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Cartilage oligomeric matrix protein (COMP) and hyaluronic acid (HA): diagnostic biomarkers of knee osteoarthritis

Abstract

Introduction: Osteoarthritis of knee is diagnosed on clinical features, functional and radiological evaluation. More recently biochemical markers are used to diagnose the condition in early stage, to assess the disease progression and efficacy of treatment.

Aims & Objectives: The aim of the study is to assess role of serum Cartilage oligomeric matrix protein (COMP) and serum Hyaluronic acid (HA) levels as diagnostic biomarker and burden of disease biomarker in primary knee osteoarthritis.

Materials and Methods: Radiographic assessment (K-L grading) and functional assessment (WOMAC score) was done for 100 cases and 50 control subjects. Serum COMP and HA levels were estimated for all the subjects.

Results: Mean HA levels in mild cases was 14.07+7.04 ng/ml, in moderate cases was 38.28±41.34 ng/ml and in severe cases was 148.41+133.06 ng/ml ($p<0.001$). Mean COMP levels in mild cases was 606.08 ±105.27 ng/dl, in moderate cases it was 702.44±133.16 ng/dl and in severe cases it was 898.24 ±82.09 ng/dl ($p<0.001$). HA levels show good discriminant ability of between cases and control (sensitivity: 95.0%, specificity: 90.0%), between mild and moderate case (sensitivity: 87.6%, specificity: 86.0%) and between moderate and severe cases (sensitivity: 92.3 %, specificity: 93.1%). COMP show excellent discriminant ability between cases and controls (sensitivity: 98%, specificity: 98.0%), between mild and moderate cases (sensitivity: 92.9%, specificity: 93.2%) and in between moderate and severe cases (sensitivity: 100%, specificity: 97.7 %). COMP estimation shows higher sensitivity, specificity and accuracy as compared to HA as diagnostic and burden of disease biomarker.

Conclusion: COMP estimation shows higher sensitivity, specificity and accuracy as compared to HA as diagnostic and burden of disease biomarker.

Keywords: biomarkers, osteoarthritis, COMP, HA, KOA

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Abbreviations: COMP, cartilage oligomeric matrix protein; HA, hyaluronic acid; OA, osteoarthritis; KOA, knee osteoarthritis; ELISA, enzyme linked immuno-sorbent assay; ROC, receiver operator curve; SPSS: statistical package for social sciences

Introduction

Osteoarthritis (OA), leads to considerable morbidity and disability in elderly.[1] The condition is diagnosed basically on clinical presentation and radiographic findings. By the time changes are visible on radiographs the disease is fairly advanced. Radiographic changes are apparent only after a year or two, but changes in biomarker levels are apparent within a few months.[2] Biomarkers are used to diagnose the condition in early stage, to assess the disease progression and efficacy of treatment. Serum cartilage oligomeric matrix protein (COMP) and serum Hyaluronic acid (HA) are the two diagnostic biomarkers which are most often used.[3,4] Only few studies are found in literature of comparing the sensitivity and specificity of COMP and HA. The aim of this study is to assess the role of COMP (biochemical marker for cartilage degradation) and HA (biochemical marker for synovial inflammation) in early diagnosis of knee osteoarthritis (KOA).

Materials and methods

The study was conducted in the out-patient department of a tertiary care centre during a period of 2 years. Clearance from ethical and research committee of the institution was taken. An Informed and written consent was taken from all those included in the study. Patients aged 40 years or more reporting to us with complaints of non-traumatic knee pain fitting into the clinical criteria of American college of rheumatology were included in this study. All those with

a. Secondary osteoarthritis,
b. Current medications for treatment of osteoarthritis,
c. Hepatic, renal and malignant disease,
d. Any other disease affecting knee joint,
e. Lactating/pregnant females,
f. Involvement in heavy physical activity,
g. Substance abuse was excluded from the study.

Controls were selected from, preferably, the first degree relatives of the cases with no signs and symptoms of knee osteoarthritis and above 40 years of age.

