Chemerin as an independent predictor of cardiovascular event risk

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Ther Adv Endocrinol Metab

2016, Vol. 7(2) 57–68

DOI: 10.1177/2042018816629894

***Abstract*:** Currently, coronary artery disease (CAD) is considered a major ailment in humans with widespread prevalence. CAD also accounts for high mortality rates around the world that involves several known risk factors. Chemerin is a novel adipokinine that is associated with inflammation and adipogenesis. Furthermore, experimental and clinical data indicate that localized as well as circulating chemerin expression and activation are elevated in numerous metabolic and inflammatory diseases including psoriasis, obesity, type 2 diabetes, metabolic syndrome and cardiovascular disease. Chemerin is accepted as being a strong marker because the serum chemerin levels are increased in a CAD condition. However, the chimeric characteristics of chemerin have not been fully investigated. Although chemerin is known to be responsible for CAD development among other factors, authors still investigate it at the marker level. This review focuses on chemerin expression, processing, biological function and relevance to human diseases, and on the role of chemerin in the maintenance of a cardiovascular disease.

Keywords: cardiovascular disease, chemerin, marker

Introduction

The World Health Organization classifies cardiovascular diseases as the disorders encountered at an increased prevalence in the general population in the 21st century. Cardiovascular diseases are characterized by high mortality: morbidity levels and decreased quality of life, and are associated with serious economic problems [Heart Failure Society of America, 2006]. Predisposing factors such as diabetes mellitus, high blood pressure, high levels of cholesterol, smoking, chronic kidney disease, obesity and sedentary lifestyle, as well as factors such as age, sex, ethnic origin and genetic characteristics play important roles [Kenchaiah *et al.* 2002; Cole and Sperling, 2004]. The frequency of coronary artery disease (CAD) is increasing in recent years. Studies have shown that cardiovascular diseases are responsible for nearly 80% of the cardiovascular deaths occurring in countries with low and medium incomes [World Health Organization, 2010].

The role of chemerin in the development of cardiovascular diseases, and especially atherosclerosis, has been investigated. A positive correlation was shown between the chemerin secretion at the perivascular tissue and aortic and coronary atherosclerosis in autopsy studies on humans [Spiroglou *et al.* 2010]. In cross-sectional studies, chemerin was shown to be associated with peripheral arterial stiffness [Yoo *et al.* 2012] and with the number of noncalcified plaques in patients with stable chest pain [Lehrke *et al.* 2009]. A positive correlation was shown between patients with CAD and serum chemerin levels in case-control studies, and it was reported to play a role in determining the severity of the coronary lesions [Yan *et al.* 2011; Dong *et al.* 2011]. Echocardiography studies have detected an association between epicardial fat tissues that are responsible for a significant portion of chemerin secretion and CAD [Jeong *et al.* 2007]. This review highlights that chemerin may be used both as a marker and as an independent predictor of cardiovascular events.

Cardiovascular disease

Cardiovascular disease is the most frequent cause of death occurring in the USA in the last 50 years. According to the data from the USA, more

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than 900,000 people died and more than 12 million were newly diagnosed as having cardiovascular disease (from 1990 to 1997) [Cooper *et al.* 2000]. Atherosclerosis causes cardiovascular disease by atherosclerotic plaques developing on the endothelium of medium to large arteries. Atherosclerosis generally develops in vessels of all dimensions from weak to hard [Guyton, 2011]. Atherosclerosis is a chronic inflammatory response of the arterial wall to endothelial injury and the inflammation cascade [Steinberg, 2002]. The development of atherosclerotic plaques starts with the attachment of monocytes and lipids to adhesion molecules that are present on damaged or dysfunctional endothelial cells. This initial adhesion or attachment may be due to cytokines such as tumor-necrosis factor, mechanical denudation, hemodynamic forces, immune-complex deposition, irritation or chemicals. The tunica intima of the vessel wall is exposed, which is followed by monocyte diapedesis and differentiation of monocytes to macrophages by the induction of the cytokine macrophage colony-stimulating factor [Hansson, 2001]. Activated macrophages internalize the accumulated lipoproteins by becoming foam cells and creating visible fatty streaks, oxidizing them. The fatty streaks show increased amounts of polar amino acids containing elastin, which enable calcium and connective-tissue material to generate plaques [Gotleib, 1982]. Eventually, fibroblasts of the plaque-deposit-dense connective tissue cause stiffening of the arteries. Calcium salts settle with cholesterol and other lipids after stiffness and cause bony calcifications [Guyton, 2011]. Risk factors for cardiovascular diseases cause structural and functional endothelial dysfunction [Marti *et al.* 2001]. The endothelium is the major regulator of vascular homeostasis and maintains the balance between vasodilatation and vasoconstriction, stimulation and inhibition of smooth muscle proliferation and migration, and thrombogenesis and fibrinolysis [Lüscher and Barton, 1997; Kinlay *et al.* 2001]. High blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking, glucose intolerance and left ventricular hypertrophy are physiologic risk factors for cardiovascular diseases [Anderson *et al.* 1991]. There is also evidence that social isolation, depression, maladaptive coping methods, excessive alcohol and tobacco consumption and physiologic stress factors increase inflammation and cause endothelial dysfunction and cardiovascular diseases [Weidner, 2002].

