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RESEARCH PAPER

Association of Serum Chemerin Levels with Coronary Artery Disease: Pathogenesis and Clinical Research

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Abstract

Recent studies have revealed that chemerin plays an essential role in the development of cardiovascular diseases. Autopsy studies found a strong correlation between the secretion of chemerin in peripheral tissues and aortic and coronary atherosclerosis. Plasma chemerin is a marker of systemic inflammation and is associated with metabolic syndrome. Chemerin plays a vital role in vascular inflammation and atherogenesis. Plasma chemerin levels are increased in patients with dilated cardiomyopathy, and chemerin is associated with left ventricular dysfunction. In this review, we focus on chemerin expression, chemerin processing, its biological function, and its role in the diagnosis of cardiovascular diseases.

Keywords: atherosclerosis; chemerin; heart failure; coronary artery disease; inflammation; metabolic syndrome

Introduction

The World Health Organization classifies cardiovascular diseases (CVD) as illnesses that are increasingly prevalent in the 21st century. CVD are characterized by high mortality, high morbidity, and low quality of life. The incidence of coronary artery disease (CAD) has increased in recent years. Studies have shown that CVD is responsible for 80% of deaths in low- and middle-income countries [1, 2].

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Chemerin plays an essential role in the development of CVD. Autopsy studies found a strong correlation between the secretion of chemerin in peripheral tissues and atherosclerosis. Chemerin is associated with the number of noncalcified plaques in patients with stable angina pectoris or peripheral artery disease. Case-control studies reported a relationship between CAD and serum chemerin levels. Echocardiographic studies found an association between CAD and epicardial adipose tissue, which is the primary source of chemerin secretion [3–5]. Therefore, chemerin may play a role in determining the severity of coronary lesions. This review suggests that chemerin may be a promising marker in CVD and an independent predictor of cardiovascular events.

Serum Chemerin Level as a New Indicator in Heart Failure

Chronic heart failure (CHF), a complex clinical syndrome characterized by ventricular remodeling, cardiac dysfunction, and hemodynamic abnormality, is the end-stage manifestation of various CVD. Many biomarkers have been identified and associated with the diagnosis and prognosis of CHF. These biomarkers may facilitate risk classification and treatment in CHF patients [6].

Chemerin is a recently discovered adipokine that is capable of regulating adipocyte differentiation and stimulating the chemotaxis of dendritic cells and macrophages. Increasing evidence has shown the association of chemerin with inflammation, obesity, metabolic syndrome, and CAD. Leiherer et al. [7] showed that high chemerin levels were associated with renal dysfunction and predicted cardiovascular events in patients with stable CAD.

Chemerin is an immune system regulator that works with chemokine-like receptor 1 (CMKLR1) and plays critical roles in metabolic and inflammatory processes [8]. Gao et al. [9] found that chemerin messenger RNA and the protein were expressed in epicardial adipose tissue of patients with CAD and that the severity of coronary atherosclerosis was associated with chemerin expression. Rodríguez-Penas et al. [10] reported that chemerin, regulated by cardiac metabolic and inflammatory mediators, might induce apoptosis and inhibit protein kinase B phosphorylation in cardiomyocytes. Besides, chemerin promotes adhesion of macrophages to vascular cell adhesion molecule 1 (VCAM-1) and fibronectin by aggregation of VLA-4 (also known as integrin $\alpha 4\beta 1$) and VLA-5 (also known as integrin $\alpha 5\beta 1$), contributing to inflammation [11]. Inflammation plays an active role in the development of CVD, including hypertension, CAD, and CHF. Therefore, chemerin is involved in the pathogenesis of CVD through inflammatory mechanisms [12, 13].

Xiaotao et al. [14] showed that high chemerin levels correlated with CAD and could reflect the severity of coronary atherosclerosis. Zhang et al. [15] reported increased plasma chemerin levels in patients with dilated cardiomyopathy. Also, chemerin was associated with an inflammatory response and left ventricular dysfunction. A recent study by Menzel et al. [16] showed a significant correlation between chemerin and CHF risk factors.

The Relationship between Chemerin Levels and *RARRES2* Polymorphism in Coronary Artery Disease

Tönjes et al. [17], using a genome-wide meta-analysis, emphasized the role of genetic variants in controlling circulating chemical equilibrium. Two other genome-wide association studies showed no relationship between *RARRES2* genotypes and chemerin levels [7, 18].

