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Review Article

Role of Chemerin as a Putative Biomarker of Cardiovascular Risk in Metabolic Syndrome: A Brief Review

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ABSTRACT

Cardiovascular disease (CVD) is one of the major alarming causes of morbidity and mortality with widespread prevalence around the world. The major risk factor for cardiovascular disease is metabolic syndrome (MetS) and is most prevalent among obesity-related comorbidities. The main causative factors linking metabolic syndrome and cardiovascular disease are assumed to involve the expansion of adipose tissue and chronic inflammation. In addition to storing surplus fat, adipose tissue also produces adipokines which act through autocrine, paracrine and endocrine functions in the body. Increasing evidence suggests that the altered secretion of adipokines may play a role in the pathogenesis of metabolic syndrome but the mechanisms underlying are not fully known. To date, only leptin and adiponectin are the best-studied adipokines among the variety of adipokines secreted by adipose tissue. However, recent studies have implicated the novel adipokine chemerin as a regulator of adipogenesis, inflammation and glucose metabolism which demonstrates its multifaceted actions. Furthermore, they also found that elevated circulating levels of chemerin in metabolic syndrome acts as a significant risk factor for cardiovascular disease. Chemerin has gained considerable interest due to its role as a pro- or anti-inflammatory mediator is still controversial and the effect of chemerin on glucose metabolism is a matter of debate. Thus, the purpose of this review is to focus primarily on chemerin expression, processing, signaling of receptors, biological actions and pathophysiological implications and the role of chemerin as a biomarker of cardiovascular disease in metabolic syndrome.

Key words: Chemerin, Cardiovascular disease, Diabetes Mellitus, Inflammation, Metabolic syndrome.

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INTRODUCTION

Over the last few years, adipose tissue has gained considerable interest as it is associated with an increasing prevalence of obesity and associated metabolic disorders.[1] Expansion of adipose tissue mass and deregulation of adipokine secretion collectively contributes to the progression of metabolic diseases.[2] To date, more than 600 potentially secretory proteins have been identified as putative and novel biomarkers associated with metabolic diseases.[3] In recent times, the rapidly growing adipokine family has been extended to include chemerin, a 16-kDa protein that has been identified as a chemokine and adipokine with well-established roles in inflammation and obesity.[4] Chemerin was initially discovered to be a protein linked to normal skin function contrasting the setting of psoriasis in 1997.[5] Chemerin is structurally similar to the cathelicidin and cystatin family of proteins and was rediscovered in 2003 following reverse pharmacology screening of orphan G protein-coupled receptors (GPCRs).[6] Moreover, with the discovery of multiple receptors and a broad association with different pathologies, chemerin has a global impact on regulating chemotactic, autocrine/paracrine, adipogenic, angiogenic and reproductive functions.[7] Other names of chemerin are Tazarotene-Induced Gene 2 (TIG2) or Retinoic Acid Receptor Responder 2 (RARRES2).[8]

Structure, Expression, Secretion and Processing of Chemerin

The predicted secondary structure of chemerin suggests that it may have a structure similar to other chemokines but in a reversed orientation. This predicted structure has a disordered carboxyl-terminus (COOH-terminal), three β- pleated sheets and an amino-terminal α-helical domain (NH2-terminus).[9] Chemerin has three disulfide bonds stabilizing its structure and is predicted to be structurally similar to cathelicidins, cystatins, defensins and other related proteins such as kininogen (a bradykinin precursor).[9] Chemerin is expressed at the highest levels in placenta, liver and white adipose tissue (WAT), at moderate levels in lung and brown adipose tissue and lower levels in tissues such as heart, ovary and kidney.[10-13] White adipose tissue is typical among the body's tissues and shows elevated

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concentrations of chemerin as well as CMKLR1. While the levels of chemerin display a diurnal pattern similar to that of other adipokines, leptin, adiponectin and omentin in mice, this is thought to be limited in humans.[14,15] The expression of chemerin is regulated by various factors including receptor activation, growth factors and cytokines. For example, nuclear receptors, free fatty acids (FFA) and many pro-inflammatory stimuli, including tumor necrosis factor (TNF)α, lipopolysaccharide (LPS), interferon (IFN)γ and interleukin (IL)-1ß, have been shown to up-regulate chemerin expression in adipocytes and synoviocytes while gonadotropin and follicle-stimulating hormone have been shown to decrease chemerin expression in granulosa cells.[16-18] Regulation of chemerin expression is often cell type-specific, suggesting local control of chemerin levels.[19]

