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STUDY OF THE RELATIONSHIP BETWEEN SERUM CRP VALUES AND THE SEVERITY OF KNEE OSTEOARTHRITIS (KOA)

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ABSTRACT

Osteoarthritis (OA) is a joint disease that occurs primarily in the elderly and is characterized by the destruction of articular cartilage, enlargement of the bone at its edges, subchondral sclerosis, and a group of biochemical and morphological changes at the level of the synovial membrane and the joint capsule. The study aims to study the role of CRP as a prognostic indicator of the severity of the disease and study the relationship between knee Osteoarthritis and: age, gender, and body mass index. A cross-sectional study was conducted that included 103 patients with primary knee Osteoarthritis, aged between 40-80 years. A comprehensive clinical examination was performed for active and passive movements of the joints, BMI, WOMAC, VAS calculation, a simple radiograph of the knees anteroposteriorly and in the standing position, and the KL score was determined. Reactive protein - C(CRP) was performed for all patients, and values less than 5 mg/L were considered negative. The current study showed that: About 70% of the patients were older than 50 years, and the percentage of females was 76.7%. Pain was the most frequently observed clinical symptom. CRP, BMI and stage III are independent risk factors for predicting disease severity, with a positive association between CRP and WOMAC, especially pain. ROC curve analysis showed that the area under the curve (AUC) of CRP levels for predicting injury severity is 0.88 within the confidence interval [0.79-0.94] with P<0.001, and the standard point is 6.9 having the best sensitivity of 89% and specificity of 94%.

KEYWORDS: Knee Osteoarthritis, CRP, WOMAC index, KL score, VAS.

INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disease that occurs basically in the elderly and is characterized by the destruction of articular cartilage, osteophytes, subchondral sclerosis, and a synovium inflammation. The Changes in the advanced stages of osteoarthritis are softening, ulceration, and focal fragmentation of the articular cartilage in additional to occur Synovitis. The most symptoms are Pain and stiffness are.[1] Previously, it was thought that OA is occur in cartilage. It is considered primary in the absence of other reason. Currently, it is considered a disease that affects all components of the joint.[2] Prognostic factors for the severity of knee osteoarthritis are: age, gender, and body mass index.[2]

The most important cytokines that are high in the serum of knee osteoarthritis patients are: IL-1, IL-6, and TNF and they are also high in the synovial fluid in the knee.[3] These cytokines Cartilage cells stimulate the production of proteases, and one of the most important proteases is collagenase, which dissolves collagen in cartilage and stimulates a group of processes, the result of which is the hydration of the cartilage, its cracking, and ultimately its degeneration.[4] Therefore, it is considered an inflammatory disease due to inflammatory mediators that are released from tissues exposed to mechanical stress and inflammatory effects, and these inflammatory mediators are considered future targets for modern treatment.[4]

CRP (C-reactive protein)

It is a polypeptide with a pentagonal structure, meaning it consists of five subunits, and each subunit consists of 206 amino acids linked to each other. It was first discovered in 1930 by Tailet and Francis.[5] It is produced by a group of cells, the most important of which are hepatic cells, which produce it and its levels increase in serum in inflammatory conditions.

The hepatic cells produce it through stimulation by cytokines, the most important of which are: interleukin-6 (IL-6), interleukin-B1, (IL-1B) and tumor necrosis factor TNF-a. Other cells produce it other than liver cells, but

in low concentrations, such as renal cells, nerve cells, and lymphocytes.[6]

2.1. CRP and Inflammation

Serum CRP levels rise as a type of the body's response to tissue damage, infection, inflammatory conditions, or immune conditions in high numbers, but recently studies have directed to studying its role in particular in inflammation. CRP is considered the most important inflammatory mediator, which rises in the inflammatory response in the acute phase. Some studies indicate that CRP binds to damaged membranes and increases the inflammatory response. The role of CRP is clear in the inflammatory episode through its activation of the C1q compound on the path to complement, and as a result, it leads to the occurrence of the opsonization process that helps in completing the inflammatory response.[6]

2.2. The role of CRP as a biochemical marker in osteoarthritis

Osteoarthritis was previously known as a degenerative disease in which an inflammatory event does not occur, and this is what was described in the past, but now, in recent studies, an important role of inflammation has been shown in the development of the disease, its progression, and its poor prognosis, as well as increasing the severity of the clinical symptoms. It was later shown that the synovial membrane is involved in the pathogenesis of osteoarthritis.[7] Osteoarthritis occurs in the endothelial layer of the synovial membrane with an increase in the number of inflammatory cells, especially at the level of macrophages. This is what we must understand well: the role of inflammation of the synovial membrane and the role of inflammatory mediators released by the bone and articular cartilage into the joint cavity and the subsequent complete inflammatory response. The most important of these Inflammatory mediators are cytokines, which stimulate the liver, especially Kupffer cells, to synthesize acute phase proteins, the most important of which is CRP.[8] Therefore, we can say that measuring the level of serum CRP is an indirect indicator of the activity and degree of activation of inflammatory cytokines.[9] Studies have shown that serum CRP levels in OA patients are clearly increased.

