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Chemerin Level in the Serum of Knee Osteoarthritis Patients and its Relation to Disease Severity

Fadia A. Abd Elghany[1], Eman S. Algharabawy[2], Aziza B. Shehatah[*1], Ibrahim T. Abd Elal[1]
Departments of [1]Rheumatology and Rehabilitation, [2] Medical Microbiology and Immunology, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author:** Aziza B. Shehatah, **E-mail:** azizabakr636@gmail.com

ABSTRACT
Background: Chemerin is a new adipokine that has been linked to joint inflammation and degeneration. It has a pro-inflammatory effect and modulates immune system activity.
Objective: The aim of the work was to assess the chemerin role in diagnosis as well as monitoring of severity of the disease in knee osteoarthritis (KOA) patients.
Patients and Methods: This case-control study included a total of 60 subjects, 30 of them had knee osteoarthritis (KOA) and 30 served as controls, attending at Department of Rheumatology, Rehabilitation, and Physical Medicine, Zagazig University Hospitals. Chemerin level was measured for all the subjects by ELISA technique. In osteoarthritis group, knee osteoarthritis was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).
Results: Statistically insignificant differences in age, BMI, as well as sex were found among the 2 studied groups. Serum chemerin levels in patients with KOA were statistically significantly higher than in controls, with a p-value of 0.001. Serum chemerin had no statistically significant correlations to age, BMI, or length of illness, while WOMAC scores, CRP, as well as ESR were strongly associated with serum chemerin levels.
Conclusion: It could be concluded that serum chemerin can be utilized as an inflammatory marker in KOA patients and it can be considered as a therapeutic target. Further studies are recommended to assess its levels in other types of OA, and other rheumatic diseases.
Keywords: Chemerin, Knee osteoarthritis, Disease severity

INTRODUCTION

As a systemic, chronic, and debilitating illness of the joints, osteoarthritis (OA) affects many people all over the world [(1)].

A progressive degradation of the articular cartilage, as well as alterations in the subchondral bone, and to a lesser extent, the synovium are hallmarks of primary and secondary osteoarthritis [(2)].

As a rule, knee pain is the most prevalent site of injury, followed by hand and hip pain [(3)]. Osteoarthritis affects around eighteen percent of women and ten percent of men aged more than sixty and is the 10th major cause of disability [(4)]. Metabolic variables, gender, age, trauma as well as obesity are all risk factors for osteoarthritis. OA's pathophysiology hasn't been outlined in any detail [(5)].

Chondrocytes, endothelial cells, synoviocytes, and other cells of the connective tissue release Chemerin (163 amino acids in length), a protein that acts as a chemoattractant [(6)], insulin resistance, adipolipidemia, hypertension, as well as low-grade inflammation may all be linked to increased levels of this molecule. There are two primary receptors for its biological activity, G protein-coupled protein 1 (GPR1), and chemokine-like receptor 1 (CMKLR1) [(7)].

For the first time, it has been discovered that the receptor 23 (Chem23) of the chemerin molecule has powerful chemotherapeutic activity, which is accompanied with enhanced production of inflammatory mediators [(8, 9)].

Serum chemerin levels in OA patients have been studied, however the results were diverse. In those patients chemerin levels have been linked to tumor necrosis alpha (TNF-α), C-reactive protein, as well as interleukin-6 (IL-6) levels implying an inflammatory component [(10)].

The aim of the current work was to assess the chemerin role in the diagnosis as well as monitoring of severity of the disease in knee osteoarthritis (KOA) patients,

SUBJECTS AND METHODS

This case-control study included a total of 60 subjects, 30 of them had knee osteoarthritis (KOA) and 30 served as controls, attending at Department of Rheumatology, Rehabilitation, and Physical Medicine, Zagazig University Hospitals. This study was conducted between June 2020 and June 2021. This study was approved by Institutional Review Board of Zagazig University.

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Inclusion criteria: Patients fulfilled the criteria for diagnosing knee osteoarthritis as per American College of Rheumatology recommendations [(11)].

Exclusion criteria: Patients suffering from diabetes mellitus, cardiovascular disease, hypertension, chronic liver disease, chronic kidney disease, other associated inflammatory arthritis, or autoimmune illnesses like systemic lupus erythematous and patients with history of knee trauma were excluded.

***Ethical Consideration*:**

An approval of the study was obtained from Zagazig University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Clinical assessment:

Clinical examinations were performed on all patients. Patients with KOA had their disease activity assessed using the Arthritis Index developed by researchers at the Universities of Western Ontario and McMaster (WOMAC) [(12)].

