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Complement Anaphylatoxin C5a, Endothelial Dysfunction and Low-Grade Inflammation in Atherosclerotic Vascular Diseases

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Objectives: The objective of the paper is to summarize the evidence in atherosclerosis research regarding the relationship of complement C5a with low-grade inflammation, endothelial dysfunction, and atherosclerosis. **Methods:** A systematic review of the literature was performed from 1990 to 2017 regarding the contribution of the complement anaphylatoxin C5a in atherosclerosis with an emphasis on new research findings. The strategy included searching the electronic databases of Web of Science by Thomson Reuters and PubMed Central®. **Results:** The targeted recherché revealed a clear pro-inflammatory role of C5a in atherosclerotic vascular low-grade inflammation. **Conclusion:** There are clear associations between complement C5a and endothelial dysfunction in low-grade atherosclerotic inflammation. Therapeutic strategies to capture C5a or the development of pharmacomimetics of the vasoprotective endothelial phenotype appear to be a potentially fruitful strategy.

Keywords: Inflammation, Atherosclerosis, Complement C5a and Endothelium

Introduction

The complement system is a part of our immune system and is a complex protein network[1]. Complement proteins are present in body fluids and tissues, either in soluble form or bound to membranes of circulating and tissue-embedded cells[1,2]. They are produced by immune cells, in liver and adipose tissue and by the endothelium[1].

The complement anaphylatoxin C5a is a small peptide fragment and one of the most potent inflammatory molecules generated by cleavage from the inactive protease C5 during the activation step[2]. C5a is highly pleiotropic in function and produces

its effects at picomolar and nanomolar concentrations[3]. C5a is the most powerful of the known anaphylatoxins in inducing chemotaxis, immune cell activation and as well as endothelial activation[2,4].

Endothelial dysfunction is considered the first step in the degeneration of blood vessels and describes the disturbed interaction of the endothelium with the blood stream and the surrounding tissues[5]. Endothelial dysfunction is associated with traditional cardiovascular risk factors such as hypertension, diabetes mellitus, and it predicts atherosclerosis progression and cardiovascular events in the general population. It has now been accepted as the first step of atherosclerotic vascular inflammation[6].

Inflammation is an indispensable and vital part of the innate human immune system[1,7]. The aim of inflammation is to transmit an alarm signal in order to overcome to danger, harmful stimuli such as tissue damage and infections. The inflammatory process is simultaneously the beginning of the healing process. Infections, wounds, and any damage to tissue would not be able to heal without an inflammatory response. Inflammatory mediators are powerful signals that induce substantial changes in a broad range of target cells and tissues[1,7]. Acute inflammatory responses, also sometimes called "high-grade inflammation", such as in acute infections or in sepsis are associated with rapid robust inflammatory response at sites of infection that become systemically expressed[8]. Unlike the high-grade inflammation, the chronic kind produces a steady, low level of inflammation (low-grade inflammation) within the body that can contribute to the development of chronic disease[9].

Increasing data demonstrate the involvement of endothelial dysfunction, complement C5a and vascular inflammation in the pathophysiological processes in the arterial vasculature underlying cardiovascular diseases (CVD). However, most reports describe these processes separately and to my knowledge there are no reports integrating these three topics together as an important cause of atherosclerotic vascular disease. Therefore, it is necessary to review and summarize the evidence to better understand the pathophysiological mechanisms and explore novel ideas.

In this review, the available knowledge has been summarized regarding the relationship of the complement anaphylatoxin C5a, endothelial dysfunction and the chronic low-grade inflammation in atherosclerotic vascular inflammation as a common cause of CVD. Especially, discussed here for the first-time are data originating from the investigation of atherosclerosis among the Mongolian population that this is connected to all the above-mentioned three topics.

The purpose of this paper is to summarize novel evidence in atherosclerosis research that gives insight into the relationship of complement C5a with low-grade inflammation, endothelial dysfunction, and atherosclerosis.