In a genome-wide association study performed in the Taiwan Biobank population study, promoter polymorphisms of *RARRES2* correlated with chemerin levels [19, 20]. The study aimed to investigate the genetic basis of chemerin levels and to confirm the critical role of chemerin and *RARRES2* polymorphisms in the long-term outcomes of angiographically proven CAD patients.

Chemerin has been suggested as an indicator of cardiovascular risk [21]. Serum chemerin may play a crucial role not only in the cause but also in the severity of CAD. Increased levels of chemerin in patients with CAD suggest that chemerin may be a new marker of coronary atherosclerosis and may play an essential role in CAD development (Figure 1) [16, 22]. Gasbarino et al. [23] demonstrated a relationship between chemerin and carotid plaque instability. Leiherer et al. [7] found that increased plasma chemerin level correlated with renal failure and was predictive of cardiovascular events in CAD patients.

Serum Chemerin Levels and Acute Coronary Syndrome

Kostopoulos et al. [24] claimed that in situ expression of chemerin and CMKLR1 in the human aorta and coronary arteries correlated with the severity of atherosclerotic lesions. Local expression of chemerin that interacts with CMKLR1 may contribute to atheromatous plaque progression by triggering complex cell-cell interactions. Chemerin and CMKLR1 seem to play an essential role in vascular inflammation and atherogenesis. Local chemerin

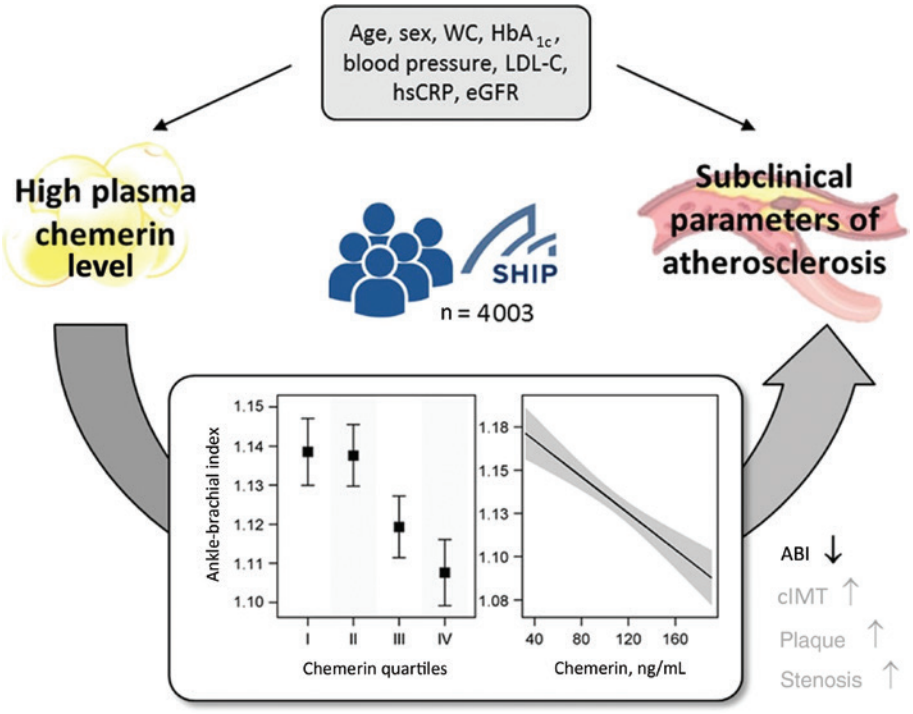

Figure 1: High plasma chemerin level and the development of coronary artery disease.
ABI, Ankle-brachial index; cIMT carotid intima-media thickness; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; hsCRP, high-sensitivity C-reactive protein; LDL-C low-density lipoprotein cholesterol; SHIP, Study of Health in Pomerania; WC, white cells.

production by several components of the vascular wall may have a distinctive effect depending on local interactions, because of proximity to lesions. Further research will explain the role of chemerin signaling in atherosclerosis [24].