MATERIALS AND METHODS

Our cross-sectional study was conducted at a medical college hospital at Tishreen University in Syria between October 2021 to October 2022. We included 103 patients with symptomatic KOA, according to the American College of Rheumatology (ACR) Radiology and Clinical Criteria for KOA. who were attending rheumatology clinics and departments. We excluded Patients who have the following: acute and chronic inflammatory joint diseases (rheumatoid disease, crystal arthritis...), Infections, Tumors, Autoimmune diseases, history of knee trauma, surgical intervention, or history of joint replacement, Antibiotic treatment, Liver failure. Demographic characteristics of patients were recorded, including sex, age and BMI. A comprehensive clinical examination of active and passive joint movements was performed. The radiographic diagnosis of knee OA determined by KL scale was chosen by the World Health Organization. The KL grading was used for classifying OA according to radiographic signs. The radiographic features are: joint space narrowing, subchondral sclerosis, osteophytes and subchondral cysts. KL scale is graded from 1 to 4.[11] Knee functions were assessed by WOMAC index that is consisting of 24 parameters that include pain (score range: 0–20), stiffness (score range: 0–8), and functional impairment (score range: 0–68). The VAS was used to evaluate the intensity of pain in the knee joint. Inflammatory Reactive Protein-C (CRP) was performed for all patients, and values less than 5 mg/L were considered negative.

3.1. Statistical Analysis

Analysis was done using the Statistical Package for Social Sciences (SPSS version 20). The quantitative variables were described as mean and standard deviation (SD), and the qualitative variables were described as frequencies and proportions. Sociodemographic and diagnostic variables were shown in both numbers and percentages. The relation between the prevalence of musculoskeletal complications of the hand and various variables was assessed using the Chi-square test. Multiple logistic regression analysis was performed to evaluate the multivariate association between hand complications and accompanying factors. Separate logistic regression models were created for each diabetic hand variable. A P- P-value < 0.05 was considered statistically significant.

3.2. Ethical Consideration

All patients were provided complete and clear informed consent after a discussion about the study. This study was performed following the Declaration of Helsinki.

RESULTS

The research sample included 103 patients who visited the Department and Clinic of Musculoskeletal Diseases at Tishreen University Hospital in Latakia during the time period 2021-2022, who suffer from knee arthrosis and met the inclusion criteria in the research. Ages ranged from 40 to 80 years, and the average age was 56.1±10.3 years.

Table 1: Distribution of study population according to gender.

Gender	Number	Percentage (%)
Male	24	23.3%
Female	79	76.7%
Total	103	100%

Table 2: Distribution of study population according to age groups.

Age groups (years)	Number	Percentage (%)
40-49	30	29.1%
50-59	32	31.1%
60-69	28	27.2%
≤70	13	12.2%
Total	103	100%

Table 3: Mean BMI and variables related to injury severity assessment in patients with knee osteoarthritis.

Variable	Minimum	The highest rate	Mean ± SD
BMI	18.5	33.4	3±26.8
WOMAC	9	90	22.3±36.6
Pain	1	20	6.7±8
Stiffness	0	6	1.3±2.7
Difficulty	5	65	16.1±25.9
VAS	3	10	2±6.2

Table 4: Distribution of study population according to BMI.

BMI	Number	Percentage (%)
Normal	20	19.5%
Overweight	67	65%
Obesity	16	15.5%
Total	103	100%

Table 5: Distribution of study population according to Clinical symptoms.

Clinical symptom	Number	Percentage (%)
Pain	63	61.2%
Stiffness	21	20.4%
Difficulty	19	18.4%
Total	103	100%

Table 6: Distribution of study population according to Kellgren.

Stage	Number	Percentage (%)
0	4	3.9%
I	55	53.4%
II	30	29.1%
III	12	11.7%
IV	2	1.9%
Total	103	100%

Table 7: Distribution of study population according to WOMAC.

