# CHEMERIN: A POTENTIAL TARGET IN CORONARY ARTERY DISEASE – A REVIEW

Anand Duraiswamy, Devanand Shanmugasundaram, **Changam Sheela Sasikumar*,** Kotturathu Mammen Cherian

*Dept of Biochemistry, Frontier Lifeline Pvt Ltd and Dr.K.M.Cherian Heart Foundation, Mogappair, Chennai, Tamilnadu, India

**E-mail of Corresponding Author:** sheelsasic@yahoo.co.in

**Abstract**

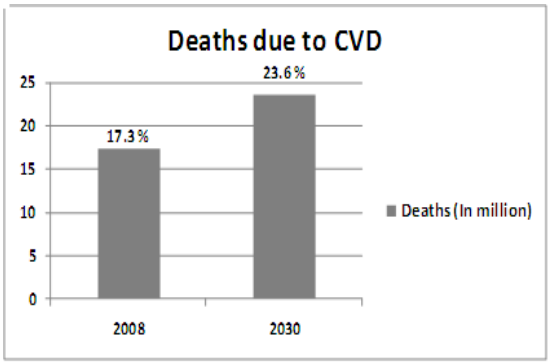
Currently, Coronary Artery Disease (CAD) is considered as a major ailment in humans with widespread prevalence. CAD also accounts for high mortality rates around the world that involves several known risk factors. Recently, it was discovered that epicardial adipose tissue (EAT) and its secretory adipokines play an imperative role in the development of CAD. Among the secretory adipokines, *chemerin*, a serpentine chemotactic agonist has been identified as one of the factor which contributes for the progression of CAD. Since serum *chemerin* levels are elevated during CAD condition, it is being considered to be a valiant marker but then the chimeric property of *chemerin* is yet to be explored. Though *chemerin* has been identified as one of the factors responsible for the development of CAD, it is still being studied at the marker level. This review aims to study whether *chemerin* can only be used as a marker or can it also be used as a novel target for treating or suppressing or delaying the progression of coronary artery disease.

**Keywords:** *Chemerin*; coronary artery disease; adipokines; marker; target

## 1. Introduction

**1.1 Coronary artery disease (CAD)** known to be the disease of rich in past, has been classified by World Health Organization as the disease of 21st century with high prevalence that can occur to almost all population without rationality. CAD can be characterized as a disease with high morbidity, mortality, reduced quality of life and substantial economic burden[1]. Even though age, gender, race and genes are responsible for the occurrence of CAD, risk factors such as dietary habits, diabetes, high blood pressure, cholesterol; smoking, chronic kidney disorders, obesity and sedentary lifestyle[2] can also lead to the development of premature CAD[3]. Presently, CAD has developed as an epidemic and is no longer restricted to geographical area or sex or age or socio economic boundaries[4]. In comparison with western countries and other parts across the world, Asia, has raised itself as a hub of CAD with increased premature mortality rates[5]. It has been studied that in low and middle income countries nearly 80% of deaths happens due to cardiovascular diseases[28].

**Fig 1: Deaths due to Cardio Vascular Diseases**




Source: World Health Organization

Lately, Epicardial adipose tissue has been identified to play a crucial role in the pathogenesis of coronary artery disease. An echocardiographical study conducted on the epicardial fat thickness and coronary artery disease significantly correlated with the severity of coronary artery disease[6]. A study conducted by Mazurek *et al.* demonstrates that epicardial adipose tissue is a source of augmented inflammatory mediators in patients with coronary artery disease[7]. The quantity of EAT during obstructive CAD and in the formation of

non-calcified plaques was seen elevated[32] and also a study shows that differential expression pattern of the adipokines such as adiponectin, leptin, vaspin, visfatin and chemerin that are locally produced adipokines affect the atherosclerotic process in different locations [33]. This review will focus on the chemokine chemerin and study whether it can be used only as a marker or can it also be used as target for the treatment of Coronary Artery Disease (CAD).

**2. CHEMERIN:**

*Chemerin*, also known as retinoic acid receptor responder protein 2 (RARRES2) or tazarotene induced gene 2 protein (TIG2) is a 14KDa, 137 amino acid residues containing active form derived from an inactive precursor pro-chemerin containing 143 amino acid residues. The inactive pro-chemerin is activated by cleavage of 6 amino acid peptide in the C-terminal end by serine proteases of the coagulation, fibrinolytic, and inflammatory cascades[8]. The active form binds to a G-PROTEIN COUPLED RECEPTOR (GPCR) namely ChemR23, also known as chemokine receptor like-1 (CMKLR-1) that is expressed in macrophages and DCs[9]. Chemerin and its receptor chemR23 play an important role in recruitment of blood NK cells and strongly connect chemerin to be a key factor for co-localization of NC cells and DC's in peripheral pathologic tissues and thus provides an evidence of the incidence also occurring *in vivo*[34]. Chemerin also plays a significant role in adipocyte differentiation, in stimulating lipolysis, in pathogenesis of obesity and metabolic syndrome[10].

**2.1 Scientific Approaches:** Chemerin, the chemokine expresses its chimeric nature through an orphan GPCR, CCRL2 which provides a distinctive mechanism through which chemerin enhances inflammation. Also chemerin derived peptides have anti-inflammatory properties that may be involved in both initiation and resolution of inflammation[11].