Chemerin

Chemerin was initially identified in 1997 using differential display, as a retinoid-responsive gene present in psoriatic skin lesions [Nagpal *et al.* 1997]. Chemerin, also known as tazarotene-induced gene 2 (TIG2) and retinoic acid receptor responder 2 (RARRES2), is a recently discovered adipokinine that has been reported to modulate immune-system function through its binding to the chemerin receptor (ChemerinR, chemokine-like receptor 1, and G protein-coupled receptor) [Roh *et al.* 2007]. Chemerin signaling is tightly regulated through a number of mechanisms including expression, secretion, processing and signaling events. The precise coordination of these regulatory mechanisms is essential for establishing chemerin levels, localization and, ultimately, the activity.

Chemerin is mostly produced in visceral adipose tissue (VAT), placenta and liver, and also to a lesser extent in the lungs, heart, ovaries, kidneys and pancreas [Goralski *et al.* 2007; Bozaoglu *et al.* 2007; Issa *et al.* 2012; Takahashi *et al.* 2011]. Although chemerin levels show a diurnal rhythm similar to other adipokinines, leptin, adiponectin and omentin in mice [Parlee *et al.* 2010], this is believed to be minimal in humans [Tan *et al.* 2009]. There are studies showing high serum levels in women and the elderly [Bozaoglu *et al.* 2007, 2009; Lehrke *et al.* 2009; Stejskal *et al.* 2008]. Chemerin is initially synthesized as the precursor of prochemerin, preprochemerin [Wittamer *et al.* 2003]. Most of the circulating chemerin is in the form of inactive prochemerin and is converted to bioactive chemerin form by a proteolytic process when needed.

Prochemerin may be produced by various extracellular proteases of the coagulation, fibrinolytic and inflammatory cascade following secretion. These enzymes are converted into bioactive isoforms by separating the C-terminal arm of prochemerin. The type of isoform depends on the number of amino acids separated. Many different mechanisms are involved in the production of chemerin, determining local and systemic chemerin activation or inactivation directly, or by limiting present precursors, indirectly. The ratio between active and inactive isoforms is important for the determination of chemerin bioactivity. Chemerin bioactivity is related to only one function or signal pathway (and is therefore relative) according to most of the studies. Whether single

