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Association of C-reactive protein positivity among groups of patients with knee osteoarthritis in Erbil

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Abstract

Background and objective: Osteoarthritis is the most common joint disease and a leading cause of disability. Increased circulating levels of C-reactive protein have been associated with prevalent knee osteoarthritis. This study aimed to assess the association between C- reactive protein positivity in patients with knee osteoarthritis in Erbil

Methods: Data from100 participants in this case-control study were enrolled from May 1st to December 1st, 2015 in Rizgary Teaching Hospital in Erbil city. Data were divided into two groups. The cases included 50 patients (17 male and 33 female) with a mean age of 58.9 ±3.8 years and diagnosed with primary knee osteoarthritis of one or both knee joints. Controls included 50 persons (17 male and 33 female) with a mean age of 58.1 ±3.9 years without knee osteoarthritis and matched for age, sex, and body mass index. C-reactive protein qualitatively measured. Patients were radiologically assessed by Kellgren and Lawrence grading scale (grade 0-4).

Results: C-reactive protein was positive in 41 out of 50 (82%) of knee osteoarthritis patients compared to 3 out of 50 (6%) of healthy controls (P = 0.001). C- reactive protein positivity among knee osteoarthritis patients were significantly associated with body mass index, positive family history of knee osteoarthritis, duration of diseases, and Kellgren and Lawrence grade (P <0.05). No significant association was found with sex, site of knee joint involvement, and knee pain severity (P >0.05).

Conclusion: C-reactive protein positivity was significantly associated with knee osteoarthritis compared to healthy controls. Furthermore, body mass index, positive family history of knee osteoarthritis, early osteoarthritis, and Kellgren and Lawrence grade II, were significantly associated with positive C-reactive protein in knee osteoarthritis.

Keywords: Osteoarthritis; Knee osteoarthritis; C-reactive protein; Kellgren and Lawrence grade.

Introduction

Osteoarthritis (OA) is the most common form of joint disease in humans.[1] It is characterized clinically by pain and functional limitations, radiographically by osteophytes and joint space narrowing, and histopathologically by alteration in cartilage and subchondral bone integrity, and synovial inflamation.[2] Rather than one uniform disease, osteoarthritis may be a primary or secondary form of arthritis in patients with other inflammatory arthritis, such as rheumatoid arthritis.[3] All joints may be affected, but the knee is the most clinically significant site of primary OA involvement.[4] The causes of disease onset and individual variation in susceptibility and progression remain elusive. A suite of OA risk factors has been identified, including genetic variation, age, sex, obesity, reproductive status (e.g., post-menopausal) in females, mechanical stresses, leg muscle strength, and related parameters, and history of previous joint trauma. The earliest symptoms of knee osteoarthritis (KOA), are Stiffness< 30 minutes, joint pain, and swelling. In contrast to inflammatory arthritis, the pain

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of osteoarthritis is often exacerbated by activity or weight bearing and relieved by rest. Early symptoms are usually of an insidious nature and often do not correlate well with radiographic abnormalities. Later, extensive bone changes, muscle weakness, and loss of joint integrity can lead to more-dramatic joint deformity and disability.[5] The acute phase protein C-reactive protein (CRP) is an important inflammatory regulator and measurement of circulating CRP is widely used as a diagnostic tool in acute inflammatory diseases. However, CRP has shown limited value in monitoring the low, but elevated level of inflammation in OA.[6,7] CRP is produced in the liver upon acutely elevated levels of circulating pro-inflammatory cytokines, such as interleukin (IL) 6.[8] When CRP is released from the liver; it binds to its receptors and is speculated to accumulate in the inflamed tissue. Here it is gradually degraded by the increased level of proteolytical enzymes and released as fragments into the circulation.[9] Although the role of inflammation in osteoarthritis has been unclear for a long time and regard as non-inflammatory arthritis, significant progress has been made in more recent years, and studies also show that there are ongoing inflammation and synovitis that result in permanent joint damage.[10] Given this greater appreciation for synovitis in patients with OA, inflammation has now been strongly implicated in the pathogenesis of OA.[11] In many research studies have demonstrated that circulating levels of CRP, a marker of low-grade systemic inflammation, are modestly elevated in KOA and are associated with decreased cartilage volume and disease progression.[12,13] This study is the first, to our knowledge, to determine the associations between circulating inflammatory markers (CRP) in KOA patients in Erbil city, Kurdistan region, and whole Iraq. This study aimed to determine the association between CRP as inflammatory markers in patients with KOA in Erbil city.

