TLAR 1947

Arch Rheumatol 2017;32(3):189-196
doi: 10.5606/ArchRheumatol.2017.6220

ORIGINAL ARTICLE

Cartilage Oligomeric Matrix Protein Levels in Synovial Fluid in Patients With Primary Knee Osteoarthritis and Healthy Controls: A Preliminary Comparative Analysis With Serum Cartilage Oligomeric Matrix Protein

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ABSTRACT

Objectives: This study aims *(i)* to compare synovial fluid and serum cartilage oligomeric matrix protein levels in patients with primary knee osteoarthritis and healthy controls, *(ii)* compare variations of synovial fluid and serum cartilage oligomeric matrix protein levels according to sex, Kellgren-Lawrence grades, and daytime sampling, and *(iii)* correlate the synovial fluid and serum cartilage oligomeric matrix protein levels with age, severity of disease, and daytime sampling.

Patients and methods: One hundred and twenty-four participants (44 males, 80 females; median age 66 years; range 42 to 87 years) were diagnosed with primary knee osteoarthritis according to the American College of Rheumatology guidelines. Additionally, 105 healthy individuals (49 males, 56 females; median age 50 years; range 30 to 75 years) were included as the control group. For both groups, a thorough clinical history and physical examination were performed. Moreover, weight-bearing anteroposterior and lateral bending 30 degrees knee X-rays were collected. Cartilage oligomeric matrix protein in serum and synovial fluid was measured by enzyme-linked immunosorbent assay.

Results: Total synovial fluid cartilage oligomeric matrix protein levels were considerably higher than total serum levels for both groups. Levels of cartilage oligomeric matrix protein in synovial fluid and serum were higher in patients than in controls for both sexes. However, only cartilage oligomeric matrix protein levels in synovial fluid were higher in female patients. The levels of synovial fluid cartilage oligomeric matrix protein were significantly higher when sampling after 12 pm. A positive correlation was found between synovial fluid and serum cartilage oligomeric matrix protein levels, age, and daytime sampling.

Conclusion: These findings may suggest a possible role for synovial fluid and serum cartilage oligomeric matrix protein as a measure for primary knee osteoarthritis. However, more studies need to be performed to address other factors that may influence the levels of cartilage oligomeric matrix protein in synovial fluid and serum.

Keywords: Cartilage oligomeric matrix protein; knee; osteoarthritis; synovial fluid.

Osteoarthritis (OA) is a common chronic degenerative and disabling disease caused by the interaction of multiple risk factors such as obesity, trauma, and hormonal and occupational factors.[1] Chronic and symptomatic knee osteoarthritis (KOA) is believed to affect around 9.3 million young adults (≥45 years) in the United States with an obvious economic burden and impact on quality of life.[2] In Mexico, the prevalence of OA is estimated at 14% and it has been considered as the fourth cause of morbidity in adults over 60 years of age.[3]

Knee osteoarthritis involves cartilage degradation, joint space narrowing, osteophyte formation at the joint margins, and subchondral changes. At present, clinical history and X-rays

Received: September 23, 2016 ***Accepted:*** December 27, 2016 ***Published online:*** April 04, 2017

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are still the most reliable methods to diagnose and establish the severity of disease. As OA initiates before the radiographic alterations can be identified, the diagnosis is usually established at a very late stage of the disease.[4,5] Hence, it is important to examine potential biochemical parameters not only to discriminate between KOA and its severity, but also to evaluate changes in markers concentrations and their relationship with other variables such as age, sex, and daytime variations, among others.[6]

Cartilage oligomeric matrix protein (COMP) is a 524-kDa noncollagenous homopentameric protein present in cartilage.[7,8] Although the function of COMP remains unclear, it has been suggested that this may have a role in endochondral ossification, interacting with collagen fibrils via each C-terminal globule, for extracellular matrix stabilization. It is also known for influencing fibril formation for collagens type I and II, accelerating fibrillogenesis and binding to aggrecan, mediating the organization of cartilage matrix for its load bearing function.[9,10] In previous studies, serum COMP has been associated with diagnosis and prognosis of clinical KOA;[11-14] however, it remains unclear whether COMP is sensitive enough to evaluate KOA patients.