WOMAC	Number	Percentage (%)
Mild	40	38.8%
Intermediate	35	34%
Severe	13	12.6%
Very severe	15	14.6%
Total	103	100%

Table 8: Demographic Variables According to The Womac Clinical Assessment Index.

Variable		WOMAC		P-value
		Mild to intermediate 75	Severe to very sever 25	
Gender	**Male**	20(26.7%)	4(14.3%)	0.1
	Female	55(73.3%)	24(85.7%)	
Age		57±10.3	53.6±10.3	0.1
BMI (kg/m2)		26±2.7	28.8±2.8	<0.001
BMI	**Normal**	16(21.3%)	4(14.3%)	<0.001
	Overweight	55(73.3%)	12(42.9%)	
	Obesity	4(5.3%)	12(42.9%)	

Table 9: Distribution according to laboratory and radiological variables and the WOMAC clinical assessment index.

Variable		WOMAC		P-Value
		Mild to intermediate 75	Severe to very sever 25	
CRP		3.87±1.56	7.96±1.84	<0.001
VAS		5.26±2.02	7.42±1.78	0.006
Kellegren Classification:	**0**	4(5,3%)	0(0%)	0.002
	I	47(62,7%)	8(28,6%)	
	II	20(23,7%)	10(35,7%)	
	III	3(4%)	9(32,1%)	
	IV	1(1,3%)	1(3,5%)	

Table 10: Distribution According to Demographic Variables and According To Kellegren.

Variable		Kellegren					P-Value
		0 (4)	I (55)	II (30)	III (12)	IV (2)	
Gender	Male	1 (25%)	14(25.4%)	6(20%)	2(16.7%)	1(50%)	0.07
	Female	3 (75%)	41(74.6%)	24(80%)	10(83.3%)	1(50%)	
Age		52.8±11.8	57.2±12.3	56.3±10.3	54.6±10.3	50.5±13.4	0.5
BMI (kg/m2)		23.7±3.1	25.9±0.98	26.6±2.9	28.3±3.3	26.05±0.21	<0.001
BMI	Normal	3 (75%)	16(29.1%)	3(10%)	2(16.7%)	0(0%)	0.08
	Overweight	1 (25%)	30(54.5%)	14(46.6%)	5(41.7%)	2(100%)	
	Obesity	0 (0%)	9(16.4%)	13(43.4%)	5(41.7%)	0(0%)	

Table 11: Distribution according to demographic variables and Kellegren.

Variable	OR	P-Value
Age	0.95[0.901.01]	0.09
BMI	1.47 [1.18-1.83]	0.001
CRP	3.56[2.02-6.27]	<0.001
VAS	1.32[0.77-2.25]	0.3
Kellegren classification III	4.49[1.76-8.87]	0.008

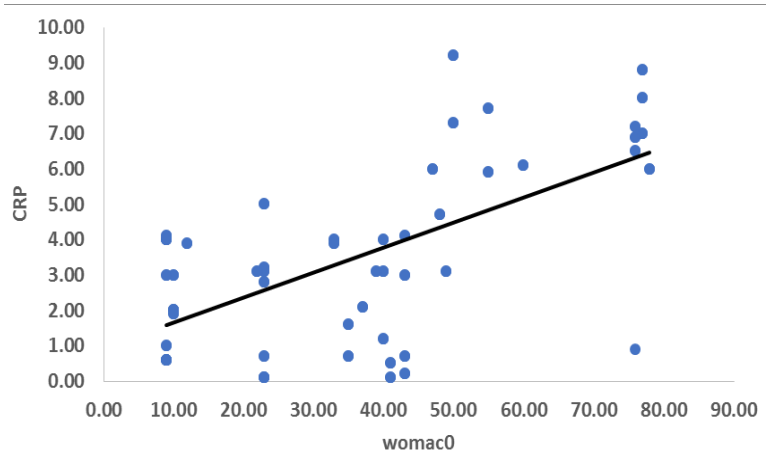

Fig. 1: Pearson Correlation between CRP and WOMAC.

The value of r: 0.62, p<0.001, and thus there is a strong positive correlation, that is, as the CRP values increase, the WOMAC score increases.

