±14.1	<0.004

centrifuged for 20 min. The supernatant fluid was stored at −20°C until analyzed. The knee joint was then aspirated to completion [16].

Quantitative measurement of aggrecan level was performed on the serum and synovial fluid samples using an immunoenzymetric technique [17]. The kit was manufactured by Medgenix Diagnostics S.A., Zoning Industrial, B-6220 Fleurus, Belgium. In this method, monoclonal antibodies (MAbs) directed against distinct epitopes of aggrecan are used. Standards or samples containing aggrecan (AG) react with capture monoclonal antibody (Mab 1) coated on the microtiter well and with a monoclonal antibody (Mab 2) labelled with horseradish peroxidase (HRP). After an incubation period allowing the formation of a sandwich: coated Mab 1–AG–Mab 2–HRP, the microtiter plate is washed to remove unbound enzyme-labelled antibodies. Bound enzyme-labelled antibodies are measured through a chromogenic reaction. Chromogenic solution is added and incubated. The reaction is stopped with the addition of stop solution and the microtiter plate is then read at 450 nm. The colour is proportional to the AG concentration.

Quantitative measurement of COMP level: The kit was supplied by Wieslab, IDEON Research Park Lund, S-223, Sweden. COMP Assay Kit is an enzyme immunoassay for the quantitation of intact or fragmented human cartilage oligomeric matrix protein in serum or synovial fluid. The assay utilizes native human articular COMP coated to well microtiter plates and a rabbit polyclonal antiserum directed to human COMP. Bound antibody is detected using an alkaline phosphatase-labelled anti-rabbit IgG conjugate.

Statistical analysis of the results was carried out using the SPSS (statistical package for social science) Version 10. To test the data distribution, the Kolmogorov Smirnov test was used which revealed the data to be parametric. Data are expressed as mean ± standard deviation ($X \pm SD$). Statistical analysis between the OA patient group and recent post traumatic control group was done using the student's *t* test. Correlation study of the OA group was using Pearson's correlation coefficient (*r*).

Results

Patients with OA were found to have higher aggrecan and COMP levels in both serum ($p=0.001$) and synovial fluid ($p=0.004$) compared with controls (Tables 2 and 3).

The body mass index in OA patients ($34.5 \pm 1.99 \text{ kg/m}^2$) was significantly higher than controls ($27.3 \pm 1.98 \text{ kg/m}^2$; $p<0.001$).

Both serum and synovial fluid aggrecan and COMP levels in the patients with OA were positively correlated with age, body mass index, disease duration, plain X-ray and MRI scores. Meanwhile, no significant correlations were observed between serum and synovial fluid aggrecan or COMP and morning stiffness, pain, periarticular tenderness, quadriceps wasting, effusion volume, maximum flexion, the presence of an extension lag or the disease severity as assessed by the method of Lequesne et al. [12] (Tables 4 and 5).

Discussion

Much attention has been focused on biomarkers such as cartilage-derived macromolecules or their fragments whose release into the circulation from the joint may reflect disturbances in joint tissue turnover [18, 19]. In addition, cartilage-specific markers, such as aggrecan and COMP have been detected in serum and synovial fluid, and their relevance in the pathogenesis of osteoarthritis needs to be determined [20]. This study aimed to measure serum and synovial fluid levels of aggrecan and COMP in patients with OA of the knee joint to find out if they could be of diagnostic value in OA. Specifically, we aimed to compare the levels of aggrecan and COMP in the serum and synovial fluid of patients with osteoarthritic and post-traumatic knee effusions. In addition, we aimed to correlate the levels of aggrecan and COMP with patient age and BMI. Finally, we wished to assess if levels of aggrecan and COMP could be correlated to disease severity as assessed by radiographic