Chemerin is initially secreted as prepro-chemerin, a 163 amino acid protein that undergoes N-terminal cleavage of a signal peptide sequence to form 18 kDa inactive pro-chemerin (Chem-163).[20] The majority of circulating chemerin is believed to exist in the relatively inactive pro-chemerin form and requires proteolytic cleavage processing of its carboxyl-terminal amino acids by serine proteases of the coagulation, fibrinolytic and inflammatory cascades to generate the 16 kDa bioactive chemerin which is present in plasma and serum to exert local biological actions.[12] The function of Chemerin varies depending on how it is processed. For example, plasmin and mast cell tryptase cleave pro-chemerin into various chemerin isoforms such as Chem- 156 has slightly less activity, Chem-155 and -158 low activity and Chem-152 and -154 are relatively inactive. The removal of six amino acids and further processing by plasma carboxypeptidase N or B can produce a highly active form (chemerin-157) which has a strong chemotactic effect and is responsible for an early inflammatory response of the immune cells, whereas chemerin-154 is anti-inflammatory acts by inhibiting macrophage activation.[5,21,22] Importantly, other proteases may process prochemerin at multiple cleavage sites (e.g. elastase, tryptase) as well as further processing of specific chemerin isoforms. This multi-step processing of chemerin provides a mechanism for local and systemic chemerin activation as well as inactivation, both directly and by limiting available precursors. Furthermore, chem-155, having low bioactivity can function as a weak antagonist in the presence of highly active chemerin isoforms and indicate that the ratio between active and inactive isoforms is an important determinant of chemerin bioactivity.[23] The gene encoding prepro-chemerin (RARRES2) is located on 7q36.1 in humans. There are 3357 base pairs in the human chemerin gene from the transcriptional start site to the polyadenylation site.[24]

CHEMERIN RECEPTORS AND SIGNALING

ChemR23 (Chemerin Receptor 23) or CMKLR1 (Chemokine-like receptor 1) is an orphan G protein-coupled receptor triggered by chemerin resulting in its biological functions which are subsequently discovered.[20,25] Chemerin can also bind to chemokine receptor-like 2 (CCRL2) and G-protein coupled receptor 1 (GPR1), the functions of which need to be explained. Chemerin binds to both CMKLR1 and GPR1 with equal affinity, but it has a lower affinity to CCRL2.[26] Therefore, all the biological actions performed by chemerin are mainly carried out by the activation of CMKLR1. These three chemerin receptors have different characteristics. CMKLR1 is expressed in high concentrations in leukocyte populations, especially in macrophages and dendritic cells (DC), adipose tissue, bone, lungs, brain, heart and placenta.[11,20] Similar to CMKLR1, GPR1 is also expressed in the adipose tissue, but is expressed in normal levels in the central nervous system (CNS) and skeletal muscles and limited amounts in the leukocytes.[27] CCRL2 is present in low amounts in the adipose tissues and higher amounts in the lungs, heart, spleen and leukocytes.[28] This variation in the localization of a receptor may lead to common and independent signaling mechanisms of bioactive chemerin and their biological functions. Literature lacking the information about signal-transduction pathways attributed to CMKLR1 and GPR1 activation. Preliminary studies have shown that CMKLR1 activation results in an intracellular release of calcium and decreases the accumulation of AMP (cAMP). For some studies, a dose of low chemerin administration has been reported to induce phosphorylation of extracellular-regulated kinase (ERK) in human adipocytes and endothelial cells.[11,29] This shows that inhibition or desensitization of signaling may occur in high concentrations.

GPR1, structurally similar to ChemR23, binds chemerin with high affinity, but signaling is inefficient. Chemerin promotes relatively modest mobilization of Ca2+ and MAPK activation in cell lines expressing the receptor and there is currently no signaling mediated in primary cells so far by GPR1.[30] Though, this receptor has poor signaling through classical intracellular pathways but capable of binding chemerin with high affinity and internalize as a result of this binding. Thus, GPR1 might be considered as a decoy receptor or chemerin scavenger. However, such a function has not been demonstrated yet. CCRL2 has an unusually high variability between species and it is the third atypical receptor in the chemokine receptor family. Chemerin does not promote any signaling pathway through CCRL2, nor it supports the internalization of the ligand-receptor complex. Therefore, CCRL2 has been suggested to increase local concentrations of chemerin and present the protein to other nearby cells displaying ChemR23 on their surface.[28] Chemerin is now recognized as a chemoattractant that promotes the recruitment of the cells to lymphoid organs and sites of tissue injury.[31,32] It has been shown to increase its expression and secretion with adipocyte differentiation. Furthermore, the reduction of chemerin or CMKLR1 activity in cell-based designs abolishes adipogenesis and changes the function of genes that are essential in glucose and lipid metabolism, including GLUT4, DGAT2, leptin and adiponectin.[11] This research has motivated the current review to study the role of chemerin as a novel adipokine and a new area of study for this protein needs to be established.

