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Research Article

Chemerin: A Novel Biomarker of Coronary Artery Disease

C Sahaya Jency[1], D Ponnudhali[2]

[1]Final Year Postgraduate Student, [2]Professor & Head, Department of Biochemistry, Vinayaka Missions Kirupananda Variyar Medical College, Salem, Tamil Nadu, India.
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I N F O

Corresponding Author:
C Sahaya Jency, Department of Biochemistry, Vinayaka Missions Kirupananda Variyar Medical College, Salem, Tamil Nadu, India.
E-mail Id:
jency.sahaya@gmail.com
Orcid Id:
https://orcid.org/0000-0003-1253-8425
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A B S T R A C T

Introduction: Dysregulated secretion of adipokines causing adipose tissue dysfunction can contribute to the pathogenesis of obesity-linked complications like atherosclerosis. Chemerin, a newly discovered adipokine, secreted by visceral adipose tissue and liver, is involved in the regulation of glucose and lipid homeostasis. Elevated levels of chemerin in the blood have been associated with atherosclerosis and coronary artery disease.

Aim: To examine the chemerin levels in coronary artery disease (CAD) patients, to determine its association with CAD, and to find the correlation of chemerin with HsCRP and other lipid parameters.

Materials and Method: This is a cross-sectional study that included 100 participants divided into two groups namely, group I comprising CAD patients, and group II healthy individuals. Serum levels of chemerin were measured by ELISA. HsCRP were measured by immunoturbidimetry method. Atherogenic index of plasma (AIP), LDL and TC/ HDL ratios were calculated parameters.

Results: Chemerin levels were significantly increased in CAD patients (48.66 ± 12.7) (ng/ml) compared to healthy controls (32.92 ± 17) (ng/ml) (p = 0.04). AIP was significantly increased in CAD patients (6.92 ± 3.10) compared to healthy controls (3.27 ± 1.42) (p = 0.000). Chemerin had a good correlation with AIP (p = 0.001). Logistic regression analysis showed a significant association of chemerin with the occurrence of CAD (OR = 1.09, 95% CI, p = 0.004). ROC curve obtained with the area under the curve being 0.79.

Conclusion: Chemerin, a pro-inflammatory adipokine, could play an important role in atherosclerosis and can be used as a marker for the diagnosis of CAD patients.

Keywords: Chemerin, Coronary Artery Disease, Atherosclerosis, Adipokine

Introduction

Coronary artery disease is the single most common cause of death globally and the burden falls on low and middle-income countries accounting for 7 million deaths.[1] In the area of cardiovascular diseases, CAD has gained importance in recent years among developing nations including India[2] and has evolved as a major cause of death in all parts of India including rural areas and poorer states.[3]

Atherosclerosis plaque formation is the underlying cause of coronary artery disease leading to high morbidity and mortality.[4] Major risk factors of coronary artery disease include advancing age, diabetes mellitus, hypertension, smoking, obesity, homocystinuria, and psychological stress.[5] Recently, adipose tissue is being considered an endocrine organ that plays an important role in obesity-mediated cardiovascular diseases[6] through autocrine and paracrine mechanisms. It secretes a number of adipose tissue-derived factors known as adipokines such as adiponectin, leptin, resistin, visfatin, C-reactive protein, amyloid-A, adiponectin, and chemerin which influence cardiovascular function.[7,8]

Among the adipokines secreted, chemerin exerts pro-inflammatory activity on the endothelial cells. It is a 16kDa protein, called retinoic acid responder 2 (RARRES-2) identified as a product of Tazarotene-induced gene (TIG-2), isolated from psoriatic skin lesions.[9] It is secreted maximally by visceral adipose tissue, liver, and placenta and minimally in lungs, heart, ovaries, and kidneys.[10-12] Chemerin regulates adipocyte differentiation and modulation of the expression of adipocyte genes such as glucose transporter-4 involved in glucose and lipid homeostasis.[10]

