International Journal of Research in Medical Sciences
Sharma NR et al. Int J Res Med Sci. 2015 Mar;3(3):757-762
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: 10.5455/2320-6012.ijrms20150343

Research Article

Correlation between WOMAC score and hyalrunoic acid levels in knee osteoarthritis

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Received: 30 January 2015
Accepted: 8 February 2015

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ABSTRACT

Background: Osteoarthritis, a whole organ disease is diagnosed on clinical and radiological features, but plain radiographs show changes only in moderate to advanced stage of disease. Biochemical marker such as Hyaluronic Acid (HA) is used as a diagnostic tool in early stages. Hyaluronic acid level estimation has limited use in developing world due to cost and availability.
Methods: A case-control study was done to correlate role of WOMAC score and serum Hyaluronic acid levels in knee osteoarthritis. All subjects were asked to fill the WOMAC questionnaire and were subjected to knee radiography. Blood samples of all subjects were tested for serum levels of Hyaluronic acid by Enzyme Linked Immuno-Sorbent Assay (ELISA). The assessment of severity was done by K-L grading of the radiographs.
Results: The mean age in case group was 51.28 ± 7.93 years and in control group was 46.08 ± 4.81 years (P <0.001). A statistically significant difference in WOMAC score, HA levels and K-L grading of cases and controls was found (P <0.001). The results show a mild association of HA (r=0.421), moderate association of age (r=0.570), and strong association of K-L grade (r=0.910) with WOMAC scores and all these associations were highly significant (p<0.001). Multivariate analysis shows only WOMAC score >60 is independently associated with the outcome.
Conclusion: WOMAC scores are significantly associated with knee osteoarthritis and can play a crucial role in identification, gradation and management of patients with knee osteoarthritis and can be used singly along with clinical features in situations where treatment cost and assessment of serum HA levels is of concern.

Keywords: WOMAC score, Hyaluronic acid, HA levels, K-L grade, Osteoarthritis, KOA

INTRODUCTION

Osteoarthritis (OA) a well-known entity has been recently labeled as a whole organ disease since changes are also seen in periarticular muscle, ligaments, synovium, meniscus and neurosensory system alteration in these patients.[1] Morphological, biochemical, molecular, and biomechanical changes of both cells and matrix occur which leads to softening, fibrillation, ulceration, loss of articular cartilage, sclerosis and eburnation of subchondral bone, osteophytes formation, and subchondral cysts. Clinically the disease is characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion and variable degrees of inflammation without systemic effect.[2] The disease involves synovial joints and knee, hand and hip joints are most commonly involved.[3] The diagnosis is based on clinical and radiological features, but plain radiographs show changes only in moderate to advanced stage of disease.[4] In early stages, biochemical markers such as Hyaluronic Acid (HA) is used as a diagnostic tool for the investigation and evaluation of OA.[5-7] In patients

with knee OA the serological hyaluronan level correlates with the degree of synovial proliferation, osteophytes and with the degree of joint space narrowing.[8] The use of estimation of serum Hyaluronic acid levels is of limited use in developing world due to cost and availability.

Aims and objectives

To correlate WOMAC scores and serum hyaluronic acid levels in diagnosis of knee osteoarthritis.

METHODS

A case control study was conducted in the orthopaedics department of a medical college of north India over a period of 2 years. The study was approved by research cell and the ethical committee of the institute. The recruitment of the subjects (cases & controls) was done after an informed and written consent.

Inclusion criteria: All patients between 40 and 85 years of age reporting to outpatients department of orthopaedics department with complaints of non-traumatic knee pain and those who fit into the clinical criteria of American college of rheumatology were included in this study.[9]

Exclusion criteria: Patients with secondary osteoarthritis, any other pathology affecting knee joint, renal, hepatic or malignant disease, on treatment of osteoarthritis, alcohol or drug abuse, have hypersensitivity to nonsteroidal anti-inflammatory drugs, pregnant and lactating mothers or active sports person were excluded.