All subjects were asked to fill the WOMAC questionnaire and were subjected to weight bearing knee radiography. The blood samples were tested for serum levels of Hyaluronic acid (HA) and

cartilage oligomeric matrix protein (COMP) by enzyme linked immuno-sorbent assay (ELISA). Disease severity was graded as per K-L grades and the Cases group were grouped as mild grade (K-L Grade II), moderate grade (K-L grade III) and severe grade (K-L grade IV) of the disease. Subjects having K-L grade I but having signs and symptoms of the disease were included in Case Group as mild cases whereas subjects with K-L grade I with no complaint pertaining to the disease were included in Control Group. A part of the data of this study was reported by us earlier.[5] The data was analyzed by SPSS (Statistical Package for Social Sciences) Version 16.0 Statistical Analysis Software.

Results

There were 100 subjects (34 males and 66 females) in the Case Group while Control Group had 50 subjects (16 males and 34 females). Male to female ratio was 1:2. The average age in the study in Case Group was 51.28±7.93 years and in Control Group was 46.08±4.81 years ($p<0.001$). All cases except 3 had a bilateral knee joint involvement. Both male and female subjects of Case group had a higher serum COMP levels and serum HA levels than in Control Group in subjects of same gender ($p<0.001$). But within the groups there was no statistical difference in levels of HA and COMP between genders ($p>0.05$) (Table 1). The BMI of Case Group (21.22±2.25 kg/m^2) and Control Group (21.20±2.08 kg/m^2) was statistically similar ($p=0.438$). Serum levels of COMP and HA increased insignificantly with increased BMI in both Control Group and Case Group ($p>0.050$).

Control Group (50 Cases) included 12 cases having K-L Grade I but was asymptomatic for knee osteoarthritis (KOA). In Case Group (100 cases) 44 were graded as mild cases, 43 as moderate cases and 13 cases as having severe grade of disease. There were 5 cases with K-L grade I but symptomatic for KOA, hence included as mild cases. WOMAC score of Control Group ranged from 0-32.3 (17.19±7.18) and in Case Group it ranged from 15.6 - 92.7 (55.66±17.01). HA levels of Control Group ranged from 0.1-9.0(3.46±2.46) ng/ml and in Case Group from 3.5-429.7(41.94±68.79) ng/ml. COMP levels in Control Group ranged from 390.5 to 578.4 (475.99±46.48) ng/dl and from 508.5 to 1477.3 (858.52±224.10) ng/dl in Case Group (Table 2).

Mean HA levels in mild cases (K-L grade I and II) was 14.07±7.04 ng/ml, in moderate cases (K-L grade III) was 38.28±41.34 ng/ml and in severe cases (K-L grade IV) was 148.41±133.06 ng/ml and this difference was statistically significant ($p<0.001$). Mean COMP levels in mild cases was 606.08±105.27 ng/dl, in moderate cases it was 702.44±133.16 ng/dl and in severe cases it was 898.24 ±82.09 ng/dl and again this difference was significant ($p<0.001$) (Table 3).

Pearson's correlation coefficient of HA level and COMP level with Age, WOMAC score and K-L grade was calculated. The results are shown in Table 4.

Receiver operator curve (ROC) analysis was done for HA levels and COMP levels for evaluating their discriminate ability between Control group and Case group, and between mild, moderate and severe grades. The results are shown in Table 5.

Discussion

The diagnosis of knee osteoarthritis is traditionally based upon clinical presentation, functional evaluation (WOMAC score) and radiological evaluation (K-L Grade). Joint tissue degeneration is already advanced by the time clinical diagnosis is made hence the research focus has shifted to diagnose this condition at the early stage of the disease. Biochemical markers of cartilage and synovial tissue metabolites estimation in serum or synovial fluid give an indication for early diagnosis. HA and COMP are two such biomarker. We aimed to find out the association of serum values these two biochemical markers in disease initiation and progression. This is the first study done in India.

Analysis of our results shows that there is no gender bias between males and females in either HA levels or COMP levels. In Case group males had a higher COMP values and in Control Group females had a higher COMP values but these differences were not statistically significant ($p=0.256$, $p=0.258$). Similarly, in Case group males had a higher HA values and in Control Group females had a higher HA values but these differences were not statistically significant ($p=0.111$, $p=0.610$) (Table 1). Significantly higher mean serum HA levels have been reported in men, but data of our study does not support that.[5] Case Group though had a higher levels of serum COMP and HA than Control Group, but the increase was not attributable to higher BMI ($p>0.05$). This has been also supported by other studies.[6–8] The similarity of BMI can be attributed to the fact that controls being the siblings or first degree relatives of the cases of nearly the same age. Positive correlation of HA levels and BMI has also been reported earlier.[9] Both males and females had higher mean HA and COMP level in Case Group when compared to subjects of same gender in Control Group ($p<0.001$) (Table 1).

