DOI: https://doi.org/10.54393/pjhs.v6i4.1880

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 04 (April 2025)

Original Article

OPEN ACCESS

Relationship of Systemic Inflammatory Markers and Body Mass Index with Primary Osteoarthritis

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ARTICLE INFO

Keywords:
Osteoarthritis, Inflammatory Markers, Body Mass Index, Radiographic Progression

How to Cite:
Gulzar, R., Mahmud, T. E. H., Rasheed, A., Hafeez, U., & Ahmed, F. (2025). Relationship of Systemic Inflammatory Markers and Body Mass Index with Primary Osteoarthritis: Inflammatory Markers and Body Mass Index in Osteoarthritis.Pakistan Journal of Health Sciences, 6(4), 111-115. https://doi.org/10.54393/pjhs.v6i4.1880

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Received date: 8th June, 2024
Revised date: 12th January, 2025
Acceptance date: 13th April, 2025
Published date: 30th April, 2025

ABSTRACT

Osteoarthritis (OA) is degenerative disorder which involves synovial inflammation. Erythrocyte sedimentation rate, Body mass index and C-reactive protein are commonly used markers to determine infection or inflammation. **Objective:** To measure the level of raised levels of erythrocyte sedimentation rate and C-reactive protein in primary osteoarthritis and to identify the association of body mass index with osteoarthritis in Pakistani population. **Methods:** This descriptive cross-sectional study was conducted at Department of Rheumatology, Shaikh Zayed Hospital, Lahore, Pakistan from July 2021 to April 2022. A total of 216 patients were enrolled. All patients over the age of 30 years with primary osteoarthritis were included. Association of C-reactive protein and erythrocyte sedimentation rate with OA grade and highest score in case of multiple joints were checked by using chi-square test and odds ratio. **Results:** Most were females and large group of individuals were overweight or obese. Mean BMI was 29.50 ± 4.94 kg/m^2.The radiographic progression of OA was seen more in women compared to men for Grade 4 OA.The systemic inflammatory markers erythrocyte sedimentation rate and C-reactive protein were plotted against the Grade of OA and it was found that erythrocyte sedimentation rate was elevated in (n=118) most individuals however C-reactive protein was normal in the majority (n=196). Radiographic advancement of OA with the rise of these acute phase reactants was not significant i.e. p-value was 0.804 for erythrocyte sedimentation rate and 0.497 for C-reactive protein. **Conclusion:** There was no significant correlation between raised inflammatory markers and radiographic progression of osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) is common degenerative disease of joints and is a frequent cause of morbidity. OA of the knee is one of the most common forms of arthritis in synovial joints and it is usually present in the elderly. Synovial inflammation and wear and tear process in joints is thought to play a dominant role in the development of joint pain, swelling and cartilage destruction [1]. Patients can have primary or secondary osteoarthritis based on absence or presence of any prior medical condition respectively [2]. However Primary OA can be associated with risk factors like advancing age, female gender, body mass index (BMI) >30, body habitus, muscle weakness, and joint injury from sports or as an occupational hazard. Predisposing medical conditions include trauma, congenital joint disorders, inflammatory and infectious arthritis, avascular necrosis, connective tissue disorders and metabolic problems are common causes of secondary OA [3]. Body mass index is found to be associated with development and progression of knee osteoarthritis [4]. Obese (BMI >30) individuals have higher risk of developing knee OA than people with normal weight (BMI <25) [5, 6]. Aiming at weight reduction and physical rehabilitation as a non-pharmacological therapy for management of OA has been proven effective in many studies [7, 8]. The diagnosis of OA almost always involves clinical and radiographic assessment of joint damage, which is useful only after the disease process has been underway for several months. The radiological evaluation gives grading and level of osteoarthritis [9]. When it comes to diagnosing and tracking inflammatory disorders including infections, autoimmune diseases, and