Methods

This case-control study was conducted in the Rheumatology and Medical Rehabilitation Center in Rizgary Teaching Hospital in Erbil Governorate in Iraqi-Kurdistan region. The data was collected from May 1st to December 1st, 2015. A total of 50 patients with osteoarthritis of one or both knees (KOA), diagnosed according to revised criteria of the American College of Rheumatology (ACR) for classification of idiopathic OA of the knee,[14] were selected by a convenience method of sampling. They were compared with 50 healthy individuals as a control group and matched for age, sex, and BMI of patient's group. Their ages were 50 years and more. Patients with any of the following were excluded: other etiologies of knee joint disease such as post-traumatic and post septic arthritis, primary nodal OA of hand, secondary OA due to systemic inflammatory disease such as rheumatoid arthritis, infectious diseases, cancer, inflammatory rheumatic diseases such as rheumatoid arthritis, connective tissue diseases, gout, and others, acute coronary heart disease, metabolic disorders (such as diabetes), liver failure, renal failure, pregnancy, patients who were on drugs like oral corticosteroids, intra-articular injection, oral non-steroidal anti-inflammatory drugs (NSAID), obese patients (BMI≥30 kg/m^2). Data were collected and recorded on a specially designed questionnaire after getting verbal consent from all participants and after approval from the ethics committee of the College of Medicine at Hawler Medical University and Erbil Directorate of Health (DoH). Full history was taken from all individuals including: age, sex, site of knee OA (unilateral, bilateral), duration of disease, knee pain (pain was assessed using verbal rating scale VRS to (none, mild, moderate, severe),[15] knee stiffness <30 minutes, and crepitus, family history of knee OA, history of drug intake and

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thorough clinical examination was done for individuals in both groups. BMI was calculated by the equation BMI =weight (kg) /height (m^2), and the patients were classified afterward according to BMI into normal weight <25 kg/m^2, overweight 25-<30 kg/m^2, obese ≥30 kg/m^2. The duration of KOA was classified[16] to (very early<1 year, early between 1-3 years, late >3 years). Patients were currently on paracetamol, topical non-steroidal anti-inflammatory drugs (NSAID). Weight-bearing antero-posterior and lateral X-rays of both knees were taken for patients and controls. Patients were radiologically graded according to the Kellgren-Lawrence grading scale (KL scale) grading range between (grade 0 _ grade 4).[17] 10 ml of blood were withdrawn from the vein by VACUTAINER and collected in VACUTEST gelatin tube. Within 3 hours, the serum was separated by centrifugation using KUBOTA 5200 at 1000 rpm for 3 minutes. The sera were stored at (-30) degrees centigrade to investigate CRP by CRP latex kit (L21-CRP.v2). Statistical analysis was done by entering the data on the computer using Microsoft Excel. The statistical package for the social sciences (version 21) was used for data analysis. The results were analyzed using frequency distribution, students' independent two samples t-test and Chi square test. A *P* value of ≤0.05 was considered statistically significant.

Results

There was a non-significant statistical difference between study groups for age, BMI and sex of participants. The mean ± SD of age and BMI of cases and control group were very close to each other. The mean ± SD of age and BMI for cases were (58.9 ±3.8, 24.2±1.8 respectively) and for controls were 58.1 ±3.9 and 24.1 ± 1.9, respectively (*P* = 0.6). Most of the participants in both groups were female (66%), (*P* = 0.9). There was a significant statistical association between study groups and family history. Most cases had a positive family history (74%) in contrast to 18% of the controls (*P* = 0.001) as shown in Table 1. There was a significant statistical association between the study groups and CRP. The majority of KOA patients (82%) had positive CRP results in reverse; the majority of controls (94%) had negative CRP findings. Those with positive CRP results had greater chance to acquire KOA (OR =71.3) in contrast to negative CRP (*P* = 0.001) as shown in Table 2.

Table 1: Demographic baseline characteristics of study groups.

Characteristics	Categories	Study groups		*P* value
		Cases	Controls	
Age	Mean ± SD	58.9 ±3.8	58.1 ±3.9	0.6
BMI	Mean ± SD	24.2±1.8	24.1 ± 1.9	0.31
Sex	Male	17(34%)	17(34%)	0.9
	Female	33(66%)	33(66%)	
Family history	Positive	37(74%)	9(18%)	0.001
	Negative	13(26%)	41(82%)	

Table 2: Association between study groups and CRP positivity.