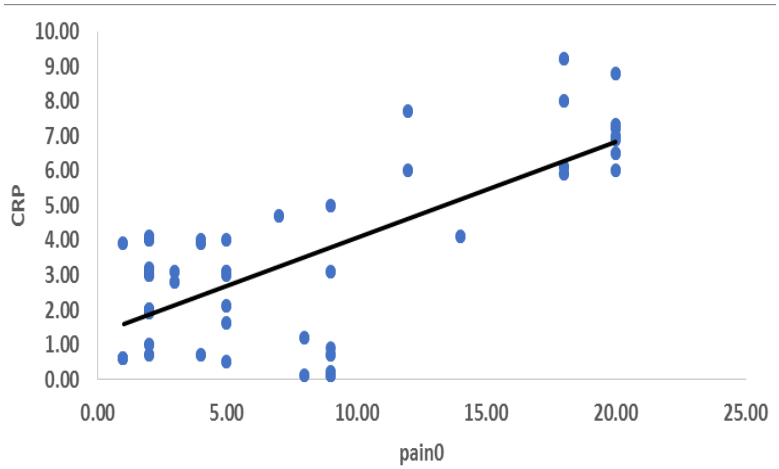

Fig. 2 Pearson Correlation between CRP and pain.

The value of r: 0.72, p<0.001, and therefore there is a strong positive correlation, that is, as the CRP values increase, the degree of pain increases.

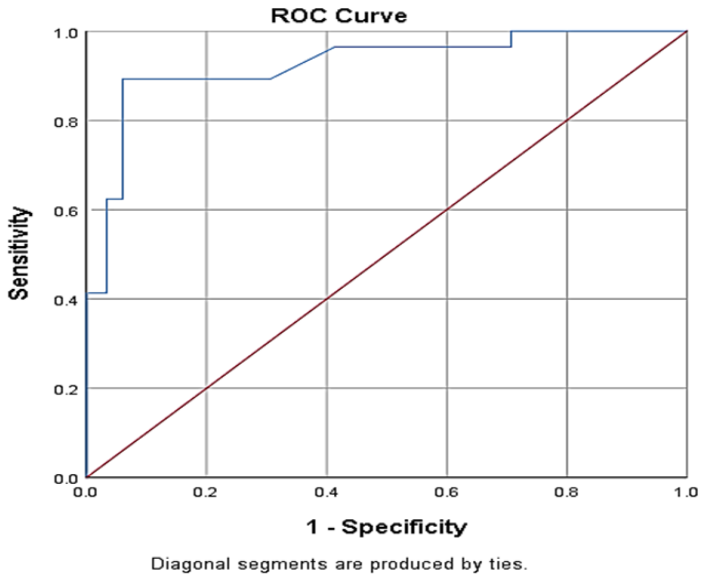

Fig. 3: ROC diagram showing the sensitivity and specificity of CRP.

ROC curve analysis showed that the area under the curve (AUC) of CRP levels for predicting injury severity is 0.88 within the confidence interval [0.79-0.94] with P<0.001, and the standard point is 6.9 having the best sensitivity of 89% and specificity of 94%.

By dividing the sample into two groups according to the new standard value of CRP and then comparing the variables according to the two new groups, we obtained the following table:

Table 12: Demographic variables according to CRP.

Variable		CRP		P-value
		77 < 7	26 ≤ 7	
Gender	Male	20(26%)	4(15.4%)	0.2
	Female	57(74%)	22(84.6%)	
Age		57±10.3	57.2±10.3	0.6
BMI (kg/m2)		26±2.7	26.2±2.7	<0.001
BMI	Normal	16(20.8%)	4(15.4%)	<0.001
	Overweight	57(74%)	10(38.5%)	
	Obesity	4(5.2%)	12(46.2%)	

Table 13: Distribution according to laboratory, radiological, and CRP variables.

Variable		CRP		P-Value
		77 < 7	26 ≤ 7	
WOMAC		26.7±15.1	65.7±12.5	<0.001
Pain		4.6±3.2	18.2±2.8	<0.001
Stiffness		2.2±0.8	4.1±1.6	<0.001
Difficulty		20±13.1	43.5±10.1	<0.001
VAS		5.54±1.98	7.25±1.87	0.002
Kellegren Classification:	0	(0%)0	(0%)0	0.001
	I	8(30.8%)	8(30.8%)	
	II	10(38.5%)	10(38.5%)	
	III	7(26.9%)	7(26.9%)	
	IV	1(3.9%)	1(3.9%)	

DISCUSSION

The current study of 103 patients with osteoarthritis of the knee joint and investigators showed inclusion criteria in the study as follows:

About 70% of the patients in the study sample are older than 50 years. It may be related to age-related changes in collagen and proteoglycans as well as to a lack of nutrients to the cartilage, as age represents an independent risk factor that exposes chondrocytes in the joint to programmed cell death and the expression level of apoptosis-inducing genes is higher in aged cartilage.[12]

The number of females was 79, or 76.7%, and the number of males was 24, or 23.3%.