METABOLIC SYNDROME

Metabolic syndrome (MetS) is characterized by the coexistence of multiple interrelated cardiovascular (CV) risk factors in a single individual.[33] It is characterized by increased abdominal obesity or waist circumference (WC), insulin resistance with or without glucose intolerance, atherogenic dyslipidemia, hypertension, prothrombotic state and a proinflammatory state.[34] MetS affects 25% of the world population and its incidence is increasing gradually.[35] It's increasing prevalence challenges modern medicine and represents a clinical burden and reducing the quality of life and longevity. While the literature lacks possible explanations for understanding its pathophysiology, the pathogenesis of MetS may involve an association between genetic and lifestyle factors. MetS contributes to an enhanced risk for atherosclerosis, coronary artery disease (CAD) and type 2 diabetes mellitus.[36] A range of efforts has been made to establish standardized criteria for the diagnosis of metabolic syndrome. According to the World Health Organization (WHO) criteria for the diagnosis of metabolic syndrome, there should be evidence of insulin resistance along with at least two of these four criteria, i.e., hypertension, hyperlipidemia, obesity and microalbuminuria.[37] National Cholesterol Education Programme (NCEP) Adult Treatment Panel (ATP) III (2005) has suggested other criteria for metabolic syndrome. It requires the presence of at least three of the five factors such as increased waist circumference, hypertension, hypertriglyceridemia, low HDL cholesterol, fasting blood glucose >110 mg/dl for diagnosis of metabolic syndrome.[38] NCEP criteria of metabolic syndrome have been shown to have greater

Table 1: Criteria for Clinical Diagnosis of Metabolic Syndrome by various Organizations.

Clinical Measure	WHO 1998[39]	EGIR 1999[40]	IDF 2005[41]	NCEP ATP III 2005[42]
Insulin resistance (IR)	IR or diabetes plus any two of the following	Hyperinsulinemia plus two of the following	None, but any two of the following	None, but any three of the following
Body weight	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI > 30 kg/m2	waist circumference ≥94 cm in men or ≥80 cm in women	Increased Waist Circumference (population specific)	waist circumference ≥ 90 cm or 40 inches (male), ≥ 80 cm or 35 inches(female)
Lipids	TGs ≥150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women	TGs ≥150 mg/dL and/or HDL-C <39 mg/dL in men or women	TGs ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women (or on treatment)	TGs ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women (or on treatment for dyslipidemia)
Blood pressure	Blood pressure: ≥ 140/90 mmHg	Blood pressure ≥ 140/90 mmHg or antihypertensive medication	Systolic BP > 130 or diastolic BP >85 mm Hg (or on treatment)	Blood pressure ≥ 130/85 mmHg (or on treatment for hypertension)
Glucose	Impaired glucose tolerance or T2DM	Impaired glucose tolerance but not diabetes	Raised fasting plasma glucose (FPG): >100 mg/dL	Raised fasting plasma glucose (FPG): >110 mg/dL
Others	albumin excretion ratio ≥ 20 µg/min or albumin: creatinine ratio ≥ 30 mg/g	None	None	None

Note: World Health Organization (WHO), the European Group for the study of Insulin Resistance (EGIR), the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III), International Diabetes Federation (IDF)

clinical applicability, although it does not include inflammatory or hemostatic variables (Table 1).

Pathophysiology of Metabolic Syndrome

There is no clear, established pathophysiological mechanism behind MetS and three possible and potential etiological categories tend to exist: abdominal obesity, insulin resistance and a pro-inflammatory state. Among the three, insulin resistance is given greater importance in the pathogenesis of the metabolic syndrome. It is characterized as resistance to the biological effects of insulin by key target organs i.e. adipose tissue, liver and muscle.[43] Central obesity is the prominent risk factor in which Free fatty acids (FFAs) are released in abundance from an expanded adipose tissue mass. FFAs result in an increased production of glucose, triglycerides and secretion of very-low-density lipoproteins (VLDLs) in the liver.[44] It is associated with reductions in high-density lipoprotein (HDL) cholesterol and elevated low-density lipoproteins (LDLs). FFAs also reduce muscle responsiveness to insulin by inhibiting insulin-mediated glucose uptake, resulting in decreased glycogenesis and increased accumulation of triglyceride (TG). An increase in circulating glucose and FFA increases secretion of pancreatic insulin, resulting in hyperinsulinemia that can lead to enhanced sodium reabsorption and increased sympathetic nervous system (SNS) activity and contribute to hypertension. The pro-inflammatory state i.e., enhanced secretion of interleukin 6 (IL-6) and tumor necrosis factor (TNF-) produced by adipocytes and monocyte-derived macrophages results in more insulin resistance and lipolysis of adipose tissue triglyceride stores to circulating FFAs. IL-6 and other cytokines also promote hepatic glucose production, VLDL production by the liver and insulin resistance in muscle. As a result of increased FFAs and altered secretion of cytokines, the hepatic production of fibrinogen and adipocyte production of plasminogen activator inhibitor 1 (PAI-1) increases, resulting in a prothrombotic state. Altered secretion of circulating cytokines also stimulates the hepatic production of C-reactive protein (CRP) (Figure 1). MetS is also associated with decreased production of the anti-inflammatory and insulin-sensitizing cytokine such as adiponectin.[45]