CRP	Cases (n=50)	Control (n=50)	OR	*P* value
Positive n (%)	41(82%)	3(6%)	71.3	0.001
Negative n (%)	9(18)	47(94%)		

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There was a non-significant statistical relationship between C-reactive protein and both of gender and site of KOA. Most of CRP negative and positive cases were female and had bilateral KOA (*P* >0.05). There was a significant statistical relationship between CRP and BMI and family history. The majority of the overweight patients and those with positive family history showed positive CRP results (*P* = 0.02, and 0.001, respectively). Among all factors, positive family history and overweight were associated with the highest risk of developing KOA with positive CRP, their odds ratio (OR) were 57.6 and 5.45 consequently. Negative family history and normal BMI associated with decreased risks and they were protective as shown in Table 3.

Table 3: Association between CRP and baseline characteristics of KOA.

Characteristic	Category	Total n=50	Positive CRP n=41	Negative CRP n=9	O.R	*P* value
Sex	Male	17	15 (88 %)	2 (12 %)		
	Female	33	26(78 %)	7(22 %)	2.01	0.41
BMI	Overweight	33	30(90%)	3(10 %)		
	Normal	17	11(64 %)	6(36 %)	5.45	0.02
Family history	Positive	37	36(97 %)	1(3 %)		
	Negative	13	5(38 %)	8(62%)	57.6	0.001
Site of KOA	Unilateral	15	14(93%)	1(7 %)		
	Bilateral	35	27(77 %)	8(23%)	4.14	0.17

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There was a non-significant statistical relationship between CRP positivity and degree of knee pain and drug intake by patients. In KOA patients with positive CRP had (81%) moderate knee pain, (91%) mild pain and (60%) severe knee pain (*P* = 0.31). On the other hand, 91% of CRP positive patients were on paracetamol, whereas (100%) on topical NSAID and (75%) combinations of topical NSAID and paracetamol (*P* = 0.25).There was a significant statistical association between duration of KOA with positive CRP and radiological KL grades, in which (93%) of CRP positive patients had the disease durations between 1-3 years (early OA). Also,(76%) of them less than 1 year (very early OA), few of them (33.3%) with late OA (*P* = 0.002), furthermore regarding KL grades (93%) of positive CRP patients had Grade 2 ,and (81%) they were with grade 3, in contrary (100%) negative CRP were with grade 1 and grade 4 (*P* = 0.001). The details are shown in Table 4.

Discussion

It is recognized that inflammation is a contributing factor in OA pathology.[18] Local productions of inflammatory mediators are well known to contribute to cartilage degradation and synovial cell activation in OA.[19]That synovial inflammation may be an important etiological factor in OA was supported by raised serum C reactive

Table 4: Relationship of CRP positivity and associated factors among Knee OA patients.

Variables	Categories	Total n=50	Positive CRP n=41	Negative CRP n=9	*P* value
Duration	<1 year	13	10(76 %)	3(24 %)	0.002
	1-3 years	31	29(93%)	2(7 %)	
	> 3years	6	2(33.3 %)	4(66.7 %)	
Pain	Mild	12	11(91 %)	1(9 %)	0.31
	Moderate	33	27(81%)	6(19%)	
	Severe	5	3(60 %)	2(40 %)	
Drug intake	Paracetamol	12	11 (91 %)	1(9%)	0.25
	Topical NSAID	5	5(100 %)	0(0%)	
	Paracetamol & Topical NSAID	33	25(75 %)	8(25%)	
KL	Grade 1	1	0(0 %)	1(100%)	0.001
	Grade 2	30	28(93 %)	2(7%)	
	Grade 3	16	13(81 %)	3(19%)	
	Grade 4	3	0(0%)	3(100%)	