This is consistent with epidemiological studies that the disease is more common in females, and also that the majority of patients are of advanced age as estrogen decreases after menopause and cartilage cells have functional receptors for estrogen. In addition, the higher percentage of body fat in females and therefore higher levels of leptin derived from fat compared to males contribute to the increased incidence.[13]

Overweight was present in about two-thirds of patients, and this can be explained by the fact that obesity increases the mechanical stress of the joints bearing the body's weight, and is an inflammatory risk factor for osteoarthritis, as it is associated with an increased level of adipose tissue-derived cytokines (systemic and intra-articular), which promote chronic low-grade inflammation in the joints. The joint.[13]

Pain was the most frequently observed clinical symptom, and this may be explained by the fact that synovitis causes increased levels of IL-6 and IL-8, which may be a factor in the pain associated with osteoarthritis.[14] This is consistent with the 2018 Bulgarian study by Stoilov et al and the 2018 Turkish study by Ozler and colleagues.[19]

The majority of patients are mild to moderate depending on clinical and radiological evaluation.

Obesity and high CRP were more frequently observed in severe forms of the disease.

The link between clinical symptoms and radiographic changes is controversial and there is no clear relationship between them, but in our study, it was found that pain is most frequent in stage III and functional disability in stage IV.

The frequency of pain at this stage can be explained by the appearance of osteophytes, the invasion of newly formed vessels and nerves into the bone with the beginning of an increase in the rate of bone turnover, the formation of blood vessels in the subchondral bone, and the invasion of articular cartilage tissue, as this process is considered another mechanism for causing pain in osteoarthritis.[14],[20],[21]

CRP, BMI and stage III are independent risk factors for predicting disease severity, with a positive correlation between CRP and WOMAC, especially pain. No significance has been determined in stage IV and this may be due to the small number of patients in this stage.

The CRP cut point of 6.9 gave the best sensitivity and specificity for predicting disease severity, and elevated CRP levels were significantly associated with the presence of:

- Obesity: This can be explained by the fact that adipose tissue actively contributes to the inflammatory cascade through secreted cytokines and adipokines. Many adipokines play the role of the main regulator in the process of bone and cartilage metabolism, and the subpatellar adipose pad acts as a local source of adipokines in the joint.[4]

In additional to the production of leptin (one of the adipokines) by osteoblasts and chondrocytes.[15] This is in contrast to the 2018 Bulgarian study, where no statistically significant differences appeared regarding BMI.[18]

- High levels of WOMAC and VAS: As a result of inflammation of the synovial membrane, which causes significant production of proteolytic enzymes, as well as hyperresponsiveness of peripheral nerve cells, changes in Hoffa's fat pad are also a possible cause of knee pain in osteoarthritis,[2],[16],[22]
- Class III of the radiological classification. This is consistent with the Chinese study in 2015 conducted by Yongato Mao et al, which showed that there was a correlation between CRP levels and radiological damage, and it was higher in class IV, but the difference here is due to the small number of patients in our study in class IV.[17]

CONCLUSION

The current study showed the following:

The standard value for CRP was 6.9, and the patients were divided into two groups, the first 7≤26 and the second 77 <7. Osteoarthritis was more frequent in older ages, females, and in the presence of obesity. Pain represented the most frequent clinical symptom. BMI, CRP and radiographic stage III represented predictive risk factors for disease severity. High CRP levels were more noticeable in obese people, with higher VAS levels, and in advanced stages of the disease according to the clinical and radiological classification.

RECOMMENDATIONS

It is recommended that CRP be calibrated in patients with osteoarthritis, as it is considered an easy-to-administer, quick-to-apply, and inexpensive indicator that reflects the pathological activity of osteoarthritis and thus contributes to determining the prognosis of the disease.

It is recommended to conduct future studies to determine the prognostic role of CRP analysis in the disease in the long term by following up patients.

It is suggested to conduct studies that include larger numbers of patients and with various joint injuries to confirm this relationship between CRP and disease severity.

Conduct future studies using highly sensitive CRP.

Conduct future studies using magnetic resonance imaging because of its great benefit in showing early changes.

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