Chemerin has been associated with various metabolic disorders, inflammation and atherosclerosis. Circulating chemerin levels were associated with various diseases causing chronic inflammation like Crohn's disease, ulcerative colitis, and chronic kidney disease.[13,14] The adipokine chemerin has the chemoattractant property for immune cells including dendritic cells and macrophages[15] and has a well-established role in inflammation and obesity.[16] There is evidence suggesting elevated blood levels of chemerin in patients with coronary artery disease[17] and it is also positively correlated with aortic and coronary atherosclerosis[18]. The studies have found a strong linkage between chemerin, obesity, and metabolic syndrome which can collectively increase the risk of diabetes mellitus and cardiovascular disorders. This study has attempted to identify the association of serum chemerin with coronary artery disease, in a small group of the south Indian population in and around, Salem, Tamil Nadu.

Objectives

- To assess serum chemerin levels in coronary artery disease patients and compare them with those in normal subjects
- To assess the correlation of serum chemerin levels with the inflammatory marker (HsCRP) and lipid parameters
- To determine the role of chemerin as a marker for the diagnosis of CAD

Method

Study Design

The present study is a hospital-based cross-sectional study conducted on patients attending the outpatient department in the Department of General Medicine, Vinayaka Mission's Kirupananda Variyar Medical College & Hospitals, Salem. The duration of the study was 10 months and it was conducted between January 2022 and October 2022. The sample size was calculated from already reported mean chemerin levels among CAD patients (42.10 ± 6.59 ng/ml) and normal healthy controls (38.23 ± 5.90 ng/ml).[19] A total of 100 participants were recruited for the study.

We had divided the study population into 2 groups: Group I consisted of 50 patients diagnosed with coronary artery disease who had undergone coronary angiography and Group II consisted of 50 healthy individuals who were friends and family members of patients, and staff members working in the hospital. All the subjects in both groups were age and gender-matched. The present study protocol was approved by the institutional ethics committee. Informed consent was obtained from all participants after explaining the study protocol to them.

Coronary Angiography

Coronary angiography was done for the CAD patients and evaluated by the cardiologists. Patients who had been diagnosed with coronary heart disease for a minimum of 5 years duration, were aged more than 40 years, with or without diabetes mellitus, and had at least 50% luminal narrowing of coronary arteries, were included in the study. Patients with acute/ chronic infection, hepatic dysfunction, renal dysfunction, severe heart failure, and any other endocrine disorders like hypo or hyperthyroidism, pregnancy, and malignancy were excluded from the study.

Laboratory Analysis

5 ml of venous blood was collected from each study participant after an overnight fast of more than 8 hrs. Soon after blood collection, patients' serum/ plasma were centrifuged and separated. Fasting blood glucose and lipid profile parameters were analysed after blood collection. 0.5 ml of serum was stored at -20° C for the analysis of chemerin.

Fasting blood sugar and fasting lipid profile, including total cholesterol, triglycerides, and HDL, were analysed using a fully automated analyser ERBA EM 200 in the clinical biochemistry laboratory, VMKVMCH in Salem. Serum chemerin levels were measured using FineTest

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human CHEM ELISA kit and HsCRP levels were analysed by immunoturbidimetry method. Low-density lipoprotein (cholesterol) was calculated using Friedewald's formula. Very-low-density lipoprotein (cholesterol) was derived from LDL values.

Calculated Parameters

The total cholesterol (TC) to high-density lipoprotein (HDL) ratio and LDL were calculated manually for both cases and controls. Atherogenic index (AI) was measured using the equation log (TG/ HDL).

Statistical Analysis

All the parameters were compared in both groups using the student independent 't' test and Pearson's correlation was made using SPSS 26 version software. Binomial logistic regression analysis was done for the association of chemerin and other metabolic parameters like BMI and HsCRP, and Odds ratio was calculated using Jamovi software version 2.3.18. ROC curve analysis was done for serum chemerin and cut-off values were obtained using SPSS 26 version software.