Materials and Methods

A systematic review of literature was performed from 1990 to 2017 regarding the contributions of the complement anaphylatoxin C5a, endothelial dysfunction in atherosclerotic vascular inflammation was performed and the most relevant and newest findings on the role of C5a in modulation of vascular responses was dissected from the literature review. The search strategy included searching the electronic databases of Web of Science by Thomson Reuters and PubMed Central® Databases using the following keywords in combination "complement C5a and atherosclerosis", "complement C5a and inflammation", and "complement C5a and inflammation and atherosclerosis". Among 2419 publications in PubMed Central® Databases and 218 publications in Web of Science by Thomson Reuters were selected and cited here the most relevant and important with emphasis on 51 recent publications.

Results

The targeted analysis of these data revealed the clear relationship of pro-inflammatory role of C5a, which plays an important role in chronic low-grade vascular inflammation, and endothelial dysfunction in atherosclerosis. The results are presented as the topics that follow.

Endothelial dysfunction and complement anaphylatoxin C5a

The endothelium is the inner surface of the blood vessels, which as barrier and transfers signals from the blood stream into the outer vessel layers and the surrounding tissue, and vice versa[9]. Healthy endothelial cells are involved in vasodilation through nitric oxide release, which also inhibits platelet adhesion and aggregation, as well as leukocyte adhesion[5]. Conversely, injured endothelial

cells can develop a vasoconstrictive, pro-inflammatory, and procoagulant phenotype[9]. Endothelial dysfunction is considered the first step of vascular changes in vascular diseases and describe the disturbed interaction of the endothelium with the blood stream and the surrounding tissues[5,10]. In the context of atherogenesis, early endothelial cell dysfunction is characterized as loss of anatomical integrity of the intima, as originally formulated by Ross and Glomset in the "response-to-injury" hypothesis[11]. Here, the initiating event in the atherogenic process was some form of overt injury to the intimal endothelial lining, induced by noxious substances (e.g. oxidized cholesterol, constituents of cigarette smoke, hyperhomocysteinemia, hyperglycemia, etc.) or altered hemodynamic forces (e.g. blood flow disturbances generated by hypertension)[6,11,12]. Among all the factors, endothelial dysfunction is mostly caused by lipid disorders, smoking and hypertension[6]. The next stage of endothelial dysfunction is the formation of atherosclerotic plaque, and that is characterized by harmful deposition of lipids and immune cells in the vessel wall. Atherosclerotic deposits/ plaques can be present in such a degree that they narrow the arteries and cause a restriction of blood stream[10]. This results in insufficient oxygen delivery to the surrounding and distal tissues (ischaemia). Plaques can additionally destabilize the vessel and as a result, abrupt ruptures along the plaque and surrounding vessel surface can occur[6,10].

Complement anaphylatoxin C5a is strong inflammatory mediator that can promote local as well as systemic inflammation. C5a is thought to contribute to atherosclerotic vascular inflammation because C5a can activate endothelial cells (ECs), immune cells such as macrophages and neutrophils, smooth muscle cells and platelets[2,3,13]. In addition, it is known that C5a can elevate vascular permeability. Enhanced vascular permeability by C5a is an important means to deposit lipids and immune cells in the vascular wall in the initial stage of atherosclerotic vascular inflammation[2,3,13].

Moreover, ECs express the classical C5a receptor 1 (C5aR1, CD88) and the activation of ECs by C5a can induce the secretion of a variety of inflammatory mediators from ECs: chemokines and cytokines, like IL-1, IL-6 (Interleukin), MCP-1 (Monocyte Chemotactic Protein 1), TNF-α (Tumor Necrosis Factor-α, adhesive molecules such as E-selectin, ICAM-1 (Intercellular Adhesion Molecule 1), VCAM-1 (Vascular Cell Adhesion Molecule 1), growth factors such as VEGF (Vascular Endothelial Growth Factor), PDGF (Platelet-derived growth factor) and transcription factor NF-kappaβ (nuclear factor 'kappa-light-chain-enhancer' of activated B-cells)[2,6,14-20]. For example, VCAM-1 was found to have a selective adhesivity for mononuclear leukocytes and lymphocytes to arterial wall[21]. Some studies implicated components of oxidized low-density lipoproteins (oxLDL), as potent stimuli for its expression from ECs, thus mechanistically linking VCAM-1 induction to the atherogenic process[21].