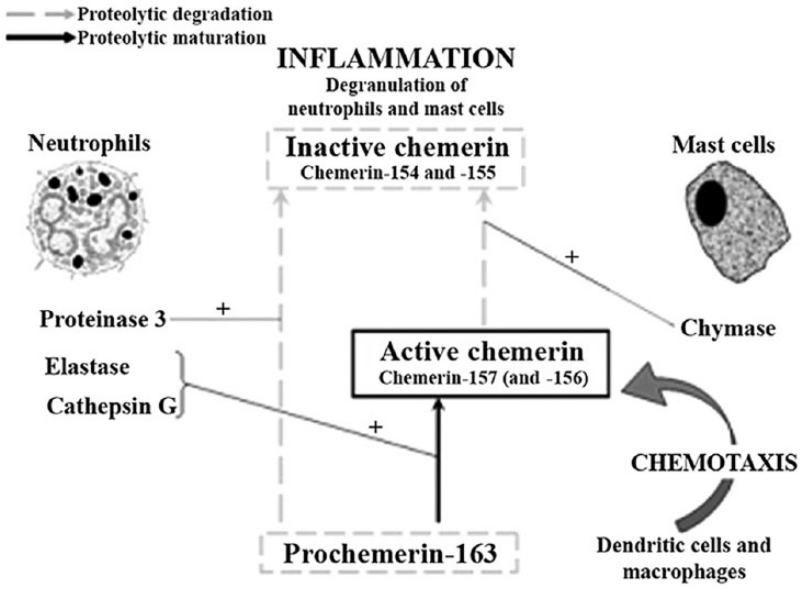

Figure 1. Proposed model for (pro)chemerin maturation and degradation. Proteinase 3 (PR3) can act as a down-regulating protease by processing prochemerin into an inactive chemerin variant.

chemerin isoforms have distinctive bioactivity in multiple pathways or functions is not yet clearly known [Zabel *et al.* 2004; Guillabert *et al.* 2008] (Figure 1).

Although data on chemerin processing and bioactivity are mostly derived from *ex vivo* studies, many endogenous chemerin isoforms are isolated from human samples. Different patterns of chemerin isoforms are produced *in vivo* in human blood (Chem-155, -157, -158), acid (Chem-157), synovial fluid (Chem-158), and cerebrospinal fluid (Chem-158). All proteases play a role in the regulation of chemerin activity via the C-terminal branch [Guillabert *et al.* 2008].

Currently, no information is available regarding the effect of this C-terminal processing on the tertiary or quaternary structure of chemerin, or the functional relevance of particular amino acids or amino-acid motifs within the remainder of the protein. Thus, further characterization of chemerin-isoform generation is necessary in order to fully understand the local chemerin bioactivity and the biological functions of chemerin [Guillabert *et al.* 2008].

Chemerin chemokine-like receptor 1 (CMKLR1) is the receptor associated with chemerin that was discovered in 1996 [Gantz *et al.* 1996]. Chemerin receptor 23 was found later (ChemR23) [Samson *et al.* 1998]. Although these were reported separately, they were in fact similar. Zabel and colleagues discovered this in 2004 [Zabel *et al.* 2004], and the relationship between chemR23 and chemerin was found in 2003 [Meder *et al.* 2003; Wittamer *et al.* 2003]. The most recent receptor related to chemerin is chemokine (CC motif) receptor-like 2 (CCRL2), which was discovered in 1998 [Fan *et al.* 1998]. Its association was also unknown until Zabel and colleagues discovered its mechanism [Zabel *et al.* 2008]. Chemerin and these other receptors may play multifunctional roles in the human body similar to chemokine, adipokinine and growth factors.

Although chemerin was shown to bind and inactivate G-protein-coupled receptor (GPR1) similarly to CMKLR1, [Barnea *et al.* 2008], there are no data on signal-transduction pathways in relation to GPR1. In addition to CMKLR1 and GPR1, chemerin is a ligand for a third receptor, CCRL2, that has phylogenetic homology to CC chemokine-receptor subfamilies. CCRL2-linked chemerin is not clearly known yet, and it is not believed to be a signaling receptor [Zabel *et al.* 2008]. On the contrary, CCRL2 is believed to focus on chemerin localization *in vivo*, to exert a positive effect on local chemerin concentrations, to transmit to nearby cells and thus contribute to CMKLR1, and potentially to CPR1-mediated processes [Muruganandan *et al.* 2010] (Figure 2).