Results

Baseline Characteristics

The baseline characteristics and comparison of lipid profiles have been shown in Table 1. The coronary artery disease patients in group I had a mean age of 57.3 years while the healthy controls in group 2 had a mean age of 47.3 years. They were age and gender-matched. The waist circumference and BMI were significantly higher among participants of group I compared to those of group II with p values of 0.02 and 0.001respectively.

Serum LDL, VLDL, and TC/ HDL ratios were significantly higher while serum HDL was significantly lower in cases compared to controls ($p < 0.05$). Serum HsCRP, an inflammatory marker also showed a similar increase in cases as compared to controls ($p = 0.05$). The mean FBS levels were also significantly high in the coronary artery disease patients compared to controls ($p < 0.05$). AIP was significantly increased in the CAD patients as compared to the controls ($p = 0.000$) and it was significantly correlated with serum chemerin levels ($p = 0.001$).

Serum Chemerin Levels

Serum chemerin levels were significantly increased in the coronary artery disease patients of group I compared to controls in group II ($p < 0.05$). As shown in Table 2, serum chemerin levels showed a significant negative correlation with HDL levels and a positive correlation with HsCRP and other lipid profile parameters. Figure 1 shows that area under the curve (AUC) was 0.79, which signified that it could be considered a marker of coronary artery disease. Figure 2 shows the levels of chemerin between cases (group I) and controls (group II).

Table 1.Comparison of Serum Chemerin and Other Parameters in Coronary Artery Disease Patients with Normal Healthy Controls

Baseline Clinical Characteristics	Controls (Group 2) Mean ± SD	Cases (Group 1) Mean ± SD	p Value
Age (years)	47.3 ± 11.8	57.3 ± 10.9	0.3
Gender			
Male	74%	36%	0.01*
Female	26%	64%	
BMI	23.16 ± 1.9	27.06 ± 3.4	0.001*
Waist circumference (cm)	67.96 ± 8.5	96.7 ± 5.07	0.02*
Fasting blood sugar (mg/dl)	102.14 ± 21.4	142.2 ± 52.4	0.04*
Total cholesterol (mg/dl)	161.3 ± 28.3	162.52 ± 27.83	0.84
Triglyceride (mg/dl)	140.3 ± 55.9	150.4 ± 48.01	0.33
HDL (mg/dl)	44.06 ± 6	23.7 ± 7.4	0.01*
LDL (mg/dl)	92.34 ± 23	113.9 ± 30.2	0.04*
VLDL (mg/dl)	29.52 ± 11	35.9 ± 18.6	0.04*
TC: HDL ratio	3.69 ± 0.64	7.49 ± 2.9	0.03*
HsCRP (mg/L)	1.24 ± 0.87	4.65 ± 8.31	0.05*
Atherogenic index of plasma (AIP)	3.27 ± 1.42	6.92 ± 3.10	0.000*
Serum chemerin (ng/ml)	32.92 ± 17	48.6 ± 12.7	0.04*

*$p < 0.05$ is significant.

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Table 2.Correlation of Serum Chemerin with Age, BMI, Waist Circumference, and Lipid Profile Parameters

S. No.	Parameters	Correlation Coefficient (r)	p Value
1.	Age	0.24	0.016*
2.	BMI	0.24	0.01*
3.	Waist circumference	0.43	0.000*
4.	FBS	0.26	0.009*
5.	Total cholesterol	0.15	0.13
6.	TGL	0.20	0.042*
7.	HDL	-0.36	0.00*
8.	LDL	0.158	0.116
9.	VLDL	0.322	0.001*
10.	TC/ HDL ratio	0.32	0.001*
11.	Atherogenic index of plasma (AIP)	0.332	0.001*
12.	HsCRP	0.16	0.09

*p < 0.05 is significant.