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protein levels, which were associated with progression of OA.[16,20] In our case-control study results have demonstrated that there is a significant association between study groups and CRP, in which majority of knee OA patients group (82%) had positive CRP results in reverse; the majority of controls group had negative CRP findings. Those with positive CRP results had greater chance to acquire knee OA in contrast to negative CRP findings which had a protective effect. This is in accordance with the three studies done in USA[20-22] where they found a correlation between patients with elevated CRP and the presence of inflammatory changes in patients with KOA. They illustrated that the elevated CRP levels seen in these patients might reflect local inflammation within the joint and Interleukin 6(IL-6) is known to be the chief regulator of CRP production and may have a role in the inflammatory OA process.[23]Strong correlation between CRP levels and synovial fluid IL-6 levels in OA implicates that IL-6 not only act as a regulator of CRP in OA but also as a possible mechanistic link between elevated CRP.[23] In Sturmer et al. [24] studies they found modestly elevated in the plasma of patients with OA compared to age-matched controls, while study done by Pearle et al [22] in 2007 revealed that the mean CRP level in patients with inflammatory infiltrates was significantly higher than those without inflammation (4.7± 5.0 mg/L vs. 1.7 ± 3.6 mg/L, P = 0.003). We did not found any relation between age and positive CRP in our patients that's similar to Pearle et al.[22] studies, this is against many epidemiological studies.[25] Several studies have reported relationships between CRP and various features of KOA, in Spector et al.[26] and Sturmer et al.[24] studies a population based, cross sectional study observed increased CRP values in women with radiographically defined knee OA. In contrast, our results showed no significant relationship between C-reactive protein and sex. However, most of CRP negative and positive cases were female, in agreement with Stannus et al.[25] studies, and our results were very similar with Virgina et al.[27] studies in which 63.7% of KOA patients were female. One reasonable explanation for this difference could be due to potential geographical factors. However, there was no significant association of positive CRP and site of knee joint involvement, in agreement with another study.[24] In this study, with a tightly controlled patients group for BMI (obese patients were excluded), regression analysis demonstrated a significant relationship between CRP and BMI. Most of CRP positive knee OA patients were overweight in contrast to CRP negative patients, were the majority of them had normal BMI so overweight were associated with the highest risk of developing Knee OA with positive C-reactive protein, this finding was in consistence with Engström et al.[28] and Virginia et al.[27] In USA a study done in 2007 contrasted our finding's as they observed no association between systemic CRP (r = 0.09, P = 0.56) and BMI (r = 0.004 ,P = 0.97) in KOA patients.[22] Another interesting finding in our study was a significant association between CRP and family history. Most of CRP positive knee OA patients had positive family history, this agreed with Vonk et al.[29] reported that Micro RNAs (mi RNAs) most likely modulate cartilage metabolism through metabolic and inflammatory mechanisms in OA.[30] However, no significant association found between CRP positivity and degree of knee pain and drug intake by patients. This contrasted other studies (Miller et al.,[31] Marta et al.[32]) but agreed with Arendt et al.,[33] Sturmer et al..[22] There were highly significant associations detected in this study between duration of Knee OA and positive CRP and radiological KL grades (after were taken into account. for age, sex, and BMI. Most of CPR positive patients had the early OA with Grade II; in contrary, most of CRP negative patients had late OA with Grade IV. These results are inconsistent with findings of studies done in Denmark 2014,[33] Sweden 2003,[34]

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Ireland 2005[16] and studies in Japan 2015[35,36] revealing that high-sensitivity CRP was associated with the K/L grade and early OA, furthermore increased serum CRP in early phases of OA suggests the presence of low-grade inflammation, which supports a pathophysiological role of inflammation at early stages of the disease process. But this was not observed by Sturmer et al.[24] and Sowers et al.[20] in which CRP was mostly related with late KOA and grade IV. Our study has several potential limitations. First our sample size is relatively small. Secondly, we measured CRP for positivity and negativity by qualitative measurement without measuring the level of CRP in which sometimes there is increasing in low level of CRP which is more significant as a marker for local inflammation. The key strength of the present study lie in the measurements of inflammatory markers (CRP) in KOA patient and comparing it with healthy controls with very closely matched for age, sex and BMI, another strength of this study is the exclusion of the confounding factors correlate with positive CRP in KOA like obesity, advanced age, and cardiovascular comorbidity.

Conclusion

Positive CRP is associated with knee osteoarthritis patients in Erbil city. In patients with KOA relative factor like BMI, positive family history of knee OA, early duration, and KL grade II were significantly associated with positive CRP. These data raise the possibility that systemic inflammation may play a role in the pathogenesis of knee OA. Other findings show no association between positive CRP and age, the severity of knee pain in most of the patients. Longitudinal follow-up studies employing quantify measurement for CRP level, synovial fluid analysis for IL6, TNF-alpha, arthroscopy and sensitive imaging modalities will be required to determine if the intensity of synovitis and local inflammation plays a critical part in progressive joint damage and pathogenesis of KOA with their relation with CRP level.

Conflicts of interest

The authors report no conflicts of interest.

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