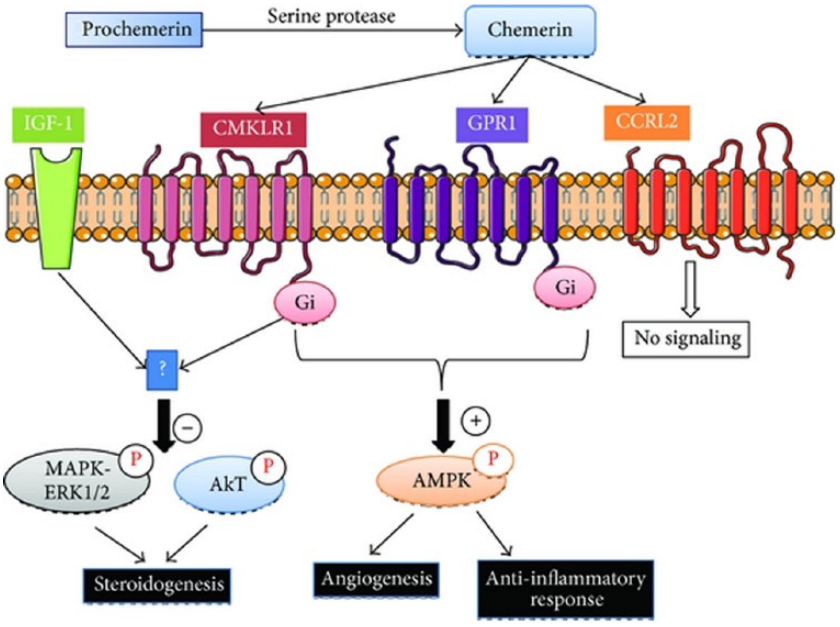

Figure 2. Chemerin receptors, chemerin chemokine-like receptor 1 (CMKLR1), G-protein-coupled receptor (GPR1), and chemerin chemokine-like receptor 2 (CCRL2) signaling pathways.

The three chemerin receptors have similar and dissimilar characteristics. CMKLR1 is expressed in high levels in the leukocyte populations, especially in macrophages and dendritic cells (DC), adipose tissue, bone, lungs, brain, heart and placenta [Goralski *et al.* 2007; Wittamer *et al.* 2003]. Similar to CMKLR1, GPR1 is also expressed in the adipose tissue; but GPR1 is expressed in normal levels in the central nervous system (CNS) and skeletal muscles, and in limited amounts in the leukocytes [Regard *et al.* 2008]. CCRL2 is present in low amounts in the adipose tissues, and in higher amounts in the lungs, heart, spleen and leukocytes [Zabel *et al.* 2008]. This variability in receptor localizations may contribute to common and independent signaling mechanisms of bioactive chemerin and biological functions originating from this. Little is known on signal-transduction pathways attributed to CMKLR1 and GPR1 activation. Preliminary studies have shown that CMKLR1 activation results in intracellular calcium release and decrease in AMP (cAMP) accumulation. Low-dose chemerin administration was reported to induce phosphorylation of extracellular-regulated kinase (ERK) in human adipocytes and endothelial cells by some studies [Goralski *et al.* 2007; Kaur *et al.* 2010]. This shows that inhibition or desensitization of signaling may occur in high concentration. In order to explain signaling pathways related to chemerin activity in more detail, more studies focusing on chemerin receptors are needed. Future studies should be designed to elucidate both overlapping and differential CMKLR1/GPR1 signaling pathways in a way to expose singular pathway activations of chemerin isoforms in detail.

Role of chemerin in inflammation and its relationship with systemic illness

It is now generally recognized that white adipose tissue, in addition to serving as a long-term energy store, is also an active endocrine organ that secretes a number of bioactive molecules collectively termed as adipokinine. Adipokinines are important regulators of adipose-tissue development and function that have a significant influence on glucose metabolism in various tissues, and also have an influence on the overall energy balance at the systemic level [Bluher, 2012; Pardo *et al.* 2012]. Chemerin, a recently discovered adipocytokine, has been shown to regulate the adipocyte differentiation and modulate the expression of adipocyte genes, such as glucose transporter-4, adiponectin, and leptin that are involved in glucose and lipid homeostasis [Goralski *et al.* 2007]. Consistent with this proposal, in 2007, chemerin was identified as a novel adipokinine that regulates adipogenesis and adipocyte metabolism as evidenced by experimental data showing that the loss of chemerin or CMKLR1 abrogates adipocyte differentiation and modifies the

expression of genes critical in glucose and lipid metabolism. Subsequent studies confirmed these findings and have provided experimental evidence for additional roles of chemerin in diverse biological processes including cell proliferation and differentiation, angiogenesis, renal function, and energy metabolism [Muruganandan *et al.* 2010]. Moreover, two additional chemerin receptors have been identified, CCRL2 and GPR1 [Zabel *et al.* 2008]. While chemerin is known to bind CCRL2 and GPR1, all of the biological actions currently ascribed to chemerin are elicited through the activation of CMKLR1.