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malignancies, primary care physicians frequently turn to inflammatory indicators like Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP). The slowest of these inflammatory measures, erythrocyte sedimentation rate is the millimeters that erythrocytes settle in one hour of anticoagulated whole blood. Because it increases at a faster rate than the other two tests when inflammation occurs, C-reactive protein is commonly believed to be the best indicator of infection severity [10]. The pathophysiology of OA involves loss of cartilage due to lack of functional chondrocytes and decrease remodelling of subchondral bone which in turn starts the inflammatory cascade to bring about the cartilage breakdown [11]. Cytokines, chemokines, and mixed matrix metalloproteinase are some of the molecules that play a role in the regulation of the joint anabolism and catabolism process [12] Because of the apparent absence of systemic inflammation in OA, acute-phase response proteins (APPs) have not been as extensively studied in OA as they have been in RA. There are several recent reports that ESR and CRP are slightly elevated in OA. In a study done by Mitsuru Hanada in 2016 ESR and high sensitivity CRP concentrations were higher in patients with knee osteoarthritis than in patients without knee OA due to inflammation of the involved joint [13]. This study determined the direct association of BMI with the development and progression of OA in Pakistani population. Whether the systemic inflammatory markers rise in response to the severity of OA was also observed through this cross sectional survey.

METHODS

This descriptive cross sectional study was conducted among outdoor patients visiting rheumatology clinic Shaikh Zayed Hospital, Lahore, Pakistan from 1st July 2020 to 30th April 2021 with an ethical approval Ref No. SZMC/IRB/0088/2021, obtained from Institutional Review Board (IRB) prior to data collection. Informed written consent was taken from patients for detailed demographics.Patients with age >30 and having primary osteoarthritis were included.Patients with secondary OA and acute infection were excluded.Non probability consecutive technique was used for sampling. Sample size (216) was calculated by using the formula, n=(Z^2 * p*(1-p))/ E^2 with 95% confidence interval (Z=1.96), 5% margin of error (E=0.05) and an estimated prevalence of osteoarthritis of 6% (p=0.06) [17].A well designed questionnaire filled by researcher about their basic demographic profile, height and weight measurement for calculation of BMI and running investigations like X-ray of involved joints, ESR and CRP for study population.The ESR was measured with Westergren method[14] where ESR< 15 is normal 15-50 is elevated, >50 is high.The CRP was calculated with latex agglutination test.The CRP <6 is normal, 6-12 is elevated and >12 is high. The height and weight was taken for every patient and Body mass index (BMI) calculated. The patients are categorized as underweight: <19, Normal: 19-24, Overweight: 25-29, Obese: 30-35, severely obese: 35-40, morbidly obese: >40. Patients with history of fever, cough, sputum, abdominal disturbance or urinary burning or pus in urine were excluded. The patients of primary osteoarthritis i.e. not secondary to a disease were graded based on their X-ray findings of the involved joints and must not have any clinical features of other rheumatic diseases the grading on X ray of involved joint was done as per Kellgren Lawrence classification of OA Grade 1 (doubtful joint space narrowing and possible osteophyte lipping), Grade 2 (minimal; definite osteophytes and possible joint space narrowing), Grade 3 (moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends) and Grade 4 (large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends). [15, 16] The highest grade of OA in all joints was documented if many joints were involved. Data analysis was carried out using SPSS version 25.0. Data for age, BMI, ESR and CRP levels were described using mean ± SD for normally distributed variables and Median (IQR) otherwise data for OA score, Gender, no. of joints involved, status of joint, obesity status and raised ESR CRP levels are defined by using frequency and percentages. To determine whether there is a correlation between ESR CRP and advanced OA, multinomial logistic regression was employed. P value <0.05 was considered significant.

RESULTS

The mean age was 54.23 ± 11.21 years with 50 (23.14%) male and 166 (76.85%) female participants. The mean height was 161.07 ± 7.99 centimetres and weight was 76.32 ± 12.36 kilograms. Mean BMI was 29.50 ± 4.94 kg/m^2 (Table 1).

Table 1: Descriptive Statistics of the Patients (n=216)

Variables	Mean ± SD
Age (Years)	54.23 ± 11.21
Height (cm)	161.07 ± 7.99
Wight (Kg)	76.32 ± 12.36
BMI	29.50 ± 4.94
ESR	25.83 ± 20.16
CRP	5.55 ± 1.93

Grade 3 OA was most common, 48.1% radiological presentation followed by Grade OA 35.2%. Of the studied individuals; 2 joints were commonly affected with OA and nearly all times, it was knee joints. More than half 116 (53.7%) of the subjects were homemaker. Most of the study population 104 (48.1%) fell into overweight category (BMI 25-30) (Table 2).