While serum and urine sampling are easy to obtain, levels of biomarkers from both anatomical sides exhibit large interindividual variations, leading to the requirement of highly sensitive techniques to avoid such variations. Serum and urine levels of COMP may be influenced not only by metabolism and clearance, but also by other factors such as non-joint tissues, age, sex, or daytime variation. Thus, the specificity of this marker for KOA may be diminished, limiting its use in the assessment of patients. To clear this issue, synovial fluid (SF) markers may be more informative than systemic markers as they relate to structural changes and damage within a joint. Therefore, SF markers may be useful as diagnostic and prognostic tools, and to measure efficacy of intervention.[15]

A limited number of studies have been found in the literature related to the analysis of COMP levels in SF and/or comparing levels of COMP between SF with serum.[16-18] In those studies, a high level of COMP was detected in both fluids, showing higher concentrations in SF than in serum indicating preferential release from the affected joints (Table 1).

In this study, we aimed *(i)* to compare SF and serum COMP levels in patients with primary KOA and healthy controls, *(ii)* compare variations of SF and serum COMP levels according to sex, Kellgren-Lawrence grades, and daytime sampling, and *(iii)* correlate the SF and serum COMP

Table 1. Previous studies on synovial fluid cartilage oligomeric matrix protein

Author	Year	Disease	Participants	Sample	Reference
Saxne and Heinegård[16]	1992	RA, OA, reactive arthritis, juvenile chronic arthritis	155	SF/serum	Br J Rheumatol 1992;31:583-91
Lohmander et al.[29]	1994	KOA, knee injury, healthy volunteers	353	SF	Ann Rheum Dis 1994;53:8-13
Petersson et al.[30]	1997	KOA grade I, knee pain, controls	45/45/8	SF	Ann Rheum Dis 1997;56:64-7
Neidhart et al.[17]	1997	Cadaveric, KOA, RA, controls	209	SF/serum	Br J Rheumatol 1997;36:1151-60
Kühne et al.[31]	1998	Knee trauma	30	SF/serum	Rheumatol Int 1998
El-Arman et al.[21]	2010	KOA, knee trauma as controls	66/20	SF/serum	HSSJ 2010;6:171-6
Åhrman et al.[18]	2014	Acute trauma, knee pain, OA, RA	75	SF	J Biol Chem 2014;289:20908-16
Gheita, et al.[22]	2015	KOA	23	SF/serum	Abstracts/Osteoarthritis Cartilage 2015;23:A85

RA: Rheumatoid arthritis; OA. Osteoarthritis; SF: Synovial fluid; KOA: Knee osteoarthritis.

levels with age, severity of disease, and daytime sampling.

PATIENTS AND METHODS

Two hundred and twenty-nine participants (93 males, 136 females; mean age 59 years; range 30 to 87 years) were recruited between March 2015 and May 2016 from Hospital General ISSSTE in Torreon, Mexico. One hundred and twenty-four participants (44 males, 80 females; median age 66 years; range 42 to 87 years) were diagnosed with primary KOA according to the American College of Rheumatology guidelines. Disease severity was classified using the Kellgren-Lawrence criteria (grade II, mild; grade III, moderate; grade IV, severe). Patients were males and non-pregnant females above 40 years of age with recent diagnosis of primary KOA. All patients with secondary arthritis of knee joint, rheumatic, inflammatory or septic joint disease, treatment for osteoarthritis, renal, hepatic or malignant disease, participating in any athletic or heavy working activity, or SF contamination with blood or pus were excluded. Additionally, 105 healthy individuals (49 males, 56 females; median age 50 years; range 30 to 75 years) were included as control group. Controls were males and non-pregnant females above 40 years of age with no evidence of any articular disease. For both groups, a thorough clinical history and physical examination were performed. Moreover, weight-bearing anteroposterior and lateral bending 30 degrees knee X-rays were collected.

Of the total 229 participants, 77 samples corresponded to SF only, 78 samples to serum only, and for 74 individuals, both SF and serum samples were taken. The study protocol was approved by the Clinica del Magisterio Ethics Committee. All patients provided written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki.