A recent prospective cohort study showed an association between chemerin levels and the severity of myocardial infarction, regardless of risk factors [25]. Chemerin, as a chemokine and an adipokine, plays a vital role in the pathophysiology of CAD, involving multiple metabolic and immune-inflammatory mechanisms. Chemerin is involved in the activation of immune cells and migrates to endothelial cell damage sites [26]. Chemerin receptors are present in the endothelium of the blood vessels and the underlying smooth muscle layers [26]. Damage can expose chemerin receptors in endothelial smooth muscle cells and cause atherosclerosis [27].

Ji et al. [27] found that chemerin levels increased in acute coronary syndrome (ACS) but did not change in stable angina. This finding suggests that chemerin may serve as a new biomarker in ACS. However, in this study, long-term follow-up of ACS patients as required to evaluate the short-term and long-term significance of chemerin levels was not performed.

Chemerin induces the production of the adhesion molecules intercellular adhesion molecule 1 (ICAM-1) and E-selectin, and interacts with endothelium by promoting blood vessel remodeling and release of matrix metalloproteinases in vitro experiments [28]. Chemerin's ability to regulate matrix metalloproteinases and other growth factors may play a role in the formation and progression of thromboembolism. Chemerin activates apoptosis in cardiomyocytes in a dose-dependent manner. This activation plays a role in the pathophysiology of CVD, such as acute myocardial infarction and CHF [10]. Chemerin also plays an essential role in metabolic disorders [29]. Chemerin affects lipid and glucose metabolism possibly changes inflammatory infiltration into the endothelium, which contributes to the pathogenesis of CAD [30].

In contrast, Aronis et al. [31] demonstrated no association of chemerin levels with ACS. Although there is evidence that chemerin may have some detrimental effects on vascular homeostasis and may

be associated with the development of coronary atherosclerosis, they argued that studies showing a causal relationship between chemerin levels and CAD were lacking. Prospective studies are needed to evaluate the incidence of stable CAD and ACS in high-risk individuals with different baseline levels of chemerin [31].

Serum Chemerin Levels and Other Cardiac Conditions

Kammerer et al. [32] observed increased chemerin levels in patients with severe carotid artery stenosis and CAD. In the same study, systemic inflammation parameters were associated with cerebrovascular symptoms. Zhang et al. [33] showed the association of serum chemerin concentration with atrial fibrillation. Besides, chemerin levels were associated with atrial remodeling assessed by left atrial size. Lachine et al. [34] suggested that serum chemerin and high-sensitivity C-reactive protein may be considered as markers of subclinical atherosclerosis; therefore, they might be used for early detection of macrovascular disease in type 2 diabetes. Chemerin activates macrophage adhesion to fibronectin and VCAM-1. The secretion of chemerin by perivascular adipose tissue may cause contraction of vascular smooth muscle cells and plays a role in the development of hypertension [26].

Serum Chemerin Levels and Metabolic Syndrome

Herová et al. [35] showed a relation between plasma chemerin levels and systemic inflammation markers and metabolic syndrome. In addition, they showed that low-dose aspirin treatment reduced proinflammatory cytokine secretion by macrophages, which might lead to reduced secretion of chemerin by adipocytes, and that aspirin could be a cause of low chemerin levels in CAD patients.

Several studies showed that the current chemical balance was associated with various cardiometabolic parameters and the severity of atherosclerosis [16]. Yan et al. [36] showed a relation between high chemerin levels with an increased risk of CAD and the severity of atherosclerosis, independent of other cardiovascular risk factors. Besides, serum chemerin levels were associated with lipid profile, insulin resistance, and metabolic syndrome. These results suggest that chemerin may be a new link between metabolic signals and atherosclerosis. Further studies are needed to confirm current findings and to determine whether chemerin is a predictor of overt or silent CAD.

Conclusion

Adipokines have a role as regulators of appetite and energy homeostasis through the endocrine/systemic effect in the brain. Circulating adipokine levels vary depending on adipocytes. Therefore, they contribute to metabolic changes such as metabolic syndrome. As an inflammatory adipokine, chemerin has been identified as a new indicator in the development of ACS and CHF. Chemerin might provide an alternative diagnostic tool for ensuring optimal treatment of patients with CAD.