The anti-inflammatory and pro-inflammatory effects of chemerin were first shown by Cash and colleagues [Cash *et al.* 2008]. Chemerin was shown to exert both pro-inflammatory and anti-inflammatory effects via the CMKLR1 receptor. Experimental studies on animal- and cell-based models show that chemerin and CMKLR1 have both pro-inflammatory and anti-inflammatory roles in the immune process. The data on correlations between the increase in chemerin levels in humans and inflammatory mediators support these experiments. However, it is not clear whether pro-inflammatory or anti-inflammatory activity is dominant. This may be attributed to different roles played by chemerin via various isomers in different phases of inflammation. In conclusion, although chemerin is known to be involved in immune-cell recruitment and pathological processes, presence or absence of a role played by it at the initiation, maintenance or resolution of inflammation and a protective or pathological role of increasing chemerin activity in these inflammatory disorders, are issues waiting to be resolved in ongoing research.

The first pro-inflammatory activity of chemerin was shown by its chemo-attractant characteristic for leukocytes in regions of inflammation, and expression of CMKLR1 was shown in macrophages. Also in *in vitro* experiments, expression of CMKLR1 was shown in the effector cells of the immune system [Zabel *et al.* 2004; Vermi *et al.* 2005; Parolini *et al.* 2007]. Another finding supporting the pro-inflammatory activity of chemerin is the presence of a positive correlation between pro-inflammatory cytokines such as interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor alpha (TNFα), and serum chemerin levels [Weigert *et al.* 2010b; Lehrke *et al.* 2009]. Also, increased circulating chemerin levels were found in many systemic inflammatory diseases. Main examples include Crohn's disease, ulcerative colitis [Weigert *et al.* 2010b], chronic renal disease [Yamamoto *et al.* 2010; Pfau *et al.* 2010; Rutkowski *et al.* 2012], liver diseases [Kukla *et al.* 2010; Yilmaz *et al.* 2011], chronic pancreatitis [Adrych *et al.* 2012], pre-eclampsia [Stepan *et al.* 2011] and polycystic ovary syndrome [Tan *et al.* 2009]. Pfau and colleagues have shown that chemerin is an independent predictor in patients on chronic hemodialysis. Positive correlations were detected between chemerin serum levels and body mass index (BMI), fasting insulin, leptin and CRP [Pfau *et al.* 2010]. Sell and colleagues have found a decrease in body weight after bariatric surgery, a decrease in fat mass, improvement in insulin sensitivity, increase in inflammatory markers as well as an increase in plasma chemerin levels. They found a correlation between chemerin levels and BMI, insulin resistance, adipose tissue inflammation and liver inflammation [Sell *et al.* 2010]. Stejskal and colleagues have reported chemerin to be an independent marker of the metabolic syndrome, where they found chemerin to play an important role in the pathogenesis of the metabolic syndrome. [Stejskal *et al.* 2008]. Significant associations were found between chemerin and metabolic syndrome in animal experiments in type 2 diabetes mellitus and obesity [Bozaoglu *et al.* 2007] (Table 1). Chemerin was also reported to be a mediator between vascular inflammation and obesity [Landgraf *et al.* 2012]. It was shown that chemerin may be used as a prognostic factor in patients with non-small cell lung cancer [Zhao *et al.* 2011]. In light of all these data, the pro-inflammatory role played by chemerin may be attributed to its effects on both adhesion and chemotaxis of leukocytes in the inflammatory tissues via the CMKLR1 receptor.

Experimental evidence has shown that CMKLR1 receptors also possess anti-inflammatory activity. They exert this anti-inflammatory effect via roselvins, which act as potent inhibitors of leukocyte infiltration. Roselvins decrease the levels of interleukin-12 (IL-12) and TNFα via signals from CMKLR1 receptors [Arita *et al.* 2005]. Investigations on animals have shown that inhibition of endogenous chemerin activity or CMKLR1 expression increases the severity of inflammation and decreases leukocyte infiltration in some models of inflammation such as peritoneal inflammation [Wan *et al.* 2011], LPS-induced lipopolysaccharide (LPS) lung injury [Arita *et al.* 2007], and acute viral pneumonia

Table 1. The relationship of chemerin with systemic illness.