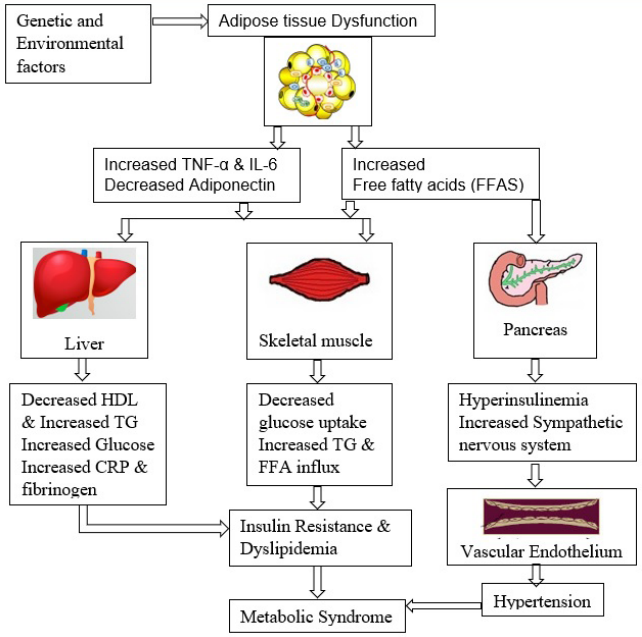

Figure 1: The schematic diagram proposing the Pathophysiology of Metabolic syndrome. Note: HDL- High-density lipoprotein; TG- Triglyceride; CRP- C- Reactive protein.

CHEMERIN AND METABOLIC SYNDROME

Since the various MetS abnormalities can be identified up to 10 years before the detection of type 2 diabetes mellitus (T2DM) or CVD, the aim of identifying people with the MetS is to minimize the long-term risk of developing diabetes, CVD, other forms of atherosclerotic disease. These are life-threatening diseases that will impact the quality of life and life expectancy in the future. Therefore, it is important to search for markers of predictive relevance that could promote the early detection of cardiovascular disease risk in metabolic syndrome and to safeguard the population from the adverse effects of these diseases in their early life.

One of the suggested metabolic markers is a recently described chemerin protein with its pleiotropic impacts on the human body.[46] Though chemerin was first identified in 1997, it took up to 2007 to recognize chemerin as an adipokine. So very few studies have addressed this adipokine and its role in metabolic syndrome as a biomarker. Several studies are conducted in the adult population, children and adolescents, animal models or *in-vitro* cell cultures have demonstrated the role of chemerin in metabolic syndrome, obesity, diabetes, cardiovascular diseases, Crohn's disease, arthritis, polycystic ovary syndrome, liver disease, chronic kidney disease and cancer. As far as our knowledge is concerned, this is the review mainly focused on the theme "The early detection of risk factors is necessary to avoid the occurrence of cardiovascular diseases in later life". Chemerin plays a role in the maturation and differentiation of adipocytes. It functions as a chemoattractor for immune cells and also affects the metabolism of carbohydrates and lipids. Elevated chemerin levels are found in individuals with obesity, diabetes and metabolic syndrome. It can, therefore, be considered to be an early predictive marker for diagnosing metabolic syndrome and its associated cardiovascular risk, even in adolescence and childhood.[46]

Role of Chemerin in Inflammation

Chemerin was identified to play a role in the recruitment and chemotaxis of leukocytes to local sites of inflammation. Chemerin is a strong chemoattractant for macrophages, immature dendritic cells (DCs), plasmacytoid dendritic cells (pDCs) and natural killer (NK), bridging innate and adaptive immunity to trigger an immune response.[20] *In vitro* studies have reported that recombinant human serum and plasma chemerin promote the migration of various CMKLR1- expressing effector cells of the immune system including, pre-B lymphocytes, macrophages, immature plasmacytoid dendritic cells and natural killer cells.[32] In addition to its role in chemotaxis, it also promotes the linkage of macrophages to extracellular matrix proteins and adhesion molecules, thus promoting the adhesion of macrophages to tissue endothelium.[47] Interestingly, expression of CMKLR1 is lost in mature dendritic and natural killer cells, indicating a function of chemerin in the initial phases of leukocyte recruitment. This idea is supported by data showing that neutrophils, generally the first cells recruited to sites of inflammation, secrete serine proteases that activate human pro-chemerin into two highly active mature forms of chemerin.[31] Wittamer *et al.* were the first to identify the chemotactic abilities of human chemerin on immature human dendritic cells using a modified Boyden chamber assay.[20,32] The chemotaxis was confirmed to be ChemR23 and $G_{\alpha i}$ dependent by the use of a blocking antibody against ChemR23 and pertussis toxin respectively.

CHEMERIN: PRO-INFLAMMATORY OR ANTI-INFLAMMATORY?

The primary function of chemerin as a pro- or anti-inflammatory mediator is still controversial. It has been documented that chemerin, which acts through CMKLR1 has both pro- and anti-inflammatory properties. Chemerin's first pro-inflammatory activity was shown by its chemo-attractant characteristic for leukocytes to sites of inflammation and expression of CMKLR1 was shown in macrophages. The expression of CMKLR1 has also been seen in *in-vitro* studies in the effector cells of the immune system.[48] Another study result supporting the pro-inflammatory role of chemerin in the presence of a positive association between pro-inflammatory cytokines such as interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor-alpha (TNFα) and serum chemerin levels.[49,50] Many systemic inflammatory diseases such as Crohn's disease, ulcerative colitis, osteoarthritis, inflammatory bowel disease and chronic hepatitis-C have also been shown to have increased circulating chemerin levels.[49] These data collectively support a pro-inflammatory role of chemerin acting via CMKLR1 which involves both chemotaxis and adhesion of leukocytes in sites of inflammation (Figure 2).