Conflict of Interest

The authors declare that they have no conflicts of interest regarding the publication of this article. The founding sponsors had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

REFERENCES

1. Heart Failure Society of America. Executive summary: HFSA 2006 comprehensive heart failure practice guideline. J Card Fail 2006;12:10–38.
2. Kenchaiah S, Evans J, Levy D, Wilson P, Benjamin E, Larson M, et al. Obesity and the risk of heart failure. N Engl J Med 2002;347:305–13.
3. Lehrke M, Becker A, Greif M, Stark R, Laubender RP, von Ziegler F, et al. Chemerin is associated with markers of inflammation and components of the metabolic syndrome

but does not predict coronary atherosclerosis. Eur J Endocrinol 2009;161:339–44.
4. Spiroglou S, Kostopoulos C, Varakis J, Papadaki H. Adipokines in periaortic and epicardial adipose tissue: differential expression and relation to atherosclerosis. J Atheroscler Thromb 2010;17:115–30.
5. Dong B, Ji W, Zhang Y. Elevated serum chemerin levels are associated with the presence of coronary artery disease in patients with metabolic syndrome. Intern Med 2011;50:1093–7.
6. Savic-Radojevic A, Pljesa-Ercegovac M, Matic M, Simic D, Radovanovic S, Simic T. Novel biomarkers of heart failure. Adv Clin Chem 2017;79:93–152.
7. Leiherer A, Muendlein A, Kinz E, Vonbank A, Rein P, Fraunberger P, et al. High plasma chemerin is associated with renal dysfunction and predictive for cardiovascular events – insights from phenotype and genotype characterization. Vascul Pharmacol 2016;77:60–8.
8. Rourke JL, Dranse HJ, Sinal CJ. Towards an integrative approach to understanding the role of chemerin in human health and disease. Obes Rev 2013;14:245–62.
9. Gao X, Mi S, Zhang F, Gong F, Lai Y, Gao F, et al. Association of chemerin mRNA expression in human epicardial adipose tissue with coronary atherosclerosis. Cardiovasc Diabetol 2011;10:87.
10. Rodríguez-Penas D, Feijóo-Bandın S, García-Rúa V, Mosquera-Leal A, Durán D, Varela A, et al. The adipokine chemerin induces apoptosis in cardiomyocytes. Cell Physiol Biochem 2015;37:176–92.
11. Hart R, Greaves DR. Chemerin contributes to inflammation by promoting macrophage adhesion to VCAM-1 and fibronectin through clustering of VLA-4 and VLA-5. J Immunol 2010;185:3728–39.
12. Dick SA, Epelman S. Chronic heart failure and inflammation: what do we really know? Circ Res 2016;119:159–76.
13. McMaster WG, Kirabo A, Madhur MS, Harrison DG. Inflammation, immunity, and hypertensive end-organ damage. Circ Res 2015;116:1022–33.
14. Xiaotao L, Xiaoxia Z, Yue X, Liye W. Serum chemerin levels are associated with the presence and extent of coronary artery disease. Coron Artery Dis 2012;23:412–6.
15. Zhang O, Ji Q, Lin Y, Wang Z, Huang Y, Lu W, et al. Circulating chemerin levels elevated in dilated cardiomyopathy patients with overt heart failure. Clin Chim Acta 2015;448:27–32.
16. Menzel J, di Giuseppe R, Biemann R, Wittenbecher C, Aleksandrova K, Eichelmann F, et al. Association between chemerin, omentin-1 and risk of heart failure in the population-based EPIC-Potsdam study. Sci Rep 2017;7:14171.
17. Tonjes A, Scholz M, Breitfeld J, Marzi C, Grallert H, Gross A, et al. Genome wide meta-analysis highlights the role of genetic variation in RARRES2 in the regulation of circulating serum chemerin. PLoS Genet 2014;10:e1004854.
18. Bozaoglu K, Curran JE, Stocker CJ, Zaibi MS, Segal D, Konstantopoulos N, et al. Chemerin, a novel adipokine in the regulation of angiogenesis. J Clin Endocrinol Metab 2010;95:2476–85.
19. Er LK, Wu S, Hsu LA, Teng MS, Sun YC, Ko YL. Pleiotropic associations of RARRES2 gene variants and circulating chemerin levels: potential roles of chemerin involved in the metabolic and inflammation-related diseases. Mediat Inflamm 2018;2018:4670521.
20. Chen CH, Yang JH, Chiang CWK, Hsiung CN, Wu PE, Chang LC, et al. Population structure of Han Chinese in the modern Taiwanese population based on 10,000 participants in the Taiwan Biobank project. Hum Mol Genet 2016;25:5321–31.
21. Dessein PH, Tsang L, Woodiwiss AJ, Norton GR, Solomon A. Circulating concentrations of the novel adipokine chemerin are associated with cardiovascular disease risk in rheumatoid arthritis. J Rheumatol 2014;41:1746–54.
22. Zylla S, Dörr M, Völzke H, Schminke U, Felix SB, Nauck M, et al. Association of circulating chemerin with subclinical parameters of atherosclerosis: results of a population-based study. Arterioscler Thromb Vasc Biol 2018;38:1656–64.
23. Gasbarrino K, Mantzoros C, Gorgui J, Veinot JP, Lai C, Daskalopoulou SS. Circulating chemerin is associated with carotid plaque instability, whereas resistin is related to cerebrovascular symptomatology. Arterioscler Thromb Vasc Biol 2016;36:1670–8.
24. Kostopoulos CG, Spiroglou SG, Varakis JN, Apostolakis E, Papadaki HH. Adiponectin/T-cadherin and apelin/APJ expression in human arteries and periadventitial fat: implication of local adipokine signaling in atherosclerosis? Cardiovasc Pathol 2014;23:131–8.
25. Eichelmann F, Schulze MB, Wittenbecher C, Menzel J, Weikert C, di Giuseppe R, et al. Chemerin as a biomarker linking inflammation and cardiovascular diseases. J Am Coll Cardiol 2019;73:378–9.
26. Watts SW, Dorrance AM, Penfold ME, Rourke JL, Sinal CJ, Seitz B, et al. Chemerin connects fat to arterial contraction. Arterioscler Thromb Vasc Biol 2013;33:1320–8.
27. Ji Q, Lin Y, Liang Z, Yu K, Liu Y, Fang Z, et al. Chemerin is a novel biomarker of acute coronary syndrome but not of stable angina pectoris. Cardiovasc Diabetol 2014;13:145.
28. Kaur J, Adya R, Tan BK, Chen J, Randeva HS. Identification of chemerin receptor (ChemR23) in human endothelial cells: chemerin-induced endothelial angiogenesis. Biochem Biophys Res Commun 2010;391:1762–8.
29. Helfer G, Wu QF. Chemerin: a multifaceted adipokine involved in metabolic disorders. J Endocrinol 2018;238:79–94.
30. Takahashi M, Okimura Y, Iguchi G, Nishizawa H, Yamamoto M, Suda K, et al. Chemerin regulates beta-cell function in mice. Sci Rep 2011;1:123.