Table 3 Serum and synovial COMP levels in OA Patients versus controls

Parameter	Patients	Controls	<i>p</i>
Serum COMP level (μg/mL)			
Mean ± SD	7.17±3.08	4.4±1.97	<0.001
Synovial fluid COMP level (μg/mL)			
Mean ± SD	66.92±28.75	26.2±9.41	<0.001

Table 4 Correlation of serum and synovial fluid (SF) aggrecan with clinical, functional and radiological parameters

Parameter	Serum aggrecan		SF aggrecan	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Age	0.350	0.027	0.370	0.019
Body mass index	0.399	0.011	0.470	0.003
Disease duration	0.499	0.001	0.399	0.011
Morning stiffness	0.175	0.280	0.023	0.887
Pain VAS	0.023	0.887	0.271	0.091
Periarticular tenderness	0.049	0.762	0.063	0.699
Quadriceps wasting	0.267	0.096	0.271	0.091
Effusion	0.250	0.119	0.175	0.280
Maximum flexion	0.080	0.623	0.125	0.441
Extension lag	0.019	0.907	0.094	0.564
Disease severity (Lequesne Index)	0.125	0.441	0.094	0.564
WOMAC functional index	0.173	0.286	0.107	0.510
Plain X-ray score	0.365	0.021	0.350	0.027
MRI score	0.422	0.007	0.631	0.001

r=Pearson's correlation coefficient

and MRI assessment of disease severity. We selected patients with recent traumatic effusions as controls since it is difficult and perhaps unethical to obtain synovial fluid from completely healthy volunteers.

In this study, both serum and synovial fluid aggrecan and COMP levels were significantly higher in patients with knee OA than controls. Elevated levels of aggrecan epitopes and COMP in OA patients probably reflect an increased synthesis of aggrecan in degenerated cartilage or increased degradation with a resultant loss from the cartilage [18, 21–28]. However, Fuller et al. [29] studied the level of aggrecan epitopes in OA synovial fluid and compared the results with that of the contralateral joint. They found no significant difference between the two sides, which could be explained by the fact that the contralateral joint is not necessarily normal to be used as a control.

In this study, the synovial fluid aggrecan or COMP was several times higher than serum levels. This result suggests that aggrecan and COMP are locally produced in the joint and high synovial fluid of these biomarkers are associated with rapid cartilage turnover [14, 23, 30].

In this study, serum and synovial fluid aggrecan levels and COMP were positively correlated with age and body mass index. In fact, it is well recognized that obesity and aging are important factors in OA knees [22, 26, 31, 32]. However, these results disagree with some authors [30, 33–35].

In this study, serum and synovial fluid aggrecan and COMP were positively correlated with disease duration. This may be explained by the fact that long duration of the disease is likely to result in more cartilage destruction with consequent release of aggrecan into the joint fluid which then appears in the serum. These findings are in agreement

Table 5 Correlation of serum and synovial fluid (SF) COMP with clinical, functional and radiological parameters

Parameter	Serum COMP		SF COMP	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Age	0.365	0.021	0.350	0.027
Body mass index	0.450	0.002	0.590	0.001
Disease duration	0.580	0.001	0.580	0.001
Morning stiffness	0.166	0.306	0.175	0.280
Pain VAS	0.299	0.061	0.280	0.080
Periarticular tenderness	0.024	0.882	0.023	0.887
Quadriceps wasting	0.152	0.350	0.170	0.294
Effusion	0.280	0.080	0.218	0.176
Maximum flexion	0.044	0.790	0.044	0.790
Extension lag	0.018	0.912	0.054	0.741
Disease severity	0.202	0.212	0.182	0.261
WOMAC functional index	0.175	0.280	0.170	0.294
Plain X-ray score	0.370	0.019	0.322	0.043
MRI score	0.654	0.001	0.651	0.001

r=Pearson's correlation coefficient

with that reported in some literatures [30, 36, 37]. However, Sharif et al. [38] and Conrozier et al. [35] disagreed with our findings and postulated that increased expression of these epitopes might reflect the response of the articular cartilage to insult requiring initiation of a high level.

