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ORIGINAL RESEARCH

Comparison of the level of serum cartilage oligomeric matrix protein (COMP) with radiological severity of knee osteoarthritis in Maharashtrian population: A case-control study

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Abstract

Background: Osteoarthritis (OA) is a common joint disease. The Kellgren-Lawrence (KL) classification is used to assess knee OA severity through radiographic images. Monitoring OA can also be done by measuring biological markers of cartilage degradation. Studies suggest that cartilage oligomeric matrix protein (COMP) levels increase with the severity of cartilage damage.This study is plan to examine the level of serum cartilage oligomeric matrix protein and compare it with the severity of kneeosteoarthritisbased onthe KL grading scale.

Methodology:50 primary knee osteoarthritis patients and 50 controls aged 40 and above underwent radiographic assessment (K-L grading) based on the American classification of rheumatology. The serum COMP level is estimated for all subjects by Enzyme-linked immunosorbent assay.

Results: The mean of serum COMP (ng/ml) is 237.11 ±177.61 in the patient group, whichis significantly higher than the mean COMPof the control group, 149.78 ±108.01, with p= 0.004. The mean of Serum COMP levels (ng/ml) are measured between control and different grades shows statistically significant difference. Sub-group analysis showed a significant difference in mean COMP levels between the control group and Grades 3 and 4.

Conclusion: In the present study,we found that serum COMP levels can effectively distinguish individuals with knee osteoarthritis (OA) from those without OA. Additionally, COMP levels are significantly higher in advanced OA stages compared to normal and early-stage OA, indicating the serum level of COMP can be used todiagnose normal and diseased individuals andto assess different grades of severity of disease.

Keywords: ACR, Cartilageoligomericmatrixprotein,KLgrading, KneeOsteoarthritis

Introduction:

Osteoarthritis (OA) is the most common degenerative joint disease, primarily affecting the knee, a major weight-bearing joint. OA affects not only cartilage but also the synovium, ligaments, tendons, muscles, subchondral bone, and adipose tissue.[1]The disease develops slowly over many years, leading to the gradual breakdown of joint cartilage and changes in the bone. This results in joint dysfunction. The disease mechanism includes a combination of biochemical and cellular changes in the joint tissues that cause structural changes over the years.[2]These structural changesare diagnosed based onsymptoms, which are usually confirmed bya plain radiograph. However, radiography is insensitive for early diagnosis and monitoring of disease progression because by the time OA is diagnosed by x-ray,it has progressed further and caused irreversible damage to joints.[3,4]Another imaging method like MRI may be useful for early diagnosis and monitoring of OA but the costs and availability limit theirapplication for routineradiographicuse.[5]Therefore, researchers have

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focused on developing disease-specific biomarkers. However, progress in OA biomarker development has faced many challenges due to the disease's unknown exact cause and its heterogeneous nature.[6] To assess the severity of OAearlier biomarkers of joint cartilage damage are needed.During the process of cartilage matrix turnover, cartilage matrix fragments, and various macromolecules are released into the synovial fluid, blood, and urine which can be useful for early diagnosis of OA.[7]One of the byproducts of cartilage metabolism is cartilage oligomeric matrix protein (COMP). It is a 524-kD pentameric glycoprotein belongs to the thrombospondin family. COMP is a cartilage marker and is considered important for extracellular matrix stability.[8,9] COMP is found mainly in cartilage, and recent studies have demonstrated that COMP expression can also be expressed in other structures such as the ligaments, menisci, tendons, and synovial membrane.[10,11]Previous studies showthe role of cartilage oligomeric matrix protein (COMP) in initiating and progressing knee OA disease.[12,13] Even Singh et al[14]show serum COMP can be used to examine different grades of severity of OA disease and differentiate between normal and diseased individuals. Very few studies have been reported in the Asian population, so the present study aims to comparethe severity of knee OA disease with the serum level of cartilage oligomeric matrix proteins(COMP) in the Maharashtrian population.

Material and Methods:

Study Design: This case control study is done at the Department of Biochemistry in association with Department of Orthopaedics of tertiary care hospital, Pune.

Inclusion and Exclusion Criteria: Inclusion criteria are newly diagnosed primary knee osteoarthritis patient aged 40 years and above. Exclusion criteria included secondary knee osteoarthritis, other knee joint diseases, chronic illnesses (renal, hepatic, or malignant conditions), and any systemic disease affecting the joints.

Selection of participants: After approval from the institutional ethical committee, 100 participants are selected, including 50 patients with primary knee osteoarthritis and 50 healthy controls, aged 40 years and above. Patients are enrolled from the orthopaedics outpatient Department of a tertiary care hospital. All participants have been provided written informed consent. Selection follows the American College of Rheumatology (ACR) clinical criteria for knee osteoarthritis. Healthy controls are volunteers or first-degree relatives of patients, aged 40 years and above, with no clinical or radiological signs of arthritis, following the same exclusion criteria as the patient group.