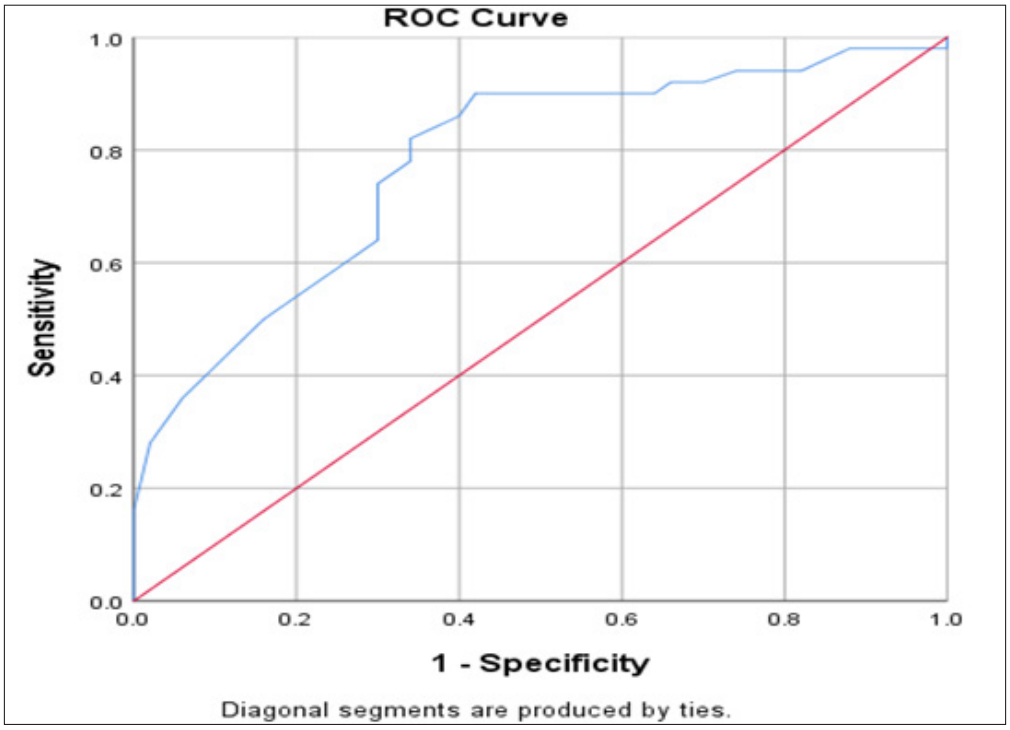

Figure 1.ROC Curve for Chemerin

AUC for Chemerin = 0.79

Binomial Regression for Chemerin with Other Parameters

As per Table 3, the binomial logistic regression model was statistically significant, **$\chi 2(2) = 83.9, p < 0.001$.** The model explained 76.2% (Nagelkerke R^2) of the CAD occurrence. In the adjusted model, chemerin, BMI, and HsCRP levels were associated with an increased likelihood of developing CAD by factors ranging from 1.09, 1.26, and 1.70 respectively with $p < 0.05$. Individuals with elevated serum chemerin levels had 1.09 times higher odds for the development of CAD than normal individuals, but the significance of association was lost after adjusting for HDL levels/ AIP.

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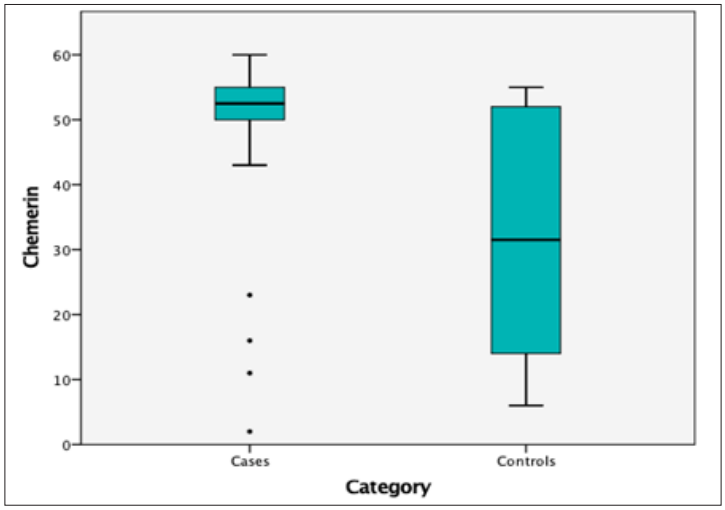