No significant correlations could be detected between aggrecan or COMP levels and any of the clinical symptoms and signs (morning stiffness, pain, local knee warmth, periarticular tenderness, quadriceps wasting, joint effusion, synovial thickening, maximum flexion as well as extension lag). Furthermore, no significant correlation could be detected between aggrecan or COMP levels and Lequesne functional index, as well as WOMAC score. These findings could be explained by the fact that clinical evaluation does not necessarily reflect cartilage changes as no close link between such parameters and the tissue process was to be expected [32, 35, 39, 40]. These results disagree with those of Campion et al. [41], Thonar et al. [42] and Bleasel et al. [30] who reported that aggrecan turnover correlated positively with the clinical signs of knee OA. Moreover, Sharif et al. [38] found that COMP levels significantly correlated with activity and severity of knee OA.

Significant correlations were observed between serum and synovial fluid aggrecan or COMP levels and plain X-ray score or MRI score since advanced disease, as expressed by higher radiological score, was associated with more cartilage destruction with subsequent increased release of aggrecan into joint fluid and serum. These results are in agreement with some authors [29, 43–47]. On the other hand, Belcher et al. [33] and Fragonas et al. [48] could not detect any significant correlation between the markers in synovial fluid and radiological findings. This is probably related to differences in patient selection.

It could be concluded that serum and synovial fluid aggrecan and COMP levels are elevated and represent useful markers in the diagnosis of knee OA. Moreover, these elevated levels positively correlated with radiological joint damage but not with clinical disease parameters. Promisingly, these markers have the potential to be used for monitoring articular cartilage destruction and response to different therapeutic modalities.