Interestingly, conversely, the above mentioned all pro-inflammatory mediators are able to induce the secretion of C5a from ECs, which leads to promote chronic vascular inflammation[13,22]. The stimulation of ECs with IL-6 or acute phase reactants such as LPS (Lipopolysaccharide) and CRP (C-reactive Protein) can lead to dramatically increased secretion of C5a form ECs[18,19,23]. In addition, it has been demonstrated that oxLDL-stimulated ECs secrete higher amounts of pro-inflammatory mediators, including C5a. Combined stimulation of ECs with oxLDL and C5a leads to a 3-fold increase in the secretion pro-inflammatory cytokine TNF-α compared to the stimulation of oxLDL and C5a alone, indicating the combined pro-inflammatory effect of C5a and oxLDL in vascular inflammation[24]. These findings thus highlight the pathogenic significance of C5a in the induction and progression of inflammatory processes in the context of atherogenesis and endothelial dysfunction.

Low-grade inflammation and complement anaphylatoxin C5a

For these reasons, low-grade inflammation and aberrancies in immune function are of particular interest in cardiovascular research. First, because inflammation and immune dysregulation contribute to several chronic diseases, next, none of the hitherto established inflammatory markers have been consistently shown to add to traditional CVD risk prediction in large studies[9]. Inflammation is the body's immediate response to dangers such as tissue damage and infection[7]. The aim of inflammation is to transmit an alarm signal in order to overcome the danger and to repair the damage[7]. Inflammatory mediators are powerful signals that induce substantial changes in a broad range of target cells and tissues[7]. It has been known that in high-grade inflammation like in sepsis, there is robust activation of the complement system in humans, as signified by the loss of hemolytic activity of complement and by the appearance in plasma of complement activation products, namely, the complement anaphylatoxins,

C3a and C5a, which can be measured by ELISA technology[8]. In humans, the levels of C5a can rise to levels as high as 100 nM[8] (normal range 4-9 nM, 5.85 nM in healthy individuals in our study)[25,26]. In addition, the normal range of plasma C5a concentration is dependent on the ELISA sensitivity, therefore, can vary from test to test. Acute phase reactants, like CRP (C-reactive protein) increase immediately in infection as well[7,8,23]. The endothelium plays an important role in inflammatory syndromes, such as sepsis and atherosclerosis as described above. In the case of sepsis, there is evidence of acute release of high levels of numerous pro-inflammatory mediators are, such as cytokines, chemokines and complement factors (CRP, TNF-α, LPS, IL-6, and FasL (Fas Ligand)) including the complement anaphylatoxin C5a[1,7,8].

Unlike high-grade inflammation, the chronic kind produces a steady, low level of inflammation within the body that can contribute to the development of chronic processes. Inflammatory mediators are produced by immune cells but can also be released from damaged tissues[27]. In the context of atherosclerosis, vascular cells continuously secrete inflammatory mediators. In chronic low-grade inflammation; however, inflammatory mediators are constantly released at a low level and not as a result of an explicit danger[10]. For example, adipose tissue itself secretes inflammatory mediators such as C5a in obesity[28]. Lifestyle factors such as smoking and sleep shortage can also lead to chronic release of inflammatory mediators such as CRP and ICAM-1[23]. Furthermore, chronic, typically Western diseases such as type 2 diabetes mellitus are characterized by chronic inflammation, endothelial dysfunction and immune dysregulation[29]. Immune dysregulation, such as complement activation incites systemic low-grade inflammation and also directly contributes to cardiovascular damage and atherosclerosis. Immune cells are characteristic constituents of atherosclerotic plaques and release humoral immune factors locally inside the vessel wall, such as antibodies or matrix metalloproteinases (MMPs)[10,30]. Thereby, immune cells such as macrophages, promote atherosclerosis and contribute to the destabilization of plaques. In addition, humoral immune factors can damage endothelial cells and can activate the coagulation system. Again, one major component of humoral immunity is the complement system[31].