Adult healthy individuals with no clinical features of knee osteoarthritis, preferably first degree relatives of the cases were taken as controls. We selected 100 osteoarthritis cases and 50 normal individuals as controls to meet our objective. All subjects were asked to fill the Western Ontario and McMaster university osteoarthritis index (WOMAC) questionnaire and they were subjected to bilateral knee radiography both antero-posterior and lateral view in standing position.[10] Five milliliter whole venous blood sample of the recruited cases and controls was drawn in syringe and collected in plain vial taking all aseptic precautions. The samples were then centrifuged and serum was separated and stored in small capped vials until tested at -20°C. Samples were tested for serum levels of Hyaluronic Acid (HA) by Enzyme Linked Immuno-Sorbent Assay (ELISA) (TECO hyaluronic acid ELISA kit. Cat no. TE1017, LOT 330213, TECO medical group, Gewerbestr, Switzerland).[11] The assessment of severity was done by K-L grading of the weight bearing knee in antero-posterior view radiographs.[12] In case group the assessment of severity was done on the basis K-L grades and the group was subdivided 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 whereas subjects with K-L grade I with no complaint pertaining to disease were included in control group. Present report is a part of a study done and reported earlier by us.[13]

RESULTS

The mean age in case group was 51.28 ± 7.93 years and in Control Group was 46.08 ± 4.81 years (P <0.001). There were 66 females and 34 males in case group while control group consisted of 16 males and 34 females. Male to female ratio was 1:2 in the study. Three cases had unilateral knee joint involvement. The mean BMI of control group was 21.20 ± 2.08 kg/m^2 as compared to case group in which the mean was 21.22 ± 2.25 kg/m^2. This difference in BMI was not significant (P = 0.438).

WOMAC score of control group ranged from 0-32.3 (mean: 17.19 ± 7.18) and that of cases group ranged from 15.6-92.7 (mean: 55.66 ± 17.01). A statistically significant difference in WOMAC score of cases and controls was found (P <0.001) (Table 1). However, within case group as well as in control group, no significant difference in WOMAC scores between two genders was observed (P >0.05). HA levels of control group ranged from 0.1-9.0 ng/ml (mean: 3.46 ± 2.46) and that of case group ranged from 3.5-429.7 ng/ml (mean: 41.94 ± 68.79) and this difference in HA levels of cases and controls was significant (Table 1). Significantly higher mean HA levels were found among the cases as compared to controls (P <0.001) (Table 1). Within case group and control group, there was no significant difference in HA levels between two genders (P >0.05). In case group males (mean: 57.22 ± 94.2 ng/ml) had a higher mean HA levels than females (mean: 34.07 ± 50.34 ng/ml) (P = 0.111). On the other hand in control group mean HA level in males (3.19 ± 2.28 ng/ml) was lower than in females (3.58 ± 2.56 ng/ml) (P = 0.610).

Table 1: Comparison of WOMAC score and serum ha levels in controls and cases.

	Controls (n=50)	Cases (n=100)	Statistical significance
WOMAC score[10]			
Min.	0	15.6	't' - 15.307 P <0.001
Max.	32.3	92.7	
Mean ± SD	17.19 ± 7.18	55.66 ± 17.01	
HA level[11]			
Min.	0.1	3.5	't' - 3.906 P <0.001
Max.	9.0	429.7	
Mean ± SD	3.46 ± 2.46	41.94 ± 68.79	
K-L grade[12]			
0	38	0	X^2 - 130.116 P <0.001
I	12*	5**	
II	0	39	
III	0	43	
IV	0	13	

*Asymptomatic controls having K-L grade I;
**Symptomatic cases having K-L grade I

Correlation coefficient of WOMAC scores with age, HA levels and K-L grade was calculated. The results show a mild association of HA (r=0.421), moderate association of age (r=0.570), and strong association of K-L grade (r=0.910) with WOMAC scores and all these associations were highly significant (P <0.001) (Table 2).

WOMAC scores and HA levels were found to be higher for higher grades radiographic osteoarthritis. WOMAC scores also showed a significant increase from 41.74 in mild cases up to 73.40 in severe cases and the difference between grades was significant (P <0.001). Similarly, the mean HA levels were 14.07 ng/ml in mild cases, 38.28 ng/ml in moderate cases and 148.41 ng/ml. in severe grade of primary knee osteoarthritis (P <0.001) (Table 3).

Table 2: Showing correlation coefficient of WOMAC with K-L grade, HA levels and age.

	Correlation coefficient (Pearson's correlation coefficient - "r")	P	Power of correlation
KL-grade*	0.910	<0.001	Strong
HA	0.421	<0.001	Mild
Age	0.570	<0.001	Moderate

*Spearman's correlation coefficient

Table 3: Comparison of radiographic severity of OA with WOMAC scores and HA levels.