References

- Kuettner K and Goldberg V (1995). Osteoarthritic disorders. In: Rosemont IL (ed). Illinois: American Academy of Orthopedic Surgeons. pp 247–60.
- Cucchiari M, Thurn T, Weimer A, Kohn D, Terwilliger EF, Madry H. (2006). Restoration of the extracellular matrix in human osteoarthritic articular cartilage by overexpression of the transcription factor SOX9. *Arthritis Rheum*; 56(1):158–67
- Neustadt DH (2006). Intra-articular injections for osteoarthritis of the knee. *Cleve Clin J Med*; 73(10):897–8.
- Frederick W and Nancy L (2002). The long-term outcome of osteoarthritis: Rates and predictors of joint space narrowing in symptomatic patients with knee osteoarthritis; *J Rheumatol*. 29 (1):139–46
- Anita W, Stephen S and Judith S (2002). The determinants of change in tibial cartilage volume in osteoarthritis knees. *Arthritis Rheum*; 46 (8): 2065–72.
- Schmidt B, Gavenis K and Kippels M (2002). New potential markers for cartilage degradation of the knee joint. *Scand J Rheumatol*; 31: 151–7.
- Altman R, Asch E and Bloch D (1986). Development of criteria for the classification and reporting of osteoarthritis. *Arthritis Rheum*; 29: 1039–49.
- Huskisson E (1982). Measurement of pain. *J Rheumatol*; 9: 678–9.
- Gunn J (1976). Clinical examination of the knee joint. *Bone joint Surg*; 5: 10–15
- Jones A, Hokinsm V and Patizick M (1992). Evaluation of a method for clinically assessing osteoarthritis of the knee. *Ann Rheum Dis*; 51: 243–5.
- Aichroth P, Freeman M and Samilli L (1978). Deformities of the knee joint. *J Bone Joint Surg Am*; 50: 60–75.
- Lequesne G, Mery C and Samson M (1987). Indexes of severity for osteoarthritis of the hip and knee. Validation value in comparison with other assessment tests. *Scand J Rheumatol*; 65 (suppl.): 85–9.
- Bellamy N, Buchanan W and Goldsmith C (1995). A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*; 15: 1833–40.
- Neidhart M, Hauser N, Paulsson M, DiCesare P, Michel B and Hauselmann H (1997). Small fragments of cartilage oligomeric matrix protein in synovial fluid and serum as markers for cartilage degradation. *Br J Rheumatol*; 36: 1151–60.
- Seliem H, Afify T and Radwan H (1998). Value of MRI in detection of disease progression in knee osteoarthritis. *Egypt Rheumatol Rehab*; 25(4): 531–8.
- Duncan S and Owen J (1997). Aspiration and injection of joints and soft tissues. In: Kelly W, Harris E, Ruddy S and Seldge C (eds): *Textbook of Rheumatology*, 5th edn. Philadelphia: Saunders. pp 591–7.
- Lohmander S, Lark M, Dahiberg L, Walakovits L and Roos H (1992). Cartilage matrix metabolism in osteoarthritis: Markers in synovial fluid, serum and urine. *Clin Biochem*; 25:167–74.
- Garnero P, Piperno M and Gineys E (2001). Cross sectional evaluation of biochemical markers of bone, cartilage, and synovial tissue metabolism in patients with knee osteoarthritis: Relations with disease activity and joint damage. *Ann Rheum Dis*; 60: 619–26.
- Peterfy G (2002). Imaging of the disease process. *Current Opinion in Rheum*; 14 (5): 590–6.
- Bruyere O, Collette J, Kothari M, Zaim S, White D, Genant H, Peterfy C, Burlet N, Ethgtn D, Montague T, Dabrowski C and Reginster GY (2006). Osteoarthritis, magnetic resonance imaging and biochemical markers: A one year prospective study. *Ann Rheum Dis*; 65 (8): 1050–54.
- Lohmander L, Inoescu M and Jugessur H (1999). Changes in joint cartilage aggrecan after knee injury and in osteoarthritis. *Arthritis Rheum*; 42: 534–44.
- Otterness G, Swindell C and Zimmerer A (2000). Analysis of 14 molecular markers for monitoring osteoarthritis. *Osteoarthritis Cart*; 8 (3): 180–5.
- Larsson S, Lohmander LS, Struglics A. (2009). Synovial fluid level of aggrecan ARGS fragments is a more sensitive marker of joint disease than glycosaminoglycan or aggrecan levels: a cross-sectional study. *Arthritis Res Ther*; 11(3):R92.
- Cawston T, Ellis J and Humm G (1995). IL-1 and 14, oncostatin M in combination promotes the release of collagen fragments from bovine nasal cartilage in culture. *Biochem Biophys Res Comm*; 215: 377–85.
- Clark A, Jordan J and Villim V (1999). Serum cartilage oligomeric matrix protein reflects osteoarthritis presence and severity. *Arthritis Rheum*; 42: 2356–64.
- Villim V, Olejarova M and Kraus B (2002). Serum levels of cartilage oligomeric matrix protein correlate with radiographic progression of knee osteoarthritis. *Osteoarthritis Cart*; 10:707–13.
- Huang K, Wu LD (2008). Aggrecanase and aggrecan degradation in osteoarthritis: a review. *J Int Med Res*; 36(6):1149–60.
- Svetlova MS, Vezikova NN, Romashina VV, Sobanina TS, Pavlov IuL, Cheplukova IA (2008). Cartilage oligomeric matrix protein, a possible marker of synovitis in early knee joint osteoarthrosis. *Klin Med (Mosk)*; 86(11):65–8.