The WOMAC assesses three different aspects: stiffness (2 items), pain (5items) as well as physical function (17 items): The scores for each item correspond to: low levels of physical disability or symptoms graded from zero to four, Each subscale is summated to a maximum score of zero to twenty (pain),zero to eight (stiffness), and zero to eighty six (physical function). None (zero), Mild (one), Moderate (two), Severe (three), and Extreme (Four). Higher scores indicating more disability. With total sum varying from 0 to 96 [(13)].

Laboratory investigations

ELISA was used to quantify serum chemerin in all individuals. Random plasma glucose, complete blood count (CBC), CRP, erythrocyte sedimentation rate (ESR), kidney and liver function tests were also performed.

Statistical analysis:

After loading data into SPSS version 20.0, the analyses were carried out (Statistical Package for Social Sciences). Based on the type of data, the following tests were used to establish the significance of discrepancies: by using the Chi square test to examine qualitative differences and relationships; quantitative continuous group representation by mean SD (X^2). ANOVA or Kruskal-Wallis tests for differences between quantitatively independent multiple groups; Spearman's tests for correlation. A P value of 0.05 was considered significant, while a P value of 0.001 was considered highly significant.

RESULTS

As regard basic characteristics of the studied groups, results indicated that participants were not significantly different as regard age, BMI, or sex among 2 groups.

Table (1): Basic characteristics of study groups.

		KOA group		Control group		P-value
		Mean	SD	Mean	SD	
Age (years)		54.0	8.7	53.6	10.3	0.872
BMI (Kg/m^2)		35.5	7.1	33.9	4.7	0.307
		No	%	No	%	P-value
Sex	**Female**	22	73.3%	17	56.7%	0.175
	Male	8	26.7%	13	43.3%)	

As regard clinical and laboratory characteristics, results indicated that there were a statistically significant differences between both groups as regard ESR and CRP levels.

Table (2): Clinical, laboratory and radiological characteristics of study groups:

	KO group		Control group		P-value
	Mean	±SD	Mean	±SD	
Disease duration (months)	59.6	38.5	-	-	-
VAS scale for pain	7.2	2.7	-	-	-
WOMAC score	29.3	12.3	-	-	-
ESR (mm/H)	22.8	5.8	12.7	3.2	0.034
CRP (mg/L)	8.14	0.85	5.26	0.99	< 0.001
Radiological					
Osteophytes:					
Positive	20	66.7%			
Negative	10	33.3%			
Diffuse joint space narrowing					
Positive	25	83.3%			
Negative	5	16.7%			

Patients with KOA had considerably greater serum chemerin levels compared to controls, according to our findings.

Table (3): Serum Chemerin levels in different study groups:

	KO group		Control group		P-value
	Mean	±SD	Mean	±SD	
Serum chemerin (mg/L)	960.6	356.3	226.4	24.8	< 0.001

Serum chemerin levels were found to have statistically insignificant link with other variables, including age, sex, BMI pain, and disease durations; on the other hand, strong positive correlations were observed between chemerin levels and WOMAC score, ESR, and CRP.

Table (4): Correlation between serum chemerin and biomarkers of knee osteoarthritis group:

Variable	Serum chemerin	
	r-value	p-value
Age (years)	0.149	0.433
Sex	-0.177	0.350
BMI (Kg/m^2)	-0.132	0.488
Pain	0.046	0.809
Disease Duration (months)	-0.231	0.220
WOMAC score	0.419*	0.021
ESR (mm/H)	0.391*	0.033
CRP (mg/L)	0.756**	<0.001