Severity of OA (K-L grading)	N	Mean HA levels			WOMAC scores		
		Mean ± SD	Min.	Max.	Mean ± SD	Min.	Max.
Mild (K-L grade II)	44	14.07 ± 7.04	3.5	32.7	41.74 ± 12.27	15.58	70.83
Moderate (K-L grade III)	43	38.28 ± 41.34	15.7	289.5	64.54 ± 9.04	44.79	82.29
Severe (K-L grade IV)	13	148.41 ± 133.06	37.7	429.7	73.40 ± 15.07	35.42	92.71
Total	100	41.94 ± 68.79	4.1	429.70	55.66 ± 17.01	15.6	92.7
Significance		F = 61.469; P <0.001			F=30.844; P <0.001		

Multivariate analysis was also done and it shows that between the two independent variables i.e. age >50 years and WOMAC score >60, only WOMAC score >60 is independently associated with the outcome. Age >50 years alone did not show a significant association with the dependent variable WOMAC score (Table 4).

Receiver operator curve analysis was done based on the direction of assessment. WOMAC score was evaluated for prediction of cut-off values between Control group and case group and also between mild and moderate and between moderate and severe cases. The results predicted a cut-off value of ≥24.480 (sensitivity: 96.0%; specificity: 92.0%) with an accuracy of 97.5% between control group and case group; of ≥49.48 (sensitivity: 91.2%; specificity: 98.7%) with an accuracy of 92.5% between mild and moderate cases and ≥69.27 (sensitivity: 71.4%; specificity: 81.4%) with an accuracy of 79.4% between moderate and severe cases (Table 5) (Figure 1).

Table 4: Multivariate analysis to find out association of WOMAC with different independent predictors.

Source	Type III sum of squares	Df	Mean square	F	Sig.
Corrected model	81093.319(a)	3	27031.106	9.030	<0.001
Intercept	122902.776	1	122902.776	41.058	<0.001
Age >50	2031.925	1	2031.925	0.679	0.411
WOMAC >60	47803.390	1	47803.390	15.970	<0.001
Age >50 & WOMAC >60	1861.000	1	1861.000	0.622	0.432
Error	437037.869	146	2993.410		
Total	645280.760	150			
Corrected Total	518131.188	149			

Table 5: ROC Analysis for evaluating the discriminator ability of WOMAC score.

Test result variable	Area	Std. error(a)	Asymptotic sig.(b)	Asymptotic 95% conf. interval	
				Lower bound	Upper bound
A) Between cases and controls					
WOMAC score	0.975	0.012	<0.001	0.953	0.998
B) Between mild and moderate cases					
WOMAC score	0.925	0.027	<0.001	0.873	0.978
C) Between moderate and severe cases					
WOMAC score	0.794	0.078	<0.001	0.641	0.948

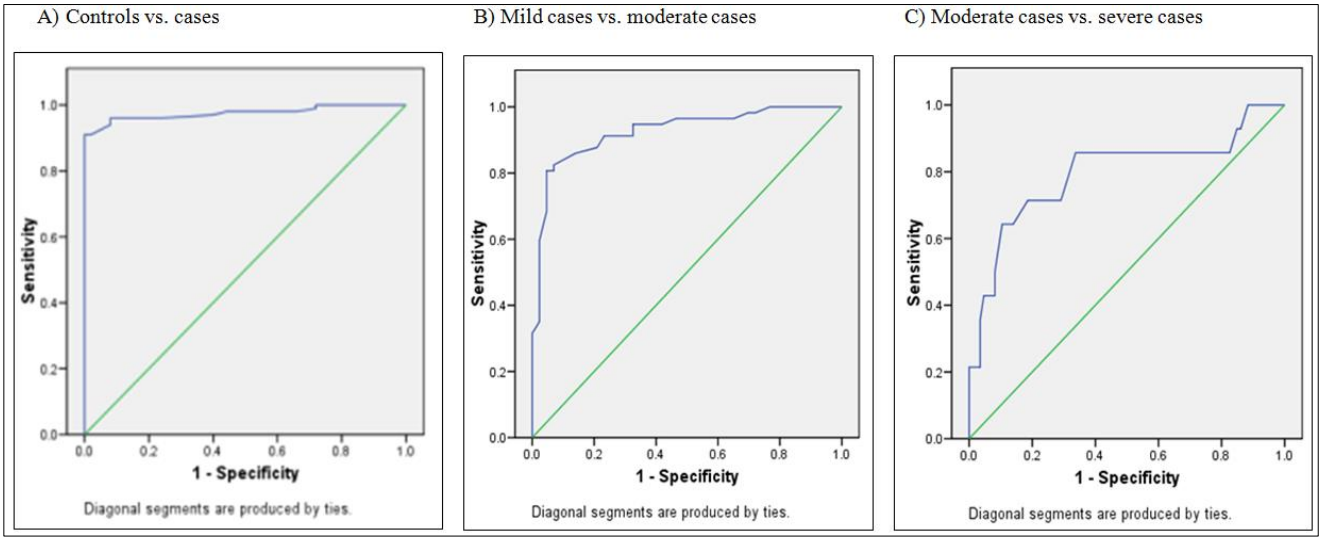

Figure 1: Receiver-operator curve analysis - severity assessment by WOMAC score.