Cash *et al*. for the first time demonstrated that chemerin exhibits both anti-inflammatory and pro inflammatory effects. The results established that classically activated macrophages have the capability to convert chemerin into potent anti-inflammatory peptides by cysteine protease mediated cleavage of the parent molecule involving calpains and cathepsin S[12].

Zabel *et al*. discloses the presence of a silent chemokine receptor – like GPCRs, which binds with its ligands and present it to the signaling receptors expressed on the neighboring cells. This proves that chemerin is a multifunctional protein having both stimulatory and inhibitory signaling capabilities, whereas cell-bound chemerin sends the stimulatory signals by bridging cells that express the silent receptor with those expressing the ChemR23 receptor[13].

Chemerin, being a secretory product of adipose tissue, many researchers have correlated its circulating levels with many disease conditions. Pfau and his co-workers showed that chronic hemodialysis (CD) is an independent predictor of chemerin. Serum levels of chemerin had been positively correlated with Body Mass Index (BMI), fasting insulin (FI), leptin and C-reactive protein (CRP)[14]. Clement *et al* revealed that after bariatric surgery elevated plasma chemerin levels came down while the weight, fat mass loss, improvement of insulin sensitivity and inflammatory markers increased. They concluded that plasma chemerin levels are correlated with BMI, insulin resistance, adipose tissue inflammation, hepatosteatosis and liver inflammation[15].

Serum chemerin levels were elevated in patients with inflammatory bowel disease (IBD) especially in Crohn's disease [16]. A pilot study conducted by Stejskal and his team on Caucasian population concluded that serum chemerin levels could serve as an independent marker for metabolic syndrome where chemerin is said to play a vital role in the pathogenesis of the metabolic syndrome[17]. Experiments in *Psammomys obesus*, an animal model of obesity and Type 2 Diabetes clearly demonstrate a strong relationship between chemerin and several key aspects of the metabolic syndrome[18]. Apart from this, chemerin also acts as a mediator between obesity and vascular inflammation [19] and is also used for prognosis in patients with non-small cell lung cancer[20]. Albanesi and his group correlated chemerin expression with psoriatic skin lesions and also with plamocytoid dendritic cell recruitment[21].

**2.2 Chemerin: Heart, EAT and CAD:** Clinical studies conducted by Lehrke *et al*, 2009 on 303 consecutive Caucasian subjects suggested that serum chemerin levels are strongly associated with the inflammatory markers and the components of metabolic syndrome but is not associated with coronary atherosclerotic plaque morphology[22]. Most recently, Becker and his co-workers reported that long-term over expression of chemerin, did not significantly affect the extent of atherosclerotic lesion area *in vivo* [24]. A study conducted in Korean patients by Yu-Jin

Hah and his co-workers explains that the serum chemerin levels had significant correlations with cardiometabolic parameters and severity of coronary artery stenosis in Korean patients with CAD[25].

However, studies conducted by Xiuying Gao and his team suggested that expression of chemerin mRNA and protein are higher in Epicardial Adipose Tissue (EAT) from Han Chinese CAD patients. They also concluded that the severity of CAD is associated with the level of chemerin mRNA in EAT rather than its circulating level[23]. Yet another study discusses that chemerin secreted locally by epicardial adipose tissue increases the risk and progression of CAD[23]. Likewise, several studies correlates that chemerin is closely associated with heart and in the progression of coronary artery disease.

**2.3 For treatment:** Though chemerin is considered as a marker for coronary artery disease, it can still be used as a target for treating CAD and also as a drug for various other inflammatory disorders. David R Greaves and his team had invented C-terminal end of chemerin protein which can be used in the treatment of inflammation and/or endotoxic shock and or treatment of wounds and/or reduction of levels of inflammatory chemokines in a subject[26] Trevor *et al*, had invented pyrrolidinone carboxamide derivatives that can be used as a therapeutic agent for treating various inflammatory diseases and metabolic syndromes including but not limited to obesity and cardiovascular diseases by modulating ChemR23, a GPCR to chemerin [27]. Recently conducted studies on adipocytes reveal that expression of chemerin is regulated by pro-inflammatory stimuli in adipocytes but not in hepatocytes. Upon treatment of the stimulated adipocytes with aspirin, chemerin expression did not reduce which suggest that aspirin reduces inflammation in adipose tissue and in turn it reduces adipocyte expression of chemerin[35]. This demonstrates that chemerin secreted by adipose tissue, especially Epicardial adipose tissue establishes itself as a factor which is actively involved in the progression or development of CAD.

## Conclusion

It is apparent from the present review that properties of the chimeric protein chemerin had been explored at the marker level alone. Nevertheless researchers have also suggested that chemerin can be used as potential therapeutic agent or inflammatory agent or can also used as a target in certain diseases or disorders. At present only few evidences are available for contemplating chemerin as a target or treatment in inflammatory disorders such as CAD. Nonetheless, a comprehensive and/or a detailed experimental study are yet to be accounted to explain the pro-inflammatory and anti-inflammatory roles of chemerin. This will provide new insights in therapeutic developments for many disorders and also for considering chemerin as a target for treating coronary artery disease (CAD).

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