29. Fuller C, Barr A and Sharif M (2001). Cross sectional comparison of synovial fluid biochemical markers in equine osteoarthritis and the correlation of these markers with articular cartilage damage. *Osteoarthritis Cart*; 9: 49–55.
30. Bleasel J, Poole R and Heinegard D (1999). Changes in serum cartilage marker levels indicate altered cartilage metabolism in families with osteoarthritis-related type II collagen gene mutation. *Arthritis Rheum*; 42:39–45.
31. Wislowska M and Jablonska B (2005). Serum cartilage oligomeric matrix protein (COMP) in rheumatoid arthritis and knee osteoarthritis. *Clin Rheumatol*; 24(3):278–84.
32. Dragomir A, Kraus V and Renner J (2002). Serum cartilage oligomeric matrix protein and clinical signs and symptoms of potential pre-radiographic hip and knee pathology. *Osteoarthritis Cart*; 10: 687–91.
33. Belcher C, Yaqub R and Fawthrop F (1997). Synovial fluid chondroitin and keratan sulfate epitopes, glycosaminoglycans, and hyaluronan in arthritic and normal knees. *Ann Rheum Dis*; 56: 299–307.
34. Petersson I, Boegard B and Svensson D (1998). Changes in cartilage and bone metabolism identified by serum markers in early osteoarthritis of the knee joint. *Br J Rheumatol*; 37:46–50.
35. Conrozier T, Saxne T and Shan F (1998). Serum concentrations of cartilage oligomeric matrix protein and bone sialoprotein in hip osteoarthritis: A one year prospective study. *Ann Rheum Dis*; 57:527–32.
36. Lohmander S, Dahlberg L and Eyre D (1998). Longitudinal and cross-sectional variability in markers of joint metabolism in patients with knee pain and articular cartilage abnormalities. *Osteoarthritis Cart*; 6:351–61.
37. Saxne T, Geborek P and Mansson B (1995). Knee joint synovial fluid content of aggrecan predicts knee/ hip joint destruction in rheumatoid arthritis. *Trans Orthop Res Soc*; 20: 344–7.
38. Sharif M, Saxne T and Shepstone L (1995). Relationship between serum cartilage oligomeric matrix protein levels and disease progression in osteoarthritis of the knee joint. *Br J Rheumatol*; 34: 306–10.
39. Otterness I, Weiner E and Swiltldell A (2001). Analysis of 14 molecular markers for monitoring osteoarthritis. *Osteoarthritis Cart*; 9: 224–31.
40. Bruyere O, Collette J and Ethgen O (2003). Biochemical markers of bone and cartilage remodeling in prediction of long-term progression of knee osteoarthritis. *J Rheumatol*; 30: 1043–50.
41. Campion G, McCrae F and Schnitzer T (1991). Levels of keratan sulfate in the serum and synovial fluid of patients with osteoarthritis of the knee. *Arthritis Rheum*; 34: 254–9.
42. Thonar J, Masuda K and Lenz M (1995). Serum markers of systemic disease processes in osteoarthritis. *J Rheumatol*; 22: 68–70.
43. Ratcliffe A, Flatow E and Roth N (1996). Biochemical markers in synovial fluid identify early osteoarthritis of the glenohumeral joint. *Clin Orthop*; 330: 45–53.
44. Chevalier X (1997). Is a biological marker for osteoarthritis within reach? *Rev Rheum Engl Ed*; 64(10): 562–77.
45. Disler G, McCauley R and Kelman G (1996). Fat suppressed three-dimensional spoiled gradient echo MR imaging of hyaline cartilage defects in the knee. *AJR*; 167: 127–32.
46. Waldschmidt J, Rilling R and Kajdacsy A (1997). In vitro and in vivo MR imaging of hyaline cartilage: Zonal anatomy, imaging pitfalls, and pathologic conditions. *Radiographics*; 17: 1392–8.
47. Villim V, Vytasek R and Olejarova M (2001). Serum cartilage oligomeric matrix protein reflects the presence of clinically diagnosed synovitis in patients with knee osteoarthritis. *Osteoarthritis Cart*; 9:612–8.
48. Fragonas E, Mlynarik V and Jellus V (1998). Correlation between biochemical composition and magnetic resonance appearance of articular cartilage. *Osteoarthritis Cart*; 6(1): 24–32.