Data Collection and Analysis: All participants underwent a thorough assessment, including medical history, clinical examination, and knee X-rays to evaluate structural damage. Body Mass Index (BMI) is recorded. Standardized anteroposterior weight-bearing radiographs of both knee joints are taken and classified using the Kellgren and Lawrence grading system (Grade 1 to Grade 4).[9] A 5 mL morning venous blood sample is collected from each participant, centrifuged at 3000 rpm for 15–20 minutes, and the supernatant is stored at -20ºC for further analysis. Serum cartilage oligomeric matrix protein (COMP) levels are measured using a competitive Enzyme-Linked Immunosorbent Assay (Human Cartilage Oligomeric Matrix Protein, COMP GENLISA™ ELISA, KBH1486, Krishgen Biosystem, Maharashtra, India). Data is collected and entered in Microsoft excel version 13 and analysed statistically using IBM SPSS version 21.0. For categorical variables frequency and percentage of the data is obtained. For Continuous variable Mean and Standard Deviation is obtained. For comparison between the Groups Students Independent t test is applied. For comparison of the Disease severity and Biomarkers Analysis of Variance ANOVA with Post Hoc Tukey's is applied. All the statistical tests are applied keeping confidence interval at 95% and ($p<0.05$) is statistically significant.

Results:

This study includes 100 subjects, consisting of 50 patients and 50 controls. The demographic data and comparison of serum COMP levelsin both groupsunder the study are shown in Table 1. In the patient group, there are 10 males and 40 females and in the control group, there are 22 males and 28 females.The mean ageis 51.68 ± 5.68 in the patient group,whichis significantly higher than the mean age of the control group 48.42 ±5.11with p= 0.0002. The mean BMI is 26.51 ±4.31kg/m^2 in the patient group is significantly higher than the mean BMI of the control group 24.98 ±4.01 kg/m^2 with p= 0.05. The mean COMP (ng/ml)is 237.11 ±177.61 in the patient group is significantly higher than the mean COMP (ng/ml) of the control group 149.78 ±108.01 with p= 0.004.Mean of age, BMI, and serum COMP(ng/ml) are statistically significant in both study groups.

Table 1: Demographic characteristic and Serum cartilage oligomeric matrix protein (COMP) in both groups.

Demographic Data (N=100)	Range	Control (N=50)	Patient (N=50)	p-value
Age(year)	40-87	48.42 ±5.11	51.68 ± 5.68	0.0002*
Male (%)	32%	22(44.0%)	10(20.0%)	0.37
Female(%)	68%	28(56.0%)	40(80.0%)	

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BMI(kg/m^2)	15-35	24.98 ±4.01	26.51 ±4.31	0.05*
Serum COMP(ng/ml)	10.4 ± 699.61	149.78 ±108.01	237.11 ±177.61	0.004*

N: Sample size; SD: Standard deviation, p-value * < 0.05 is statistically significant, COMP -Cartilage oligomeric matrix proteins, ng/ml- nanogram per milliliter

Patient distribution according to K-L grade by radiograph

On radiographic assessment, the number of patients with different K-L grades is shown as Grade 1 (8%), Grade 2 (36%), Grade 3 (30%), and Grade 4(26%)in Table 2.

Table 2: Distribution of patients according to KL grading scale

		Patients (N=50)
K-L grading	**Grade 1**	4 (8%)
	Grade 2	18 (36%)
	Grade 3	15 (30%)
	Grade 4	13 (26%)

N: Sample size; KL grading scale as Grade 1, Grade 2, Grade 3, Grade 4

Comparison of Serum COMP levels and different radiographic grading of OA severity

The Mean level of serum COMP(ng/ml) in control is (149.79 ± 109.12) as compared to Grade 1 patients (156.03 ± 84.21), Grade 2 (170.72 ± 121.03), Grade 3 (277.20 ± 220.97) and Grade 4(315.04 ± 182.62) with statistically significant difference (P< 0.001)is shown in Table 3.

Table 3: Comparison of the COMP (ng/ml) between disease severity (x-ray grading)

	N	**Mean**	**Std. Deviation**	**Std. Error**	**95% Confidence Interval for Mean**		**Minimum**	**Maximum**	**F**	**P Value**
					Lower Bound	**Upper Bound**				
Normal	50.00	149.79	109.12	15.43	118.78	180.80	10.40	410.10	5.089	.001*
Grade 1	4.00	156.03	84.21	42.10	2.04	270.02	24.56	211.12		
Grade 2	18.00	170.72	121.03	28.53	110.54	230.91	22.40	376.60		
Grade 3	15.00	277.20	220.97	57.05	154.83	399.57	12.23	699.61		
Grade 4	13.00	315.04	182.62	50.65	204.68	425.39	40.35	591.85		

N: Sample size; p-value * < 0.05 is statistically significant; Severity of disease according to KL grading scale as Grade 1,Grade 2,Grade 3,Grade 4.

Further sub-group analysis by Tukey HSD showed a significant mean difference in COMP levels (ng/ml) between the control group and Grade 3 (-127.405, p = 0.026) and Grade 4 (-165.247, p = 0.003). No significant differences are found between other groups as shown in Table 4.