Elevated levels of C5a have been found in the serum of patients with numerous inflammatory acute and chronic disorders, such as rheumatoid arthritis, inflammatory bowel diseases, sepsis, peritonitis, asthma and allergy, hemorrhagic shock after trauma and burns and different infectious diseases (reviewed by Klos et al.) [2]. Several authors have described the role of elevated levels of C5a in cardiovascular diseases (CVD), like atherosclerosis, restenosis after vascular injury and myocardial infarction[24,25,31,32]. In addition, both C5a receptors, C5aR1 and C5L2 (C5a receptor-like 2) have been identified in human atherosclerotic plaques[24,33]. The increased expression of both C5aR1 and C5L2 in all pathological stages of human atherosclerotic vascular development has been previously demonstrated[24]. Recently published studies have demonstrated that plasma C5a and soluble C5b-9 (membrane attack complex) concentration are associated with the low-grade inflammation score and different manifestations of CVD[25,31]. In these studies higher concentrations of C5a and sC5b-9 were associated with endothelial dysfunction, respectively. There was a direct association between C5a and low-grade inflammation markers (IL-6, serum amyloid A, haptoglobin) as well as direct correlation with endothelial dysfunction markers like vWF (von Willebrand Factor) and soluble VCAM-1[25,31].

Taken together, these data underscore the importance of the role of C5a not only in systemic high-grade inflammation, but also its role in chronic low-grade inflammatory disorders like atherosclerotic vascular inflammation.

Discussion

Complement anaphylatoxin C5a, human atherosclerosis and low-grade inflammation

As previously reported, a large body of experimental animal studies has identified various mechanisms that implicate a causal role of the complement factors in CVD, such as in atherosclerosis, however, there are limited studies in human atherosclerosis[32,34-37]. Among complement products, C5a is a most potent soluble inflammatory mediator promoting the recruitment and activation of neutrophils and monocytes[2]. Associations between elevated C5a plasma concentrations and different manifestations of atherosclerotic vascular changes have been reported. For example, late lumen loss of drug eluting coronary stents is associated with increased serum levels of the complement components C3a and C5a[38]. Moreover, another study has demonstrated that complement component C5a predicts restenosis after superficial femoral

artery balloon angioplasty. Enhanced complement activation prior to percutaneous angioplasty, as measured by higher levels of C5a, was significantly associated with restenosis after superficial femoral artery balloon angioplasty[39]. In addition, C5a was present in human coronary lesions (locally), and its higher levels were associated with late lumen loss of drug-eluting stents, and adverse cardiovascular events have been correlated with increased C5a plasma levels[30,38,40]. Macrophages stimulated with C5a showed increased mRNA levels of MMP1 and MMP9 (matrix metalloproteinases), indicating the role of locally produced C5a in plaque destabilization[30]. Confirming these data, in our recently published study, we revealed an elevated plasma concentration of C5a in patients with an established atherosclerotic burden[26]. In our study, a significantly elevated plasma C5a protein concentration was determined in the group of patients with atherosclerosis compared to the control healthy individuals (276.3±24.8 vs. 61.6±4.4 pg/mL)[26]. The lowest measured concentration in this study was similar to the study of Speidl et al.[38]. However, the highest concentration and mean values in our study were higher than the data in this study. We therefore concluded that this may indicate more inflammatory characteristics of atherosclerosis among Mongolian population. It can be speculated that the high-fat diet consumption among Mongolian population, high body-mass index and obesity leads to a high prevalence of chronic low-grade inflammatory conditions in Mongolia. Besides the endothelial activation by modified lipoproteins, adipose tissue itself is able to secrete multiple inflammatory mediators, including C5a. Of note, both C5aR1 and C5L2 receptors are expressed in adipocytes and obese patients express not only elevated C5a levels but also both C5a receptors[28,41]. Therefore, another source of elevated plasma C5a concentration in our atherosclerosis patients who are overweight might be the locally generated C5a from adipose tissues.