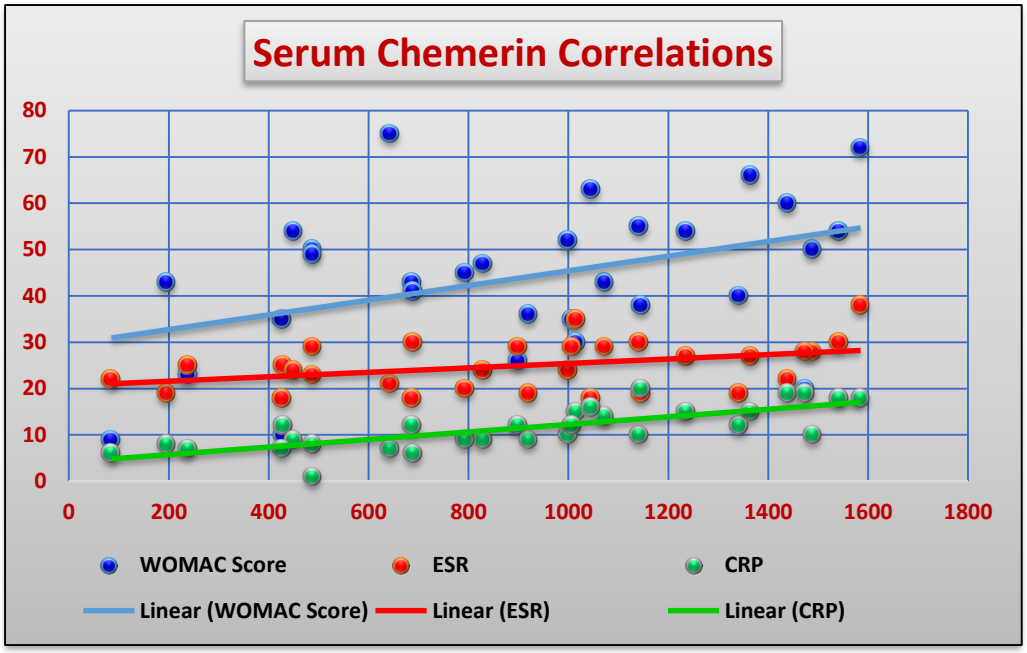

Figure (1): Correlation between serum chemerin and other variables.

DISCUSSION

Osteoarthritis is a frequent illness that has an adverse impact on the quality of life of patients, as well as on the economy. It is more common as we get older and heavier. Europe's total population is approximately 70 million people, and the direct expenditures of knee OA reach 2 billion euros. In most cases, the condition progresses slowly but eventually leads to joint dysfunction since the cartilage lacks the ability to regenerate itself. OA of the hip and knee is the 11th most common cause of disability worldwide, according to the World Health Organization's Global Burden of Disease Study in 2010 [(2)].

Studying chemerin's role in the diagnosis and severity of knee osteoarthritis was the primary goal of this investigation.

As regard clinical and laboratory characteristics, our results showed that higher ESR and CRP levels were both found in patients with KOA. This finding agreed with that of **Hanada *et al.*** [(14)] who reported in their study that People with knee osteoarthritis had elevated ESR and CRP levels compared to those without knee osteoarthritis. Also, **Huang *et al.*** [(8)] reported in their study that Serum CRP levels were greater in OA patients compared to healthy controls. Additionally, it has been demonstrated that the severity of OA is linked to CRP levels.

Serum CRP and KOA are linked in the following ways: CRP is a useful tool for assessing KOA; In people with osteoarthritis, CRP is linked to a range of symptoms including joint function and pain; Joint space narrowing, and Kallgren-Lawrence score had no statistically significant correlation with CRP [(15, 16)]. There was a strong correlation between BMI and CRP and chemerin levels in serum and synovial fluid (SF) in individuals with knee osteoarthritis, according to a study published in 2012 by **Huang *et al.*** [(8)] in serum and SF, chemerin levels were not associated with age or gender.

Ma *et al.* [(17)] found no association between serum chemerin levels and C-reactive protein levels. When compared to the OA group, The CRP serum level, Ayral score, and Outerbridge score were all positively associated with the chemerin levels in synovial fluid and synovial membrane. Patients with KOA have higher amounts of chemerin in their synovial fluid and synovial membranes, which is linked to the severity of the condition.

Patients with KOA were found to have higher serum chemerin levels compared with controls with p-value: <0.001. As previously observed by **Santana *et al.*** [(18)], a group of patients with primary osteoarthritis of the hand, knee or hip exhibited elevated chemerin levels in comparison to controls. While against this finding was **Ma *et al.*** [(17)] who reported that chemerin levels were not statistically different between patients with KOA and those without KOA, however, in synovial fluid it was elevated in patients with OA compared with non-OA group. Also, this finding disagreed with that of **Huang *et al.*** [(8)] who reported that Serum chemerin levels were higher in knee OA patients, but the difference between them and healthy controls was not statistically significant.

Our findings reveal that there is no statistically significant link between serum chemerin levels and other variables, such as age, sex, BMI, pain, and disease durations. On the other hand, chemerin levels were

strongly linked to WOMAC score, ESR, and CRP levels.

CONCLUSION

It could be concluded that serum chemerin can be utilized as an inflammatory marker in KOA patients and it can be considered as a therapeutic target.

Further studies are recommended to assess its levels in other types of OA, and other rheumatic diseases.

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