Reported chemerin level		Disease	References
Healthy level	Disease level		
125	200*	Psoriasis Vulgaris	Nakajima *et al*. [2010]
186	230*	Obese	Stejskal *et al*. [2008]
186	266*$	Obese+ Met S.	Stejskal *et al*. [2008]
94	144*	Tip 2 DM	Weigert *et al*. [2010a]
190	230*	Tip 2 DM	Chakaroun *et al*. [2012]
98	220*	Onset tip 1 DM	Verrijin Stuart *et al*. [2012]
108	121*	Sleep apne	Feng *et al*. [2012]
211	259*	Preeclampsia	Stepan *et al*. [2011]
45	65*	Renal failure	Rutkowski *et al*. [2012]
89	140	Crohn's	Weigert *et al*. [2010b]
89	124	Ulcerative colitis	Weigert *et al*. [2010b]
254	542	Chronic hemodialysis	Pfau *et al*. [2010]

*$p < 0.05$ *versus* control population.
$^{\$}p < 0.05$ *versus* comparator condition.
MetS, metabolic syndrome; DM, diabetes mellitus.

[Cash *et al.* 2008]. Synthesis of pro-inflammatory mediators such as TNFα, interleukin-1b (IL-1b), IL-6, IL-12 and Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES) were shown to be inhibited by chemerin in experimental studies [Cash *et al.* 2008]. On the other hand, this effect could not be shown clearly in independent group studies [Bondue *et al.* 2012]. This may be due to the triggering of monocyte adhesion by chemerin in non-leukocyte cells such as the endothelial cells.

Chemerin and cardiovascular diseases

The cardiovascular system is hard to understand due to its individual functional characteristics (such as the endothelial cells). The relationship between chemerin and the cardiovascular system could not be shown primarily, but its secondary effects were evaluated: as a chemokine, chemerin allows for chemo-attraction through the vasculature [Wittamer *et al.* 2003], changes endothelial adhesion levels [Yamawaki *et al.* 2012], and is extracellularly activated in the lumen [Wittamer *et al.* 2003]; as an adipokinine, chemerin adjusts lipid [Goralski *et al.* 2007] and glucose levels (through glucose intolerance) [Takahashi *et al.* 2011], possibly altering their infiltration into endothelium; and as a growth factor, it promotes micro-vessel growth to support adipocytes [Bozaoglu *et al.* 2010]. Changes in endothelial adhesion levels, adipokinine effect on adipose tissue [Goralski *et al.* 2007], and effects on glucose levels [Takahashi *et al.* 2011] are several of these effects. Chemo-attraction is one of the most important roles of chemerin, and by this way, macrophages interact with dendritic cells and natural killer cells and are targeted towards areas of damage [Samson *et al.* 1998; Zabel *et al.* 2004; Wittamer *et al.* 2003]. Similarly, intercellular adhesion molecule-1 (ICAM-1) and E-selectin interacting with the endothelium are induced by chemerin [Landgraf *et al.* 2012]. Chemerin increases the production of matrix myeloperoxydase (MMP). This was shown to have an effect on remodeling and growth of blood vessels in *in vitro* experiments [Kaur *et al.* 2010; Bozaoglu *et al.* 2010; Wang *et al.* 2014].

Atherosclerosis is among other conditions that have relationships with chemerin on multiple epidemiologic levels [Dessein *et al.* 2014; Dong *et al.* 2011]. This is due to receptors on macrophages [Samson *et al.* 1998; Wittamer *et al.* 2003] and the activity of chemerin in the inflammatory cascade [Zabel *et al.* 2004]. probably increasing the strength of macrophage activity in damaged tissues and helping immune-cell migration towards the damaged region. Presence of ChemR23s on smooth-muscle cells [Watts *et al.* 2013; Kostopoulos *et al.* 2014] may initially help healing of lesions by abnormal contractions, and

Table 2. The relationship of chemerin level with cardiovascular disease.