Figure 2.Mean Chemerin Levels in CAD Patients & Healthy Controls

Table 3.Binomial Regression Analysis for the Association of Chemerin and Other Laboratory Measurements with regards to Cases and Controls

S. No.	Variables	Crude Odd's Ratio (95% CI)	p Value	Adjusted Odd's Ratio (95% CI)	p Value
1.	BMI	1.35 (1.16-1.56)	< 0.001	1.26 (1.04-1.53)	0.01
2.	Chemerin	1.07 (1.04-1.103)	0.001	1.09 (1.03-1.16)	0.004
3.	HsCRP	1.47 (1.13-1.91)	0.005	1. 70 (1.062- 2.62)	0.026

$p < 0.05$ significant with 95% CI.

Discussion

Our study has been conducted on 50 patients diagnosed with CAD and 50 healthy controls. This study assessed serum chemerin levels and lipid profile parameters in both study groups. There are previous studies which have identified the association of elevated chemerin levels with cardiovascular disease as well as major adverse cardiovascular events.[20] This study showed that serum chemerin levels were increased in CAD patients but could not find any significant difference among the diabetic and non-diabetic subjects. The present study is consistent with other studies showing increased chemerin levels in coronary artery disease.[19-24]

Chemerin, a recently discovered adipokine produced by white adipose tissue, has chemoattractant properties, known to promote the recruitment of immature dendritic cells and macrophages.[25] It mediates through its receptor CMKLR1 expressed in macrophages, dendritic cells, natural killer cells, adipose tissue, bone, lungs, brain, heart, and placenta. Chemerin is known to regulate adipogenesis, adipocyte differentiation, and adipocyte metabolism through CMKLR 1 receptors.[10] The CMKLR1 receptors are also expressed in the endothelial cells which are upregulated by pro-inflammatory cytokines like TNF (alpha)-, IL-6, and IL-1(beta).[26]

There is evidence for elevated HsCRP levels in CAD[27] and it has been found to be strongly associated with markers of inflammation like HsCRP, TNF (alpha), IL-6, and IL-(beta).[28] This study showed a significant increase in HsCRP levels in CAD patients, compared to healthy individuals, but did not find any correlation with serum chemerin.

White adipose tissue is the major site of chemerin expression and its secretion from the adipose tissue increases when there is excess body fat as in obesity. Chemerin is increased in obesity when there is upregulation of chemerin expression during adipocyte differentiation which results in various metabolic effects on the immune system.[29] It has been found to be increased in morbidly obese individuals.[28] This study showed a good correlation of chemerin with BMI and waist circumference of the study participants. Also, the CAD patients had higher BMI ($p = 0.001$) and waist circumference ($p = 0.02$) when compared with controls, which could have resulted in increased chemerin levels ($p = 0.04$).

In this study, along with serum chemerin levels, the CAD patients also had significantly high LDL, VLDL, TC/ HDL ratio and low HDL levels. The present study found a positive correlation of chemerin with age, BMI, waist circumference, FBS, total cholesterol, triglycerides, LDL, TC/ HDL ratio and a negative correlation with HDL levels. There are many studies which have identified chemerin to be positively correlated with BMI, lipid parameters like TGL, total cholesterol, low HDL levels, and insulin resistance.[22,30,31]

Chemerin is also known to play an important mediator

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linking vascular inflammation and obesity. In this study, though we could not find any correlation between chemerin and HsCRP, HsCRP was significantly high in CAD patients. The atherogenic index of plasma (AIP) was significantly high in the CAD group (p = 0.000) and it had a positive correlation (p = 0.001) with serum chemerin.