Experimental evidence for CMKLR1 signaling has also been documented in support of anti-inflammatory properties. It was proposed to include resolvins, anti-inflammatory mediators derived from omega-3 poly-unsaturated fatty acids, rather than chemerin as the receptor-ligand. Resolvins are produced during the resolution phase of inflammation where they act as potent inhibitors of leukocyte infiltration. Resolvin E1 (RvE1) has been proposed to signal through CMKLR1 resulting in reduced TNF alpha-mediated signaling and production of the potent pro-inflammatory cytokine IL-12 by dendritic cells.[51] However, it is important to note that these findings have yet to be independently verified and subsequent studies indicated that the actions of RvE1 are elicited through interaction with receptors other than CMKLR1.[52,53] Both chemerin and a synthetic polypeptide derived from the last 15 C-terminal amino acids of chemerin (chemerin15) have been reported to protect mice from the development of zymosan-induced peritonitis by decreasing the production of pro-inflammatory cytokines and reducing the number of neutrophils and monocytes present in peritoneal fluid.[54] The authors stated that chemerin15 administration did not protect the CMKLR1 knockout mice from peritonitis, indicating that the anti-inflammatory actions of this peptide were dependent on CMKLR1 signaling. Subsequently, the same group stated that Chemerin15, but not chemerin, could also act in the resolution of inflammation by promoting the phagocytosis of microbial particles and apoptotic cells by macrophages both *in vitro* and *in vivo*.[55]

An anti-inflammatory role for chemerin/CMKLR1 signaling has also been described in a mouse model of lipopolysaccharide-induced lung inflammation. In this study,[55] the administration of recombinant chemerin decreased inflammation of lung tissue and alveolar infiltration by neutrophils compared to vehicle-treated mice.[54] CMKLR1-knockout mice were both unresponsive to the beneficial effects of chemerin and exhibited elevated LPS-induced neutrophil accumulation, suggesting a central role for chemerin/CMKLR1 signaling as an inflammatory mediator. At present, experimental evidence from animal and cell-based models support both pro- and anti-inflammatory roles for chemerin/CMKLR1 in immune processes. In humans, this research is supported by

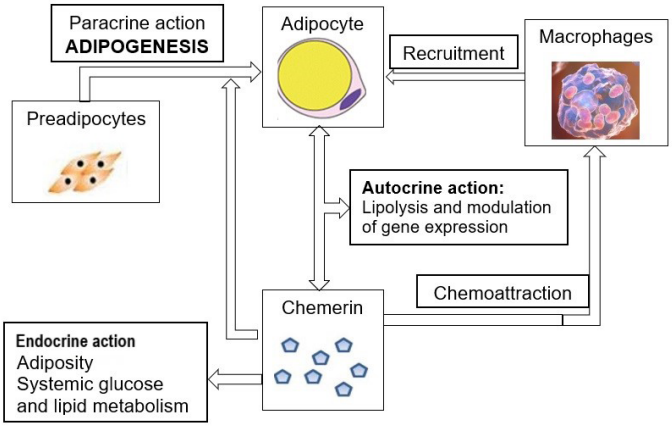

Figure 2: The schematic diagram proposing the functions of chemerin. Local production from chemerin from adipocytes regulates adipogenesis and through its receptor or possibly other receptors can modulate the expression of adipocyte genes involved in lipid and glucose metabolism. Furthermore, chemerin, through a paracrine effect, may participate in recruitment and activation of inflammatory cells (e.g. macrophages) to adipose tissue. Chemerin circulates at high levels in the serum and may have systemic effects on metabolism.

correlational data between inflammatory states and elevated chemerin levels. Although it is not clear whether chemerin contributes more to the progression of inflammation or the resolution, different chemerin isoforms are likely to have different roles in the various stages of inflammation which is likely to depend on the nature of the immune stimulus as well as a complex interplay with other signaling molecules and effector cells of the immune system.