Reported chemerin level		Disease	References
Healthy level	Disease level		
95	133*$	Met S+CAD	Dong *et al*. [2011]
246	546*	Tip 2 DM+perivascular disease	Zakareia *et al*. [2012]
62	75*$	Tip 2 DM+HT	Yang *et al*. [2010]
80 (One vessel)	87*	Multiple vessel occlusion CAD	Hah *et al*. [2011]
90	129*	Met S+CAD	Aksan *et al*. [2014]
163	201*	Met S+CAD	Leiherer *et al*. [2015]

*$p < 0.05$ *versus* control population.
$^{\$}p < 0.05$ *versus* comparator condition.
CAD, coronary artery disease; DM, diabetes mellitus; HT, hypertension; MetS, metabolic syndrome.

then act in the cells with the occurrence of fatty streaks, thus causing progression of disease. This hypothesis partially supports that chemerin induces nitric oxide dysregulation [Neves *et al.* 2014], but its relationship with vascular pathologies should be proved in *in vivo* conditions; and replication in the human body is required in order to detect the complexity of these signals. The roles played by chemerin in lipid metabolism result in an important effect in the progression of these disorders [Goralski *et al.* 2007].

Studies have recently focused on the effects of chemerin on cardiovascular diseases. It may be a risk factor for CAD via the physiopathologic mechanisms mentioned above, having a close relationship with components of the metabolic syndrome that causes a high predisposition for CAD, while contributing to the inflammatory process. There are limited and conflicting conclusions on the relationship between chemerin levels and coronary atherosclerosis in present studies. In previous studies, chemerin was shown to increase the expressions of vascular pathology markers such as E-selectin and ICAM [Landgraf *et al.* 2012; Zakareia, 2012]. In two studies on Chinese patient populations, serum chemerin levels were significantly higher in the group with CAD, in comparison with those who did not have CAD [Xiaotao *et al.* 2012; Yan *et al.* 2011]. Also, Dong and colleagues have found higher levels of chemerin in MetS patients with CAD in comparison with MetS patients without CAD [Dong *et al*. 2011] (Table 2). Although significantly high serum chemerin levels were found in CAD, it is not clearly known if this increased level represents a predictor for CAD or is a result of atherosclerotic plaque morphology [Lehrke *et al.* 2009; Hah *et al.* 2011].

Hah and colleagues have shown a significant correlation between chemerin levels and the severity of coronary arterial stenosis in 131 patients with CAD, but they were not able to show it to be an independent risk factor for multiple-vessel disease. In this study, positive correlations were reported between serum chemerin levels and fasting glucose, triglycerides, total cholesterol, and High-sensitivity C-reactive protein (HsCRP) [Hah *et al.* 2011]. A correlation between circulating chemerin levels and CAD severity were found in recent case-control studies. [Yan *et al.* 2011; Dong *et al.* 2011]. Becker and colleagues were not able to show a significant increase in the area of atherosclerosis with long-term chemerin expression in their *in vivo* study [Becker *et al.* 2010], and Lehrke and colleagues did not find an association between serum chemerin levels and coronary atherosclerosis in their study evaluating coronary atherosclerosis in 303 patients with computerized tomographic angiography [Lehrke *et al.* 2009]. There is only one study that has evaluated circulating serum chemerin levels as a predictor of acute coronary syndrome (ACS). Aronis and colleagues have found similar ACS-group and control-group results in their case-control study. They were not able to show chemerin as a predictor of ACS in their logistic regression analysis [Aronis *et al.* 2014].

Bozaoglu and colleagues found higher levels of serum chemerin in MetS patients in comparison with the control group in their studies on different populations, and showed significant correlations between chemerin and BMI, blood pressure, triglyceride (TG) levels, fasting blood glucose, and high-density lipoprotein (HDL) levels [Bozaoglu *et al*. 2009]. Similarly, Aksan and colleagues showed higher serum chemerin levels in MetS

patients in comparison with the control group, and showed a significant positive correlation between chemerin and components of metabolic syndrome such as BMI, systolic blood pressure, serum TG levels, fasting blood glucose, and a significant negative correlation with HDL-C levels [Aksan *et al.* 2014]. Leiherer and colleagues showed chemerin to be a significant predictive factor for cardiovascular events in patients with metabolic syndrome, independent of standard risk factors [Leiherer *et al.* 2015].