Table 4: Pairwise Comparison of the COMP (ng/ml) between Disease Severity

Multiple Comparisons						
Dependent Variable: COMP (ng/ml)						
Tukey HSD						
(I) X Ray Grading	**(J) X Ray Grading**	**Mean Difference (I-J)**	**Std. Error**	**P Value**	**95% Confidence Interval**	
					Lower Bound	**Upper Bound**
Normal	Grade 1	13.75980	74.20646	1.000	-192.5983	220.1179
	Grade 2	-20.93409	39.25482	.984	-130.0964	88.2283
	Grade 3	-127.40553	42.04224	.026*	-244.3193	-10.4917
	Grade 4	-165.24712	44.46041	.003*	-288.8855	-41.6088
Grade 1	Grade 2	-34.69389	78.94142	.992	-254.2193	184.8315
	Grade 3	-141.16533	80.36390	.405	-364.6465	82.3158
	Grade 4	-179.00692	81.65497	.192	-406.0783	48.0645
Grade 2	Grade 3	-106.47144	49.92694	.215	-245.3115	32.3686
	Grade 4	-144.31303	51.97958	.051	-288.8612	.2351
Grade 3	Grade 4	-37.84159	54.11548	.956	-188.3294	112.6462

The severity of disease according to the K-L grading scale as Grade 1, Grade 2, Grade 3, Grade 4, p-value * < 0.05 is statistically significant

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Discussion:

The traditional way of diagnosis of KOA is based on clinical presentation and radiological assessment (K-L grade). By the time knee osteoarthritis (KOA) is clinically diagnosed, joint tissue degeneration is already advanced. Therefore, research now focuses on early detection using biochemical markers of cartilage metabolism in serum and synovial fluid. One such marker of cartilage degradation is serum cartilage oligomeric matrix protein (COMP).[16]

In the current study, the mean age in the control is 48.42 ±5.11, and in the patients mean age is 51.68 ± 5.68 showinga statistical difference(p=0.002). Mean BMIis 24.98 ±4.01 kg/m^2 in the control group,and the mean BMI of the patient group is 26.51 ±4.31kg/m^2 with p= 0.05 statistically significant. Several studies show that age and overweight are two primary risk factors for knee osteoarthritis (OA) due to their combined impact on joint structure and function.[17-20] As people age, the ability of cartilage to repair itself decreases, leading to thinning and loss of cartilage over time. This makes the knee joint more susceptible to damage. Excess body weight significantly rise the mechanical and metabolic burden on the knee joint. Adipose tissue secretes pro-inflammatory cytokines that can lead to joint inflammation and cartilage degradation, exacerbating OA progression.

In this study, the mean serum COMP level (ng/ml) is 149.78 ±108.01 in the control group and 237.11 ± 177.61 in patients with knee osteoarthritis. The difference in serum COMP levels between patients and controls is statistically significant (p = 0.004), indicating that serum COMP can effectively differentiate between healthy and diseased knees. Previous studies showsimilar findings where the level of serum COMP can easily differentiate between normal and KOA patients.[21-24]Increased levels of serum COMP in patients with knee osteoarthritis (KOA) compared to healthy controls are primarily due to increased cartilage degradation and turnover linked with the disease. In knee osteoarthritis (KOA), cartilage degradation releases COMP into the bloodstream, increasing its level in the serum.

In the present study among patientsgroup Grade 1is (8%),Grade 2 (36%),Grade 3 (30%),and Grade 4 (26%).Serum COMP (ng/ml) level in control is (149.79±109.12),Grade 1 (156.03 ±84.21), Grade 2(170.72 ±121.03), Grade 3(277.2±220.97), Grade 4(315.04 ±182.62) arestatistically significant difference(p=0.001).The mean serum COMP shows a progressive increase with the increasein the severity of knee osteoarthritis disease.Several researchers have pointed outthe increase in level of serum COMP in patientswith different OA grading.[16,22,25-26]As KOA severity progresses, the breakdown of cartilage intensifies, leading to a greater release of COMP into the bloodstream.

Further pairwise comparison in the present study shows the level of serum COMP with disease severity depicteda significant mean difference between the control group and Grade 3 (-127.405, p = 0.026) and Grade 4(-165.247, p = 0.003).No significant difference is found between the other pairs,indicating that serum COMP levels are higher in the higher grades compared to the normal and grade 1 groups. Similar results were shown by elevated levels of serum Cartilage Oligomeric Matrix Protein (COMP),which are associated with the progression of knee osteoarthritis (KOA).[27,28] As the disease advances from early stages (Grades1 and 2) to more severe stages (Grades 3 and 4), increased cartilage degradation leads to higher serum COMP concentrations.

Conclusion:

The study found a significant increase in serum COMP levels in knee osteoarthritis (OA) patients compared to healthy controls. This suggests that serum COMP may help distinguish knee OA patients from healthy individuals. As the disease progressed, serum COMP levels were notably higher in advanced OA (Grade 3 and Grade 4) than in early OA (Grade 1 and Grade 2) compared to normal subjects. A larger prospective study is needed to confirm these findings in the Indian population.

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Conflict of Interest

There is no conflict of interest regarding the publication of this paper.

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Ethical Information

The study is ethically approved by Ethical committee on human research of BJ Government Medical College and Sassoon General Hospital, Pune.

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