HA levels, COMP levels and WOMAC scores were significantly higher ($p<0.001$) in Case Group than Control Group in our study (Table 2). These results correspond to the findings reported by many others authors.[6–11] This confirms the view that estimation of HA and COMP levels in serum can facilitate early diagnosis of knee osteoarthritis.

HA levels were found to be rising from 14.07±7.04 ng/ml in mild grade of disease severity to 148.41±133.06 ng/ml in severe grade of disease severity (Table 3). The difference in serum levels of HA in various severity grades was significant ($p<0.001$) signifying the clear cut-off points between mild, moderate and severe cases. Similar results have been reported in other studies as well.[6,8,10,12–14] Mean serum COMP levels were also higher significantly in severe grade and moderate grade than moderate grade and mild grade respectively implying increased cartilage turnover in osteoarthritis cases ($p<0.001$). Our results correlates with results reported by others.[4,9,14,15] Hence, both, serum HA levels and serum COMP levels are able to differentiate between mild, moderate and severe cases and can be used effectively to grade the disease severity. There is one study which reports that serum HA and COMP levels are elevated more in severe grade OA patients than in the less severe grade patients.[16] It has been reported that the patients with higher basic serum levels of HA have a faster radiological progression but this could not be substantiated in our study since it was not a longitudinal study.[4]

This study shows that both HA levels and COMP levels have a significant correlation with Age, WOMAC score and K-L grade. Age ($r=0.387$) and WOMAC score ($r=0.421$) shows mild association and K-L grade ($r=0.921$) shows strong association with HA levels in our study (Table 4). The association of HA levels with age has been also reported by other studies.[6,7] Similarly significant correlation of HA with K-L Grades has been reported.[6,8,10]

On evaluating the correlations of COMP levels with age, WOMAC score and K-L grade, Age ($r=0.512$) shows moderate association

while WOMAC score (r=0.796) and K-L grade (r=0.921) shows strong association. Significant correlation of serum COMP level with WOMAC score but no association with age and disease duration has been reported earlier.[17] Similarly COMP with K-L Grade correlation has been reported.[3,10,15] Present study has also shown significant strong association of both HA and COMP levels with K-L grade (r=0.921).

Table 1 Showing COMP & HA levels in cases and controls in both genders

Sex	Cases (n=100)			Controls (n=50)			Significance of difference	
	No	COMP(ng/dl) Mean(SD)	HA(ng/ml) Mean(SD)	No	COMP (ng/dl) Mean(SD)	HA (ng/ml) Mean(SD)	"t test"	"p" value
M	34	894.16 (246.2)	57.22(94.02)	16	465.1(95.0)	3.19(2.28)	6.855	<0.001
F	66	840.16 (211.4)	34.07(50.34)	34	481.1(41.8)	3.58(2.56)	9.781	<0.001
M vs F	t=1.143; p=0.256		t=1.607; p=0.111	t=1.144; p=0.258		t=0.513; p=0.610		

Table 2 Showing WOMAC score, serum COMP levels & serum HA levels in controls and cases

		Controls (n=50)	Cases (n=100)	Statistical significance
WOMAC score	Min. - Max.	0 - 32.3	15.6 - 92.7	't' - 15.307 'p' - <0.001
	Mean (SD)	17.19 (±7.18)	55.66 (±17.01)	
HA level (ng/ml)	Min. - Max	0.1 - 9.0	3.5 - 429.7	't' - 3.906 'p' - <0.001
	Mean (SD)	3.46 (±2.46)	41.94 (±68.79)	
COMP level (ng/dl)	Min. - Max.	390.5-578.4	508.5-1477.3	't' - 11.924 'p' - <0.001
	Mean (SD)	475.99 (±46.48)	858.52 (±224.10)	

Table 3 Comparison of HA levels and COMP levels in different KL-Grades

Severity Grade	n	Mean HA levels (ng/ml)				Mean COMP levels (ng/dl)			
		Mean	SD	Min	Max	Mean	SD	Min	Max
Mild	44	14.07	7.04	3.5	32.7	606.08	105.27	476.4	695.3
Moderate	43	38.28	41.34	15.7	289.5	702.44	133.16	568.34	1434.2
Severe	13	148.41	133.06	37.7	429.7	898.24	82.09	779.3	1205.3
Total	100	41.94	68.79	4.1	429.70	1292.46	124.50	1104.2	1477.3
Significance		F = 61.469; p<0.001				F = 102.011; p<0.001			