Chemerin was defined as an adipocytokine with pro-inflammatory actions, and positive correlations were found with arterial stiffness and coronary arterial plaques in cross-sectional studies [Spiroglou *et al.* 2010; Yoo *et al.* 2012; Lehrke *et al.* 2009]. Kostopoulos and colleagues evaluated the contributions of chemerin in the development of coronary atherosclerotic lesions, and detected high levels of chemerin in the periadventice adipose tissues, foam cells, vascular smooth-muscle cells in the regions of atherosclerotic lesions, and found a significant correlation between the level of chemerin released from these cells and the severity of atherosclerotic lesions [Kostopoulos *et al.* 2014]. Spiroglou and colleagues found a significant correlation between coronary atherosclerosis and epicardial chemerin levels [Spiroglou *et al.* 2010]. Hart and Greaves reported a contribution of chemerin in the progression of atherosclerosis by stimulating adhesion of macrophages to the extracellular matrix protein fibronectin and vascular cell adhesion molecule-1 (VCAM-1) [Hart and Greaves, 2010]. In addition, the chemerin molecule was shown to activate endopeptidases MMP-2 and MMP-9 belonging to matrix metalloproteinases that play a key role in plaque instability [Kaur *et al.* 2010], increase the expressions of adhesion molecules such as E-selectin and ICAM-1 [Landgraf *et al.* 2012], and was considered a new biomarker for coronary atherosclerosis.

Hyperlipidemia is considered an important risk factor in the development of cardiovascular diseases. Positive correlations between chemerin and triglycerides, low-density lipoprotein cholesterol and blood pressure levels [Bozaoglu *et al.* 2007; Tan *et al.* 2009; Chakaroun *et al.* 2012; Dong *et al.* 2011; Stejskal *et al.* 2008; Yoo *et al.* 2012; Chu *et al.* 2012; Xiaotao *et al.* 2012; Ren *et al.* 2012], and negative correlations with HDL cholesterol were shown in many studies [Sell *et al.* 2010; Chu *et al.* 2012; Ren *et al.* 2012; Alfadda *et al.* 2012]. There are also studies that have shown a role played by chemerin in the regulation of lipolysis via direct-signaling pathway [Bauer *et al.* 2011]. In *in vivo* studies with mice, chemerin was shown to exert its lipolytic effect via CMKLR1 receptors, not to change levels of TGs, and to cause an increase in cholesterol levels after intense expression [Becker *et al.* 2010]. Thus, future studies will have to concentrate on understanding the role of chemerin in lipid homeostasis better. Although the associations between chemerin and obesity, inflammation and metabolic syndrome were detected in former studies, studies of a larger scale are required to show its relationships with cardiovascular risk factors.

Although the negative effects of chemerin on vascular homeostasis and contribution to the development of coronary atherosclerosis were shown in many studies, the relationship between cardiovascular diseases and chemerin levels shown in prospective studies is not complete. Prospective chemerin studies in the detection of cardiovascular diseases in individuals in especially high-risk groups should be encouraged, and the mechanical role of chemerin in the development process of atherosclerotic plaques should be investigated. Conflicting results on the relationship between coronary atherosclerosis and serum chemerin levels may be due to study populations of different ethnic origins, use of enzyme-linked immunosorbent assay (ELISA) kits with different characteristics, and use of different atherosclerotic index evaluation methods. These studies not only support the role played by chemerin in the pathogenesis of atherosclerosis and the atherosclerotic process it contributes, but also support the autocrine and paracrine functions of chemerin in the heart.

Conclusion

Studies on chemerin as a marker seem to be more prominent among all current studies. Studies on chemerin, investigating it as a therapeutic target or as a chemerin inhibitor, as an inflammatory agent, or investigating its effects on specific diseases are considerably limited in number. There is very scarce evidence in current studies about chemerin being an independent predictor for cardiovascular diseases. More detailed and comprehensive studies are expected to provide a clearer understanding on the role played by chemerin in inflammation, and on its effects in systemic diseases, with a special emphasis on it being chosen

as a target in cardiovascular diseases and bringing forth new horizons of therapeutic developments.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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