DISCUSSION

A diagnosis of knee OA is mainly made by clinical features and radiological changes seen. Audible or palpable bony crepitus on joint movements along with history of "on and off" knee joint effusion not associated with fever usually clinches the diagnosis. Usually joint degeneration is already advanced by this time hence the research focus had shifted to a find method to diagnose this condition at an early stage of the disease. And for this very purpose biomarkers came in to vogue. Serum Hyaluronic acid level estimation though seems to be a very good and accurate laboratory test to diagnose osteoarthritis, yet it has not come in routine use in clinical practice in India. This may be because of two reasons: a) lack of free availability of the biomarker ELISA test kit and b) the high cost involved in setting up a laboratory to test serum HA levels. Hence the present study was done to correlate the radiographic criteria (K-L grading), the gold standard in diagnosis of Knee Osteoarthritis with the serum HA levels and WOMAC score.

A non-significant increment of HA levels with increasing BMI in both Case group and Control Group was seen (p >0.438). It has also been reported other studies.[8,14,15] This might be because the comparable BMI of Case group and Control group in our study as the controls were siblings or first degree relatives of the patients in the same age group. On the contrary positive correlation between HA levels and BMI has also been reported.[5]

There was no significant difference in WOMAC score (P >0.05) and HA levels (P >0.05) between males and females in either case group or control group indicating no gender bias in behavior of these tests. There are studies which show higher mean serum HA levels in men, but our study does not support that.[15]

Both WOMAC score and serum HA levels show significant association with age. Pearson's correlation coefficient of WOMAC scores with age show significant and moderate association (r=0.570, P <0.001) in this study. Similarly a statistically significant mild association of HA levels with age has been also reported by other studies.[13-15]

In our study a statistically significant difference of HA levels between case group and control group (P <0.001) was found, similar results were reported in other studies.[5,8,13-15] HA levels were found to be higher for higher grades of severity in our study (P <0.001). This again is supported by many other studies.[13,15-17]

In our study the Pearson's correlation coefficient of WOMAC score with HA shows a statistically significant association (r=0.421, P <0.001) and with K-L grade (r=0.910, P <0.001), thus implying that either of the test can be used alone or with others in diagnosing and assessing the severity of osteoarthritis (Table 2). On the contrary few studies have reported that there was no significant correlation exists between HA levels with WOMAC (P >0.05).[8,18] On univariate analysis we found that age and WOMAC scores are the two independent variables associated with HA levels but when multivariate analysis was done it shows that only WOMAC score is associated with disease severity. Multivariate analysis indicated that HA levels are directly and independently correlated with the osteoarthritis severity as measured by WOMAC scores. Correlation of WOMAC scoring with severity assessment of osteoarthritis has also been reported earlier.[19,20]

Further, the results of ROC curve analysis also shows the excellent discriminant ability of the WOMAC scores between cases and control population. ROC curve analysis predicted a WOMAC score cut-off value of ≥24.480 (sensitivity: 96.0%; specificity: 92.0%) with an accuracy of 97.5% between Control group and Case group; of ≥49.48 (sensitivity: 91.2%; specificity: 98.7%) with an accuracy of 92.5% between mild and moderate cases and ≥69.27 (sensitivity: 71.4%; specificity: 81.4%) with an accuracy of 79.4% between moderate and severe cases (Table 5) (Figure1). Hence, we believe that WOMAC scoring can be used as a diagnostic tool in cases of knee osteoarthritis. We propose a cut-off value of WOMAC scores above ≥25 as a mild severity, of ≥50 as a moderate severity and ≥70 as a severe case of knee osteoarthritis.

CONCLUSION

On the basis of our results of Pearson's correlation coefficient, multivariate analysis and ROC Curve analysis it can be concluded that WOMAC scores are significantly associated with knee osteoarthritis and are able to predict the disease severity similar to serum HA levels. Hence, WOMAC score can play a crucial role in identification, gradation and management of patients with knee osteoarthritis and can be used singly along with clinical features in situations where treatment cost and assessment of serum HA levels is of concern. We suggest corroborating these findings in different clinical settings on a larger scale.