For the patient group, knee joint aspiration was carried out under aseptic conditions for therapeutic reasons. Knee aspiration for the controls was also carried out under aseptic conditions as described by Driban et al.[19] In both groups, arthrocentesis through the superolateral patella portal was performed using a 20G × 32 mm sterile needle after local subcutaneous anesthesia with 2 mL at 1% lidocaine hydrochloride. Approximately 2 to 10 mL of SF was collected. Aliquots were centrifuged for 15 minutes and supernatants were kept frozen and stored at -80 °C. For both groups, simultaneously, venous blood sample was taken by sterile venipuncture. The separated serum was kept frozen at -80 °C for analysis.

To estimate COMP levels in serum and synovial fluid samples, a human enzyme-linked immunosorbent assay was used, following manufacturer's instructions (Cloud-Clone Corp, SEB197Hu, Wuhan, China).

To explore influence of daytime variation in COMP levels, the samples were collected during medical consultation schedules: A) from morning to late mid-day (8 am to 12 pm), and B) late day (after 13 pm to 18 pm). SF samples were collected by an orthopedist. Sample processing was performed twice; SF samples were examined to exclude septic, metabolic or rheumatoid diseases.

Statistical analysis

All statistical analyses were performed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Comparative analyses between groups were carried out using non-parametric tests. Mann-Whitney U test was used to compare medians between groups while Kruskal-Wallis test was used to compare COMP levels among severity grades of disease. In addition, Spearman coefficients were estimated to examine the correlation between COMP values with daytime variation, age, and Kellgren-Lawrence grades of severity. Finally, $p<0.05$ was regarded as indicative of a significant difference.

RESULTS

The clinical and demographic characteristics of participants of this study, along with their corresponding COMP levels, are depicted in Table 2. Total SF COMP levels were considerably higher than total serum levels (676.6 ng/mL vs 257.5 ng/mL) (Table 3). Additionally, both COMP levels in SF and serum were higher in patients than in controls (SF, $p=0.033$ and serum $p=0.035$). Interestingly, COMP levels in SF were significantly higher only in female patients ($p=0.007$) (Table 3).

Table 2. Clinical characteristics of primary knee osteoarthritis patients and healthy individuals

	Primary KOA (n=124)						Control group (n=105)			
	Mild	Moderate	Severe							
	%	%	%	Median	Range	Min-Max	Median	Range	Min-Max	*p*
Age (year)				66	42-87		50	30-75		0.0001**†
Sex										0.259‡
Male	22.7	40.9	36.4	62	49-85		50	40-75		0.0001**†
Female	13.8	55.0	31.2	67	42-87		50	30-71		0.0001**†
BMI kg/m^2				27.7		18.5-45.7	27.3		19-47.3	0.233†
Male				28.97		21.1-45.5	27.7		19-47.3	0.181†
Female				27.59	18.5-45.7		26.5		19.5-41.1	0.631†

KOA: Knee osteoarthritis; BMI: Body mass index; Min: Minimum; Max: Maximum; ‡ Chi square test; ** Significant if p<0.01; † Mann Whitney U test.

Regarding daytime variation, COMP levels were increased when sampling after 12 pm, but only KOA SF COMP levels were statistically significant when compared to controls (Table S1). Also, SF COMP levels showed a gradual increase with severity of KOA (p=0.012) (Table 4). In contrast, for serum COMP levels, this pattern was not observed. In addition, a correlation between SF and serum COMP was found. Finally, age, severity of disease, and diurnal variation were positively correlated with SF COMP levels (Table 5).

DISCUSSION

The employment of biomarkers related to cartilage degradation may be useful in the diagnosis of OA. In a previous study performed by Sudhir Singh et al.,[20] serum COMP levels were higher in patients when compared to controls. Thus, this group have suggested that COMP may be used as a potential biomarker to diagnose OA patients, suggesting also the possibility to establish cutoff serum COMP levels to discriminate between the grades of severity of disease.[2]

Our study aimed to measure and compare serum and SF COMP levels in patients with primary KOA and healthy individuals to find out whether COMP could have a potential role for diagnosis in KOA patients. Moreover, we aimed to compare SF and serum levels of this biomarker considering age, sex, severity of disease and diurnal variation. In addition, we aimed to correlate SF and serum COMP levels with diurnal variation, particularly within primary KOA patients.