Present study shows that WOMAC scores of the patients have a significant correlation with both HA and COMP levels (Table 4). WOMAC shows only mild association (r=0.421) with HA but has strong association with COMP(r=0.796). Correlation of WOMAC scores with COMP levels has also been reported by one author.[18] But, some authors believe that COMP levels are not reflection of the clinical, functional, or radiological parameters of the patients as in very early stage of the disease patient might be asymptomatic.[11] One study has claimed absence of correlation of WOMAC scores with K-L grading of disease but correlation of WOMAC scoring with radiographic severity of disease has been reported earlier.[10,11,19]

ROC curve analysis also shows a significant correlation between control and cases and with various severity grades of disease severity indicating an excellent discriminant ability of HA estimation (Table 5). HA levels show significant diagnostic potential between cases and control (sensitivity: 95.0%, specificity: 90.0%), between mild and moderate case (sensitivity: 87.6%, specificity: 86.0%) and between moderate and severe cases (sensitivity: 92.3 %, specificity: 93.1%). Our results are in concurrence with other study which has reported a high sensitivity (89.0%) and specificity (80%) of serum HA level estimation in osteoarthritis.[19] One study has reported low sensitivity (42%) but a very high specificity (100%), but has attributed low sensitivity to small (n=60 cases and 20 controls) sample size.[10] It has been reported earlier in literature that levels of serum HA have a significant positive correlation with all radiographic grades of disease.[8]

ROC curve analysis also shows a significant correlation between COMP level and severity of disease (p<0.001). The discriminant ability of COMP between cases and normal population (controls) is excellent (sensitivity: 98%, specificity: 98.0%), between mild and moderate cases (sensitivity: 92.9%, specificity: 93.2%) and in between moderate and severe cases (sensitivity: 100%, specificity: 97.7 %) in our study (Table 5). Our study has shown higher sensitivity, specificity and accuracy of COMP level estimation than reported by other study (sensitivity: 59.0% and specificity: 50%) in osteoarthritis.[20] COMP level estimation shows higher sensitivity, specificity and accuracy as compared to HA level estimation in differentiating between normal population and cases and also between mild, moderate and severe cases of knee osteoarthritis as compared to HA estimation.

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Table 4 Showing correlation of Age, K-L grade and WOMAC score

	Pearson's correlation coefficient - "r"	"p"	Power of Correlation
Serum HA			
Age	0.387	<0.001	Mild
KL-Grade*	0.921	<0.001	Strong
WOMAC Score	0.421	<0.001	Mild
Serum COMP			
Age	0.512	<0.001	Moderate
KL-Grade*	0.921	<0.001	Strong
WOMAC-Score	0.796	<0.001	Strong

*Spearman's correlation coefficient.

Table 5 Receiver-Operator Curve analysis for evaluating the discriminator ability of HA and COMP levels

Test result variable(s)	Area	Std. Error (a)	Asymptotic Sig.(b)	Asymptotic 95% conf. interval		Sensitivity	specificity
				Lower bound	Upper bound		
A) Between cases and controls							
HA (ng/ml)	0.979	0.009	<0.001	0.962	0.997	95%	90%
COMP (ng/dl)	0.993	0.006	0.000	0.982	1.004	98%	98%
B) Between mild and moderate cases							
HA (ng/ml)	0.939	0.022	<0.001	0.896	0.982	87.6%	86%
COMP (ng/dl)	0.968	0.023	<0.001	0.923	1.012	92.9%	93.2%
C) Between moderate and severe cases							
HA (ng/ml)	0.971	0.016	<0.001	0.940	1.002	92.3%	93.1%
COMP (ng/dl)	0.986	0.011	<0.001	0.964	1.008	100%	97.7%

Conclusion

In conclusion we can say that measurements of serum HA levels and serum COMP level is of diagnostic value in differentiating between normal and diseased case and also between mild case from moderate and severe case. COMP level estimation shows higher sensitivity and specificity than HA estimation hence can be a preferred mode of investigation.

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None.

Conflicts of interest

The authors declare there are no conflicts of interest.

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