ACKNOWLEDGEMENTS

The authors want to thank Mr. Varun for his kind support in providing statistical analysis of the data.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by research cell and the institutional ethics committee

REFERENCES

1. Jeremie S, Gabriel H, Frances B. Osteoarthritis: pathogenesis, clinical aspects and diagnosis. Eular Compend Rheum Dis. 2009;30:444-63.
2. Keuttner KE, Golderg VM. Osteoarthritic disorders. In: Keuttner KE, Golderg VM, eds. A Book. 2nd ed. Rosemont: AAOS; 1995: 95-101.
3. Mangat G, Balakrishnan C, Venkatachalam S, Joshi VR. Pattern of osteoarthritis in India: a hospital based study. J Indian Rheum Assoc. 1995;3(4):125-8.
4. Garnero P, Rousseau JC, Demas PD. Molecular basis and clinical use of biochemical marker of bone, cartilage, and synovium in joint disease. Arthritis Rheum. 2000;43:953-68.
5. Garnero P, Piperno M, Gineyts E, Christgau S, Delmas DP, Vignon E. 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. 2001;60:619-26.
6. Rousseau JC, Pierre DD. Biological markers in osteoarthritis. Nat Clinpra Rheum. 2007;3(6):346-56.
7. Fraser JR, Laurent TC, Laurent UB. Hyaluronan: its nature, distribution, functions and turnover. J Intern Med. 1997;242(1):27-33.
8. Turan Y, Bal S, Gurgan A, Topac H, Koseoglu M. Serum hyaluronan levels in patients with knee osteoarthritis. Clin Rheumatol. 2007;26(8):1293-8.
9. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. The American college of rheumatology criteria for the classification and reporting of osteoarthritis of knee. Arthritis Rheum. 1986;29:1039-49.
10. American College of Rheumatology. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), 2012. Available at: http://www.rheumatology.org/practice/clinical/clinicianresearchers/outcomes-instrumentation/WOMAC.asp.
11. BioVendor. Product data sheet. TECO hyaluronic acid ELISA kit. Cat no. TE1017, LOT 330213. TECO medical group, Gewerbestr, Switzerland, 2015. Available at: https://www.biovendor.cz/download/7180/Navod_TE1017-2.pdf
12. Petersson IF, Boegård T, Saxne T, Silman AJ, Svensson B. Radiographic osteoarthritis of the knee classified by the Ahlbäck and Kellgren & Lawrence systems for the tibiofemoral joint in people aged 35-54 years with chronic knee pain. Ann Rheum Dis. 1997;56:493-6.
13. Singh S, Kumar D, Sharma NR. Role of hyaluronic acid in early diagnosis of knee osteoarthritis. J Clin Diagn Res. 2014;8(12):LC04-7.
14. Elliott AL, Kraus VB, Luta G, Stabler T, Renner JB, Woodard J, et al. Serum hyaluronan levels and radiographic knee and hip osteoarthritis in African

Americans and Caucasians in the Johnston County Osteoarthritis Project. Arthritis Rheum. 2005;52(1):105-11.
15. Davis CR, Karl J, Granell R, Kirwan JR, Fasham J, Johansen J, et al. Can biochemical markers serve as surrogates for imaging in knee osteoarthritis? Arthritis Rheum. 2007;56(12):4038-47.
16. Kaneko H, Ishijima M, Doi T, Futami I, Liu L, Sadatsuki R, et al. Reference intervals of serum hyaluronic acid corresponding to the radiographic severity of knee osteoarthritis in women. BMC Musculoskel Disord. 2013;14:34.
17. Golightly YM, Marshall SW, Kraus VB, Renner JB, Villaveces A, Casteel C, et al. Biomarkers of incident radiographic knee osteoarthritis: do they vary by chronic knee symptoms? Arthritis Rheum. 2011;63(8):2276-83.
18. Darwish AF, Hosny S. Abdel-Ghany, Yasser M. El-Sherbini. Diagnostic and prognostic value of some biochemical markers in early knee osteoarthritis. Egypt Rheumatol. 2012;34:1-8.
19. Singh S, Khanna V. Correlation between clinical and radiological grading of osteoarthritis. Sci J Med Sci. 2014;3(5):320-4.
20. Kersten P, White PJ, Tennant A. The visual analogue WOMAC 3.0 scale - internal validity and responsiveness of VAS version. BMC Musculoskel Disord. 2010;11:80.

DOI: 10.5455/2320-6012.ijrms20150343
Cite this article as: Sharma NR, Singh S, Kumar D, Kumar S. Correlation between WOMAC score and hyalrunoic acid levels in knee osteoarthritis. Int J Res Med Sci 2015;3:757-62.