Results of this study showed significant differences when comparing primary KOA vs healthy individuals, in which COMP levels in SF were higher than serum in both groups of study. Similar results were found by El-Arman et al.,[21] Gheita et al.,[22] and Andereya et al.,[23] suggesting that COMP is produced in the joint and associated

Table 3. Comparative analysis of synovial fluid and serum cartilage oligomeric matrix protein levels by sex

	SF COMP (n=151)			Serum COMP (n=152)		
	Median	Min-Max	*p*	Median	Min-Max	*p*
Total levels of COMP (ng/mL)	676.6	25-2480	0.033*†	257.5	18-2542	0.035*†
KOA	777	50-2480		314	18-2542	
Control group	676.3	25-836		228	57-810	
Female KOA (ng/mL)	891.2	50-2420	0.007**†	296	18-2230	0.116†
Female healthy individuals	676.3	25-817.5		201	61-801	
Male KOA (ng/mL)	529	58-2480	0.875†	343	32-2542	0.146†
Male healthy individuals	676.3	173-836		257.5	57-810	

SF: Synovial fluid; COMP: Cartilage oligomeric matrix protein; Min: Minimum; Max: Maximum; KOA: Knee osteoarthritis; † Mann Whitney U test; * Significant if p<0.05; ** Significant if p<0.01.

Table S1. Comparative analysis of synovial fluid and serum cartilage oligomeric matrix protein levels by daytime sampling

	SF COMP (n=151)		Serum COMP (n=152)	
	Median	Min-Max	Median	Min-Max
Daytime sampling A (8 to 12 pm)	676.3	25-2394	240	18-2230
Daytime sampling B (13 to 18 pm)	891	109-2480	305	61-2542
p-value	0.028‡*		0.613‡	
Daytime sampling A (8 to 12 pm) KOA	527.0	50-2394	270.0	18-2230
Daytime sampling A (8 to 12 pm) control	676.3	25-836	235.0	57-810
p-value	0.480‡		0.158‡	
Daytime sampling B (13 to 18 pm) KOA	892.5	109-2480	325.5	61-2542
Daytime sampling B (13 to 18 pm) control	406.5	173-817.2	211.5	85-374)
p-value	0.041‡*		0.087‡	
Daytime sampling A (8 to 12 pm) KOA	527	50-2394	270	18-2230
Daytime sampling B (13 to 18 pm) KOA	892.5	109-2480	325.5	61-2542
p-value	0.018‡*		0.784‡	
Daytime sampling A (8 to 12 pm) control	676.3	25-836	235.0	57-810
Daytime sampling B (13 to 18 pm) control	406.5	173-817.2	211.5	85-374
p-value	0.128‡		0.486‡	

Min: Minimum; Max: Maximum; SF: Synovial fluid; COMP: Cartilage oligomeric matrix protein; ‡ Mann Whitney U test; * Significant if p<0.05; KOA: Knee osteoarthritis.

with cartilage turnover. The renal clearance of serum COMP is another possible explanation to those findings.

Some studies have concluded that serum COMP levels vary between sexes and among different ethnicities.[6,24] Indeed, COMP levels may vary in biologic fluids, due to several factors. Therefore, for a correct interpretation of changes in levels of molecular biomarkers, it is important to evaluate other factors that may influence such variation. Our results have shown a significant difference when comparing SF COMP levels among patients and controls, mainly in the female group. A possible explanation to these findings is that female patients were significantly older than female controls and affected males, along with a higher sample size in females compared to males. Moreover, age was correlated to SF and serum COMP levels.

In addition, Vilim et al.[25] found that serum COMP levels were correlated with age, synovitis, and an interaction of synovitis and OA severity. In our study, SF COMP was positively correlated with age, daytime sampling, and severity of disease, while serum COMP was positively correlated with age and negatively with severity of disease.