In addition, we measured plasma C5a levels in patients with native and established atherosclerotic burden[26]. In studies by Speidl et al. C5a concentrations were measured in patient undergoing cardiovascular surgery[38,40]. Therefore, it is difficult to compare our measurements with data obtained by Speidl et al.[40]. Moreover, as described above, Hertle et al. investigated the correlation of markers of endothelial activation with C5a plasma concentrations[25]. They found a direct correlation between endothelial activation markers and C5a concentrations, however, there was no significant correlation between cIMT and C5a plasma concentrations. In contrast to this study, we were able to detect a direct correlation of cIMT with C5a plasma concentrations, which underscore again the role of higher plasma C5a levels in atherosclerotic plaque development among Mongolian patients[26]. In our study as well as in the study by Hertle et al. the systemic concentrations of C5a were measured assuming that this reflects their concentrations in relevant tissues, in this case, in relation to endothelial dysfunction, this association seems relevant because endothelium is directly exposed to the circulation[25]. Moreover, similarly to Hertle et al. we measured C5a concentration as a low-grade inflammation marker in this study[25]. In contrast to Hertle et al. other complement components or different markers for endothelial dysfunction have not been determined in our study, which was a limitation in our study[25].

Beyond that, to differentiate the implications of C5a in systemic high-grade inflammation and in atherosclerotic low-grade inflammation, we measured some parameters of systemic inflammation and included only patients without signs of systemic inflammation for this study[26]. Another interesting finding in our study is the correlation of higher plasma C5a concentrations with higher plasma levels of total cholesterols in atherosclerotic patients[26]. Of note, the recent reports on the crosstalk between C5a and cholesterol crystals in the induction of atherosclerotic inflammation provides another interesting mechanistic insight in complement activation in atherosclerosis that needs to be harnessed for the treatment of atherosclerosis[42]. Taken together, we and others have demonstrated that C5a may in humans also participate in chronic low-grade inflammation, especially in atherosclerotic vascular chronic low-grade inflammation[25,26,30,38,39].

In summary, there are clear associations between complement C5a and endothelial dysfunction in atherosclerotic low-grade inflammation (Table 1).

The main limitation of this review is the search strategy used to identify publications on the role of the C5a in endothelial dysfunction and chronic inflammation from 1997 to 2017 and the possibility of bias in selecting and dissecting the most relevant and recently published data. Although, there are number of animal studies in this regard, e.g. studies using complement-deficient animals/mice, animal publications were not a focus of this review. The other limitation includes the search strategy of

Table 1. Summary of the role of complement C5a, endothelial dysfunction and low-grade inflammation in atherosclerosis