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Table 2: Demographic Information of the Patients(n=216)

Variables	Frequency (%)
Age (Years)	
30-39	24 (11.1%)
40-49	46 (21.3%)
50-59	82 (38%)
>59	64 (2.6%)
Body Mass Index (Kg/m^2)	
<19 (Underweight	2 (0.9%)
19-24 (Normal Weight)	32 (14.8%)
25-29 (Overweight)	104 (48.1%)
30-35 (Obese)	54 (25%)
36-40 (Severe Obese)	18 (8.3%)
>40 (Morbidly Obese)	6 (2.8%)
Osteoarthritis Radiological Grading	
Grade 2	76 (5.2%)
Grade 3	104 (48.1%)
Grade 4	36 (16.7%)
Number of Joints involved	
One	8 (3.7%)
Two	158 (73.1%)
Three	6 (2.8%)
Four	20 (9.3%)
Many	24 (11.1%)
Occupation	
Housewife	116 (53.7%)
Retired	18 (8.3%)
Govt. Job	33 (15.3%)

The joint involvement was seen in different type of joint like small, large or spinal joints. Knees 178 (82.4%) were mostly involved in large joints and wrists 11 (5.1%) among small joints. Only 2 patients had involvement of cervical joints among spinal joints (Table 3).

Table 3: Distribution of Joints of the Patients

Osteoarthritis	Site of Joint Involvement	Frequency (%)
Large Joints	Knee (Unilateral/Bilateral)	178 (82.4%)
	Other (Ankle, Hip, Shoulder, Elbow)	14 (6.5%)
Small Joints	Wrists (Unilateral/Bilateral)	11 (5.1%)
	Other (PIPs, MCPs, CMP, MTP Inter tarsal and Inter carpal)	11 (5.1%)
Spinal Joints	Cervical spine joints	2 (0.9%)
	Other (Lumbar, sacral, thoracic, Sacroiliac)	-

There were no patients with Grade 1 Osteoarthritis.The radiographic progression of OA was seen more in women compared to men for Grade 4 OA i.e. 30 (18%) and 6 (12%) respectively. However, for grade 2 and 3 OA; 18 (36%) and 26 (52%) were men whereas 58 (34%) and 78 (47%) were women.The BMI categories were linked to grades of OA only to find that 2 people with BMI<18 had Grade 3 OA. Among morbidly obese individuals 4 (66.7%) and 2 (33.3%) had grade 2 and grade 3 OA respectively.Most of the sample population was overweight (n=104) with 42 (40.4%), 46 (44.2%) and 16 (15.4%) having grade 2, 3 and 4 OA (Table 4).

Table 4: Association of BMI with the Grade of OA

Grade	Under Weight Frequency (%)	Normal Weight Frequency (%)	Over Weight Frequency (%)	Obese Frequency (%)	Severe Obese Frequency (%)	Morbidly Obese Frequency (%)	Total Frequency (%)	χ^2(p)
Grade 2	-	12 (37.5%)	42 (40.4%)	16 (2.6%)	6 (33.35%)	-	76 (35.2%)	14.1 (0.169)
Grade 3	2 (100%)	12 (37.5%)	46 (44.2%)	28 (51%)	12 (66.75)	4 (66.7%)	104 (48.1%)	
Grade 4	-	8 (25%)	16 (15.4%)	10 (18.5%)	-	2 (33.3%)	36 (16.7%)	
Total	2 (100%)	32 (100%)	104 (100%)	54 (100%)	18 (100%)	6 (100%)	216 (100%)	

The systemic inflammatory markers ESR and CRP were plotted against the Grade of OA and it was found that ESR was elevated in 118 most individuals however CRP was normal in the majority (n=196). CRP was not found to be high in this study population.The correlation of radiographic advancement of OA with the rise of these acute phase reactants was not significant i.e. p-value was 0.804 for ESR and 0.497 for CRP (Table 5).