Role of Chemerin in Adipogenesis and Adipocyte Metabolism

Adiposity is a condition of morbid overweight featured by excessive expansion of white adipose tissue (WAT) and is based on an increase in adipocyte size (hypertrophic obesity) and adipocyte number (hyperplastic obesity).[57] The WAT is a good indicator of metabolic disorder in humans[58] and releases a plethora of adipokines including chemerin to affect adipose tissue homeostasis, adipocyte metabolism and inflammation in fat tissue. In 2007, Bozaoglu and colleagues for the first time suggested a higher level of chemerin expression in Psammomys obesus as opposed to normoglycemic lean model, which are the animal models for obesity and type 2 diabetes (T2D).[7] Chemerin and CMKLR1 are expressed at high levels in WAT than brown adipose tissue (BAT) however, stromal vascular cells have the highest expression of CMKLR1.[11] While, BAT is associated with thermogenesis and due to its capability to produce heat instead of ATP resulting in weight loss, it has been identified as a potential target for the treatment of obesity. Thus, this would suggest that chemerin exerts its effect on weight by regulating adipogenesis rather than thermogenesis. Chemerin has been shown to regulate adipocyte differentiation and loss of chemerin or CMKLR1 expression in 3T3-L1 preadipocytes severely impairs differentiation into mature adipocytes and reduces the expression of genes involved in glucose and lipid metabolism including perilipin, glucose transporter 4 (GLUT4), diacylglycerol acyltransferase (DGAT2) (an enzyme involved in triglyceride synthesis), adiponectin and leptin.[11] The expression of chemerin and its receptor increases during the differentiation of preadipocytes into adipocytes.[59] Chemerin-CMKLR1 combination induces the phosphorylation of extracellular signal-regulated kinases 1/2 (ERK 1/2) and lipolysis in differentiated adipocytes and 3T3-L1 cells, stimulates intracellular calcium release and inhibits cAMP accumulation.[11,20,59]

Interestingly, chemerin-CMKLR1 signaling, which is regulated by peroxisome proliferator-activated receptor γ (PPARγ) (most important regulator of adipogenesis), predisposes the differentiation of bone marrow mesenchymal stem cells (BMSCs) into adipocytes rather than osteoblasts.[60] Inactivation of chemerin-CMKLR1 signaling by genetic modification or antibody neutralization shifts the adipogenic clonal expansion of BMSCs to osteoblastogenic differentiation and chemerin treatment also alters the fate of myoblast cells from myogenesis to adipogenesis.[61] Consistent with these findings, *in-vivo* disruption of the CMKLR1 gene reduces the food intake, body mass and fat deposition of mice.[62] In contrast, another more recent study showed that CMKLR1-knockout mice exhibit mild obesity but normal adipocyte differentiation.[63] It is found that the number of adipocytes in the CMKLR1-null mice is not changed, but there is an increase in the lipid storage in each of adipocytes. Inflammatory cytokines such as TNF-α and IL-1β are reported to increase the synthesis of chemerin and secretion in 3T3-L1 adipocytes, human primary adipocytes and in mouse adipocytes *in-vivo* acting through pathways involving the activation of NF-κB pathway and by phosphorylating extracellular signal-regulated Kinase (ERK) 1/2. Chemerin expression in adipocytes has also been reported to be induced by Free Fatty Acids (FFAs) through the activation of transcription factor Sterol Regulatory Element-Binding Proteins 2 (SREBP2).[64] In obese states, circulating chemerin levels positively correlate with Body-Mass-Index (BMI), Waste-to-Hip (WHR) ratio, glucose levels, hypertension and circulating triglycerides,[7] which all are well-documented risk factors for MetS, ultimately resulting in the pathogenesis of cardiovascular diseases such as atherosclerosis (Figure 2).

Role of Chemerin in Glucose and Lipid Metabolism

Both glucose-stimulated insulin secretion from the pancreas and insulin-stimulated glucose uptake in peripheral tissues contribute to the proper regulation of glucose tolerance. Currently, the precise role and significant effect of chemerin on glucose metabolism is unclear and a matter of debate. *In-vitro* studies using 3T3-L1 adipocytes have reported contradictory findings, with one study reporting decreased insulin-stimulated glucose uptake and another showing increased insulin-stimulated glucose uptake and insulin receptor substrate (IRS)1 tyrosine phosphorylation after chemerin treatment.[13,17] For example, Takahashi *et al.* reported that recombinant mouse with a short stimulation by low concentrations (nM) of chemerin modestly increased insulin-stimulated tyrosine phosphorylation of insulin receptor substrate-1 and glucose uptake in 3T3 adipocytes.[13] In contrast, Kralisch *et al.* reported that longer stimulation by higher chemerin concentrations (μM) significantly decreased insulin-stimulated glucose transport in 3T3 adipocytes.[17] Thus, the different concentrations, treatment durations and conditions might have contributed to the discrepant results. Thus. The shorter and lower dose treatment might have caused an acute increase in glucose uptake, whereas the longer and higher dose treatment might have resulted in a negative feedback response, or potentially the establishment of a resistant state that produced a net decrease in glucose uptake. Similarly, in another study, sell *et al.* reported that treatment of primary human skeletal muscle cells with 60 nM chemerin for 24 h increased phosphorylation of an IRS1 serine residue known for negatively modulating the actions of insulin associated with decreased insulin-stimulated glucose uptake.[65] A concomitant decrease in Akt, glycogen synthase kinase (GSK3a) and GSK3b phosphorylation was also observed. In mice, chemerin treatment exacerbates glucose intolerance in obese/diabetic (db/db), but not normoglycemic models by decreasing serum insulin levels, reducing adipose tissue glucose uptake and causing a significant decrease in liver and total tissue glucose uptake.[62] Chemerin-induced dysregulation of glucose uptake in adipocyte and myocyte cultures suggests an insulin-dependent GLUT4 mechanism, whereas a decrease in serum insulin levels and liver glucose uptake in obese/diabetic (db/db) mice suggests an insulin-independent GLUT2 mechanism (Figure 2).