31. Aronis KN, Sahin-Efe A, Chamberland JP, Spiro A, Vokonas P, Mantzoros CS. Chemerin levels as predictor of acute coronary events: a case-control study nested within the veterans affairs normative aging study. Metabolism 2014;6:760–6.
32. Kammerer A, Staab H, Herberg M, Kerner C, Klöting N, Aust G. Increased circulating chemerin in patients with advanced carotid stenosis. BMC Cardiovasc Disord 2018;18:65.
33. Zhang G, Xiao M, Zhang L, Zhao Y, Yang Q. Association of serum chemerin concentrations with the presence of atrial fibrillation. Ann Clin Biochem 2017;54:342–7.
34. Lachine NA, Elnekiedy AA, Megallaa MH, Khalil GI, Sadaka MA, Rohoma KH, et al. Serum chemerin and high-sensitivity C reactive protein as markers of subclinical atherosclerosis in Egyptian patients with type 2 diabetes. Ther Adv Endocrinol Metab 2016;7:47–56.
35. Herová M, Schmid M, Gemperle C, Loretz C, Hersberger M. Low dose aspirin is associated with plasma chemerin levels and may reduce adipose tissue inflammation. Atherosclerosis 2014;235: 256–62.
36. Yan Q, Zhang Y, Hong J, Gu W, Dai M, Shi J, et al. The association of serum chemerin level with risk of coronary artery disease in Chinese adults. Endocrine 2012;41: 281–8.