Daytime variation is also an important issue to be considered as the influence of associated activity may modify levels of biomarkers. It has been reported that serum COMP levels remain constant during normal daytime activities (between 8 am and 9 pm) and it is not necessary

Table 4. Comparison between synovial fluid, serum levels of cartilage oligomeric matrix protein, and different Kellgren-Lawrence grades

	Mild (n=14)		Moderate (n=50)		Severe (n=41)		
	Median	Min-Max	Median	Min-Max	Median	Min-Max	*p*
Synovial fluid COMP (ng/mL)	325.5	50-1549	765.5	85-2420	891.5	165-2480	0.012*†
	Mild (n=13)		Moderate (n=41)		Severe (n=21)		
	Median	Min-Max	Median	Min-Max	Median	Min-Max	*p*
Serum COMP (ng/mL)	296	32-2542	445	65-2230	195	18-1581	0.121†

Min: Minimum; Max: Maximum; COMP: Cartilage oligomeric matrix protein; † Kruskal-Wallis test; * Significant if p<0.05.

Table 5. Correlation analysis of synovial fluid and serum cartilage oligomeric matrix protein levels

Parameter	SF COMP (ng/mL)	*p*	Serum COMP (ng/mL)	*p*
Daytime variation	0.179	0.014*†	0.041	0.310
Daytime variation (KOA)	0.230	0.009**†	0.032	0.393
Daytime variation (controls)	-0.227	0.065	-0.080	0.245
Age	0.266	0.001**†	0.179	0.013*†
K/L grades	0.223	0.011*†	-0.200	0.043*†
Serum COMP (ng/mL)	0.212	0.035*†		
Serum COMP (ng/mL) KOA	0.232	0.043*†		

SF: Synovial fluid; COMP: Cartilage oligomeric matrix protein; KOA: Knee osteoarthritis; K/L: Kellgren-Lawrence grades of severity; † Spearman correlation; * Significant if $p<0.05$; ** Significant if $p<0.01$.

to standardize the time of serum sampling.[26] Andersson et al.[27] reported that levels of serum COMP may be affected by exercise, especially during the first 30 minutes. Therefore, serum samples for COMP analysis should be drawn after at least 30 minutes of rest. However, the authors concluded that changes in serum levels of COMP are minor and do not compromise the utility of serum COMP as a biomarker. Although authors have demonstrated daytime variation in some related biomarkers in serum and urine,[28] we did not find a modification in serum COMP levels. However, the importance of diurnal variation of COMP levels in SF has not been fully addressed in the literature. In our study, only SF showed a significant increase in COMP levels after 12 pm when comparing groups (mainly in the KOA group), highlighting the importance to consider daytime variation of COMP levels in this biologic fluid to avoid false diagnosis.

Moreover, levels of COMP in SF were increased according to the severity of disease. Also, we found a correlation in SF and diurnal variation (particularly in the KOA group). This modification in SF levels of COMP was possibly due to an increase of activities after 12 pm.

To our knowledge, this is the first study in a Mexican population that compares and correlates SF and serum COMP levels with other important variables such as age, sex, severity of disease, and daytime sampling. We do not underestimate the value of serum sampling. Conversely, we consider that if possible, both biologic fluids should be considered for analysis of biomarkers, including COMP.

Although small size and low correlation indexes may be limitations of this study, we tried to overcome these by recruiting and sampling patients and controls under same conditions and diagnostic criteria. These results may suggest a potential relationship between COMP levels and primary KOA. However, we cannot strongly ensure that COMP is a totally reliable tool for diagnosis of KOA due to the variable nature of serum and SF COMP levels. In addition, an important step in the validation process for OA biomarkers is the knowledge of the variations in their levels in different biologic fluids under different circumstances to contribute to diagnosis, prognosis, preventive medicine, and new drug development for OA. Whenever possible, serum, urine, and SF should be considered for analysis of biomarkers in the study of OA. We believe that a multicentric study with a much larger sample size will be helpful to increase the certainty of these findings.

Acknowledgments

We would like to thank to administrative personnel of the Faculty of Medicine, Torreon, Mexico, for their invaluable logistical and administrative support. This study was funded by the Faculty of Medicine, Torreon, Universidad Autonoma de Coahuila, Mexico (P/PROFOCIE-2014-05MSIJ0010R-12 to RDA) and Instituto de Ciencia y Medicina Genomica, Torreon, Mexico.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

This study was funded by the Faculty of Medicine Torreon, Autonomous University of Coahuila, Mexico (P/PROFOCIE-2014-05MSIJ0010R-12 to RDA) and Genomic Medicine Institute, Torreon, Mexico.

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