Atherogenic dyslipidemia, typically known as elevated circulating triglycerides and reduced HDL-cholesterol levels (high-density lipoprotein), occurs as a consequence of altered lipolysis in MetS and is associated with an increased risk of developing CVDs. The majority of studies report significant positive correlations of chemerin with circulating triglycerides, LDL cholesterol and blood pressure and negative correlations with HDL cholesterol.[7,66-68] In 3T3-L1 adipocytes or primary cultures of mouse white adipocytes, chemerin was reported to both promote and inhibit basal or isoproterenol-evoked lipolysis. However, very few studies have directly examined the impact of chemerin signaling on the regulation of lipolysis and contradictory findings have emerged. Some experiments with 3T3-L1 and murine primary adipocytes support chemerin's role in stimulating lipolysis,[11,59] while another reported decreased basal lipolysis following chemerin treatment.[69] Notably, effects in CMKLR1 knockout mice were blunted in the latter study, indicating that CMKLR1 does affect lipolysis in some manner. To date, only one study has investigated the effect of chemerin on *in-vivo* lipid homeostasis, with no change in triglyceride and cholesterol levels following chronic overexpression of chemerin in LDL (low-density lipoprotein) receptor knockout mice.[70] Thus, the mechanisms by which chemerin alters glucose and lipid

homeostasis remain unclear and these conflicting findings illustrate a need to clarify the role of chemerin in glucose and lipid metabolism.

CHEMERIN AS A NOVEL ADIPOKINE: LINK BETWEEN METABOLIC SYNDROME AND CVD

It is incredibly difficult to understand the cardiovascular system because of its nature and its relation to the functions of other body systems. MetS confers a 5-fold increase in the risk of T2DM and 2-fold the risk of developing CVD over the next 5 to 10 years.[33] Studies focused on the pathophysiological mechanisms linking MetS with CVD found inflammation, insulin resistance and altered circulating adipokines were reported to predict atherosclerosis and cardiovascular events. Abnormal fat accumulation, hypercoagulability state and endothelial dysfunction may also influence cardiovascular risk.[71] Chemerin has been identified in recent times as a chemokine, adipokine, paracrine/autocrine agent and growth factor. Every time chemerin is identified in one of these roles, concerning the cardiovascular system. chemerin as a chemokine allows chemoattraction through the vasculature,[20] changes endothelial adhesion levels[72] and is extracellularly activated in the lumen.[20] Chemerin as an adipokine adjusts lipid[11] and glucose levels (through glucose intolerance).[13] Chemerin as a growth factor promotes microvessel growth to support adipocytes and possibly altering their infiltration into endothelium.[7] Chemo-attraction is one of the most important functions of chemerin and in this way, macrophages interact with dendritic cells and natural killer cells and are targeted towards areas of damage.[20,73,74] Similarly, chemerin can also induce interaction of intercellular adhesion molecule-1 (ICAM-1) and E-selectin with the endothelium.[75] Chemerin increases the production of matrix myeloperoxidase (MMP). This has been shown to affect the remodeling and growth of blood vessels in *in-vitro* experiments.[12,29,76]

In previous studies, serum chemerin levels in the MetS group with CAD were found to be significantly higher than in MetS group without CAD and also found a correlation between circulating chemerin levels and CAD severity.[66,68] Chemerin was also reported to have positive correlations with arterial stiffness and coronary arterial plaques.[50,77] Kostopoulos *et al.* observed a significant correlation between the level of chemerin released from periadventice adipose tissues, foam cells, vascular smooth muscle cells in the regions of atherosclerotic lesions and the severity of atherosclerotic lesions.[78] Hah *et al.* also showed a significant correlation between chemerin levels and the severity of coronary arterial stenosis in patients with CAD and also positive correlations between serum chemerin levels and fasting glucose, triglycerides, total cholesterol and High-sensitivity C-reactive protein (hs-CRP).[79] While significantly high levels of serum chemerin were observed in CAD, Becker *et al.* were unable to show a significant increase in the area of atherosclerosis with long-term chemerin expression in their *in-vivo* study,[70] and Lehrke *et al.* also did not find any association between serum chemerin levels and coronary atherosclerosis in their study evaluating coronary atherosclerosis with computerized tomographic angiography.[75] Spiroglou *et al.* found a significant correlation between coronary atherosclerosis and epicardial chemerin levels.[80] Chemerin was also reported to contribute to the progression of atherosclerosis by stimulating adhesion of macrophages to the extracellular matrix protein fibronectin and vascular cell adhesion molecule-1 (VCAM-1).[47] It has also been shown that the chemerin molecule activates endopeptidases MMP-2 and MMP-9 belonging to matrix metalloproteinases that play a key role in plaque instability,[29] and increases the expression of adhesion molecules such as E-selectin and ICAM-1,[50] and was considered a new biomarker for coronary atherosclerosis (Figure 3).