Table 5: Association of ESR and CRP with the Grade of OA

Grade	Low Frequency (%)	Elevated Frequency (%)	High Frequency (%)	Total Frequency (%)	χ^2(p)
ESR					
Grade 2	30 (37.5%)	38 (32.2%)	8 (44.4%)	76 (35.2%)	1.625 (0.804)
Grade 3	36 (45%)	60 (50.8%)	8 (44.4%)	104 (48.1%)	
Grade 4	14 (17.5%)	20 (16.0%)	2 (11.1%)	36 (16.7%)	
Total	80 (100%)	118 (100%)	18 (100%)	216 (100%)	
CRP					
Grade-2	70 (35.7%)	6 (30.0%)	0 (0%)	76 (35.2%)	1.39 (0.479)
Grade-3	92 (46.9%)	12 (60.0%)	0 (0%)	104 (48.1%)	
Grade-4	34 (17.3%)	34 (17.3%)	0 (0%)	10.0 (16.7%)	
Total	196 (100%)	20 (100%)	0 (0%)	216 (100%)	

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The odds ratio calculated for ESR and CRP to the higher grades of OA i.e. grade 3 and grade 4 only to reveal statistically insignificant (p-value>0.05) correlation between the two (Table 6).

Table 6: Multinomial Logistic Regression CRP and ESR for Grades

Grade	Level	B	P	Odd Ratio
2	ESR	0.007	0.551	1.007 (0.84-1.03)
	CRP	-0.025	0.833	0.975 (0.770-1.235)
3	ESR	0.006	0.572	1.006 (0.985-1.029)
	CRP	0.084	0.457	1.088 (0.872-1.357)

DISCUSSION

According to the present study, the overweight individuals suffered from higher grade of OA in comparison to the normal weight population. The higher the BMI more the radiological progression is expected which is the reason weight loss and diet restrictions are suitable non pharmacological measures are important steps in management. Osteoarthritis of joint is a result of local inflammatory cytokines and adipokines triggered by inflammatory cells. These cytokines and inflammatory cells are taken up by lymphatic system in the joint and eventually enter the peripheral circulation. Here, they can be detected within the blood and is a possible cause of raised inflammatory markers in OA [17]. In previous study, 1235 patients, (or 56% female, mean age 65) had radiographs and inflammatory markers measured. Among the 729 individuals included in the study, 179 had knee OA and 694 had hand OA, indicating radiographic OA in at least one joint. No inflammatory marker was significantly associated with radiological OA. We found no indication that the presence of radiographic OA was associated with any inflammatory marker [18]. One further study looked at the correlation between inflammatory indicators and functional capacity in the elderly with osteoarthritis. There was no statistically significant correlation between physical and disease state and blood C-reactive protein levels. Consistent with previous research, this conclusion applies to 67 individuals diagnosed with knee OA [19]. Another study found that early OA was associated with higher levels of mononuclear cell infiltration and upregulation of inflammatory mediators as compared to late OA [20]. A case control study with 120 patients, 60 with osteoarthritis of knee while rest with no signs of osteoarthritis was done in 2016. The hematological markers to study inflammatory basis of idiopathic osteoarthritis of knee suggested that ESR (erythrocyte sedimentation rate) of more than 20 mm/hour and CRP (C-reactive protein) was positive in 83.3% and13.3% patients respectively. The control group has ESR less than 30 mm/hour and CRP was (<3 µg/ml). In the control group RF and ANA were similar to the normal population. The study indicates that ESR and CRP collectively can serve as surrogate markers in idiopathic osteoarthritis of knee [21]. There were few limitations to the study including the small sample size. Also, many confounders like ongoing infection and anemia affect the acute inflammatory markers which could not all be excluded, an error in the radiological based grading of OA by physician or radiologist. It is still a conflict between the two theories so further studies seem mandatory to establish the link between the inflammatory markers and osteoarthritis and the association of BMI with the development of Primary Osteoarthritis in current population.

CONCLUSIONS

There is direct link of being overweight to development of Osteoarthritis. ESR can be elevated in individuals irrespective of stage of Osteoarthritis. There is no clear co-relation with raised inflammatory markers to progression of osteoarthritis. The patients with Osteoarthritis and high acute phase reactants should be investigated more thoroughly to rule out other significant autoimmune disorders.

Authors Contribution

Conceptualization: RG
Methodology: AR, UH
Formal analysis: RG
Writing, review and editing: RG, THM
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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