There are studies which showed increased serum chemerin levels to be linked with obesity and atherosclerotic cardiovascular disease, both having an underlying chronic inflammatory state.[32-35] The pro-inflammatory activity and chemoattractant property of chemerin could play an important role in the pathogenesis of atherosclerosis leading to coronary artery disease. Chemerin was found to be positively correlated with endothelial adhesion molecules like ICAM-1 and E-selectin which interact with vascular endothelium.[35]

Aksan et al. reported that chemerin levels were higher in metabolic syndrome patients with coronary artery disease.[33] Lehrke et al., in their cross-sectional study, have found that chemerin was correlated with markers of inflammation including HsCRP, TNF-α, IL-6 and lipid parameters like LDL-c and TGL, but they could not find any association of total chemerin with atherosclerotic plaque burden.[36] Kostopoulos et al. have detected chemerin expression in periaortic adipocytes, aortic and vascular smooth muscle cells. In addition to this, they have also found the expression of CMKLR1 in foam cells of aortic atherosclerotic lesions.[37] In Han Chinese patients, higher chemerin mRNA expression in the epicardial adipose tissue along with its positive correlation with the severity of atherosclerosis was found.[38]

As per the present study results, chemerin had a good association with CAD, after adjusting for BMI and HsCRP, but when adjusted with HDL and AIP, its association was lost. This could be explained by the small sample size. Chemerin can be considered a marker of CAD with an AUC of 0.79. At a cut-off value of 48.5 ng/ml, chemerin has a sensitivity of 82% and specificity of 67%. If the cut-off value is decreased to 45.5 ng/ml, sensitivity increases to 86%, while specificity falls to 61%.

The available evidence points towards the fact that chemerin, with its pro-inflammatory action, could play an important role in the pathogenesis of atherosclerosis and coronary artery disease, but the exact mechanism linking the role of chemerin in CAD is not yet clear.

Limitations of Our Study

The sample size was less and we did not assess other adipokines and insulin resistance, which would have thrown more light on the effects of chemerin. We did not compare chemerin with the severity of CAD. Also, we did not measure the atherosclerotic plaque thickness by 2-dimensional ultrasonography/ 3D coronary computed tomography angiography (CCTA)/ MRI, which could have helped us to assess the association of chemerin with the atherosclerotic plaque thickness more precisely, thereby helping us to establish its relationship with CAD.

Conclusion

Obesity and atherosclerosis are underlying events leading to coronary artery disease. Chemerin levels are secreted in excess among obese individuals and may mediate the pathogenesis of coronary atherosclerosis leading to CAD. As per the present study, serum chemerin levels are elevated in patients with CAD and it showed a good association with its occurrence, even after adjusting for other lipid and baseline parameters. The CAD patients had higher AIP which also correlated well with the chemerin levels, suggesting the possible role played by chemerin in the atherogenic process, by its pro-inflammatory and chemoattractant properties. It can be used as a biomarker for the diagnosis of CAD, but its role as an independent predictor of CAD cannot be explained by our study and it has to be confirmed by further prospective studies in a larger population.

Author's Contribution

The study was designed and conceptualised by Dr Sahaya Jency C and Dr Ponnudhali D. Data collection, interpretation, and first draft were done by Dr Sahaya Jency C. Revision of critically important intellectual content and final approval of the version was done by Dr Ponnudhali D.

Abbreviations

CAD: Coronary artery disease, IHD: Ischemic heart disease, S. chemerin: Serum chemerin, BMI: Body mass index, FBS: Fasting blood sugar, TGL: Triglycerides, HsCRP: Highly sensitive C-reactive protein, HDL(c): High-density lipoprotein cholesterol, LDL(c): Low-density lipoprotein cholesterol, VLDL(c): Very Low-density lipoprotein cholesterol, TC/ HDL ratio: Total cholesterol to HDL ratio, AUC: Area under curve, ROC: Receiver operating curve, AIP: Atherogenic index of plasma, CMKLR 1: chemokine like receptor 1 or chemR23, VCAM-1: Vascular cell adhesion molecule, ICAM-1: Intercellular adhesion molecule, ELISA: Enzyme-linked immunosorbent assay.

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Conflict of Interest: None

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