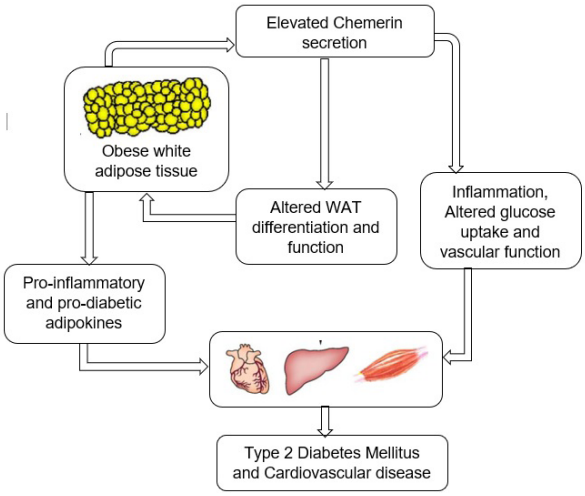

Figure 3: The schematic diagram proposing the role of chemerin in linking metabolic syndrome and cardiovascular disease. The secretion of chemerin from white adipose tissue is elevated in MetS. Chemerin from white adipose tissue promotes adipocyte differentiation, alters adipose tissue function and might play a role in angiogenesis, a process essential for the expansion of white adipose tissue. Chemerin is also a pro-inflammatory adipokine, causing an increase in the secretion of proinflammatory and prodiabetic adipokines, which further impair adipose tissue metabolic function and have negative systemic effects including impaired insulin sensitivity, altered glucose and lipid metabolism and a decrease in vascular function in other tissues. The dual role of chemerin in inflammation and metabolism suggests that it is involved in the crosstalk that integrates the inflammatory response with metabolism in MetS. The resulting changes in metabolic homeostasis and vascular function might set the stage for the development of T2DM and cardiovascular disease.

CONCLUSION

The incidence of MetS is growing in alarming proportions and there is a great need for therapeutic and preventive steps against this health issue. The leading cause of morbidity and mortality in MetS is atherosclerotic macrovascular complication mainly coronary artery disease (CAD). Traditional risk factors used in the prediction of atherosclerosis are insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state and chronic stress. HDL-C is one of the important and independent protective factors for atherosclerosis of all the lipid parameters and reduced HDL-C is considered a major risk factor. MetS constitutes all these metabolic perturbations that contribute to CVD development. Chemerin is a novel adipokine that is associated with adipogenesis, angiogenesis, inflammation and altered lipid and glucose metabolism which demonstrates a multifaceted function of this protein. Studies about chemerin and its association with cardiovascular risk factors in individuals with metabolic syndrome are still limited and scarce. This brief review allowed us to conclude that the deregulation of chemerin and its association with inflammation, insulin resistance and increased adipose tissue mass may contribute to the onset of cardiovascular diseases in metabolic syndrome subjects, suggesting that this adipokine plays a key role in early identification of individuals at risk by predicting atherosclerosis earlier and it may help to implement early preventive measures against cardiovascular disease. This review will also improve the understanding of the role of chemerin in the progression of the disease and the possibility to develop drugs targeting chemerin and their cognate receptors, representing a new therapeutic approach to treat visceral adiposity, insulin resistance and inflammation and protect patients from MetS-related diseases.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ABBREVIATIONS

CVD: Cardiovascular Disease; **MetS:** Metabolic Syndrome; **GPCRs:** G protein-Coupled Receptors; **TIG2:** Tazarotene-Induced Gene 2; **RARRES2:** Retinoic Acid Receptor Responder 2; **WAT:** White Adipose Tissue; **FFA:** Free Fatty Acids; **TNF:** Tumor Necrosis Factor; **LPS:** Lipopolysaccharide; **IFN:** Interferon; **IL:** Interleukin; **ChemR23:** Chemerin Receptor 23; **CMKLR1:** Chemokine-like receptor 1; **CCRL2:** Chemokine receptor-like 2; **GPR1:** G-protein coupled receptor 1; **DC:** Dendritic cells; **ERK:** Extracellular-regulated kinase; **IR:** Insulin resistance; **WHO:** World Health Organization; **EGIR:** European Group for the study of Insulin Resistance; **NCEP ATP III:** National Cholesterol Education Programme Adult Treatment Panel III; **IDF:** International Diabetes Federation; **VLDL:** Very-low-density lipoproteins; **HDL:** High-density lipoprotein; **LDL:** Low-density lipoproteins; **TG:** Triglyceride; **PAI:** Plasminogen activator inhibitor; **CRP:** C-reactive protein; **pDCs:** Plasmacytoid dendritic cells; **RvE1:** Resolvin E1; **GLUT4:** Glucose transporter 4 (GLUT4), **DGAT2:** Diacylglycerol acyltransferase; **PPARγ:** Peroxisome proliferator-activated receptor γ; **BMSCs:** Bone marrow mesenchymal stem cells; **SREBP2:** Sterol Regulatory Element-Binding Proteins 2; **IRS:** Insulin receptor substrate; **GSK:** Glycogen synthase kinase.

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