Topics	Complement C5a anaphylatoxin	Endothelial function and dysfunction	Low-grade inflammation
Physiological functions and general characteristics	• Small peptide cleavage fragment of C5 • Strong inflammatory mediator • Promotes local and systemic inflammation • Binds to C5aR1 and C5L2 • Induces chemotaxis of inflammatory cells • Induces immune cell activation (macrophages, neutrophils, SMCs and platelets) • Induces vascular permeability • Plasma concentration range 2,5-10 ng/ml	• Barrier and transfer signals from the blood stream to surrounding tissues • Release nitric oxide (NO) and vasodilatative characteristics • Inhibit platelet adhesion and aggregation • Inhibit leukocyte adhesion • Control vascular tone and vascular growth	• Body's reaction to dangers, tissue damage and infection • Steady and chronic inflammatory reaction • Inflammatory mediators constantly released at low levels • Related to chronic immune disorders such as chronic inflammatory diseases
Functions in atherosclerotic vascular changes	• Elevated in plasma • Elevated in local tissues at sites of atherosclerosis • Increased binding to C5aR1 and C5L2 • Activates ECs to secrete pro-inflammatory mediators such as IL-1, IL-6, MCP-1, TNF-α, E-selectin, ICAM-1, VCAM-1, VEGF, PDGF and C5a • Activates SMCs to secrete pro-inflammatory mediators, such as VCAM-1, TNF-α and C5a • Activates immune cells to secrete pro-inflammatory mediators • Elevates vascular permeability and deposition of lipids • Activates ECs together with oxLDL • Induces low-grade inflammation	• Loss of anatomical integrity of the intima • Elevated permeability of the intima e.g. diffuse and accumulate lipids • Endothelial cell (EC) injury • Vasoconstictive characteristics of ECs • Pro-inflammatory phenotype of ECs • Procoagulant phenotype of endothelial surface • Elevated secretion C5a from ECs • Elevated secretion of pro-inflammatory mediators from ECs by stimulation of C5a • Atherosclerotic deposits and development of plaques	• Lifestyle factors such as smoking and HFD can induce low-grade inflammation • C5a induces low-grade inflammation • Adipose tissues secrete constantly C5a and other inflammatory markers and induce low-grade inflammation • Induces the vicious circle of inflammatory condition in the vessel wall and promotes atherosclerosis

Abbreviations used: C5aR1 (C5a receptor 1), C5L2 (C5a receptor-like 2), SMCs (smooth muscle cells), ECs (endothelial cells), oxLDL (oxidized low-density lipoprotein), HFD (high-fat diet), IL(Interleukin), ICAM-1 (Intercellular Adhesion Molecule 1), VCAM-1 (Vascular Cell Adhesion Molecule 1), VEGF (Vascular Endothelial Growth Factor), PDGF (Platelet-derived growth factor), MCP-1 (Monocyte Chemotactic Protein 1), TNF-α (Tumor Necrosis Factor-α)

this study. The search strategy of this review has been based only on electronic databases of Web of Science by Thomson Reuters and PubMed Central® Databases and each keyword included the word "complement". With this limitation it was not possible to include some publications from national journals or some other atherosclerosis-related publications of the Mongolian population such as older work by Galtsog Lodon (Dissertation in Russian language) in 1978 or some recent works by Uurtuya et al.[43]

Current situation and future aspects in cardiovascular research

Cardiovascular disease (CVD) is a major global health issue[44]. According to the World Health Organization (WHO), CVD is the leading cause of death worldwide[44]. CVD denotes malfunction of the heart and/ or the blood vessels. Coronary heart diseases, myocardial infarction, stroke and limb amputations are advanced clinical endpoints of CVD, but actually, malfunction/dysfunction of blood vessels is a chronic process that starts early in life and progresses over many years (Figure 1).

The morphological correlation of these processes is chronic inflammation of the vascular wall[10,45]. Endothelial dysfunction, atherosclerosis and atherothrombosis are the pathophysiological processes in the arterial vasculature underlying CVD[10]. Over the last few decades, considerable progress has been made in treatment and also in prevention of CVD. As a result, cardiovascular mortality has been continuously decreasing in high-income countries since the widespread use of lipid-modifying, anti-hypertensive and anti-thrombotic medication[31]. However, there are still problems that need to be addressed in order to preserve the current state and to potentially further reduce the burden of CVD. One of these problems is that CVD is a comorbidity of several metabolic and degenerative diseases, such as diabetes mellitus, fatty liver disease and rheumatoid arthritis[46]. Another current challenge is that the burden of CVD is now rising excessively in low-income countries. This suggests that identification of further mechanisms contributing to CVD and its background disease atherosclerosis could potentially

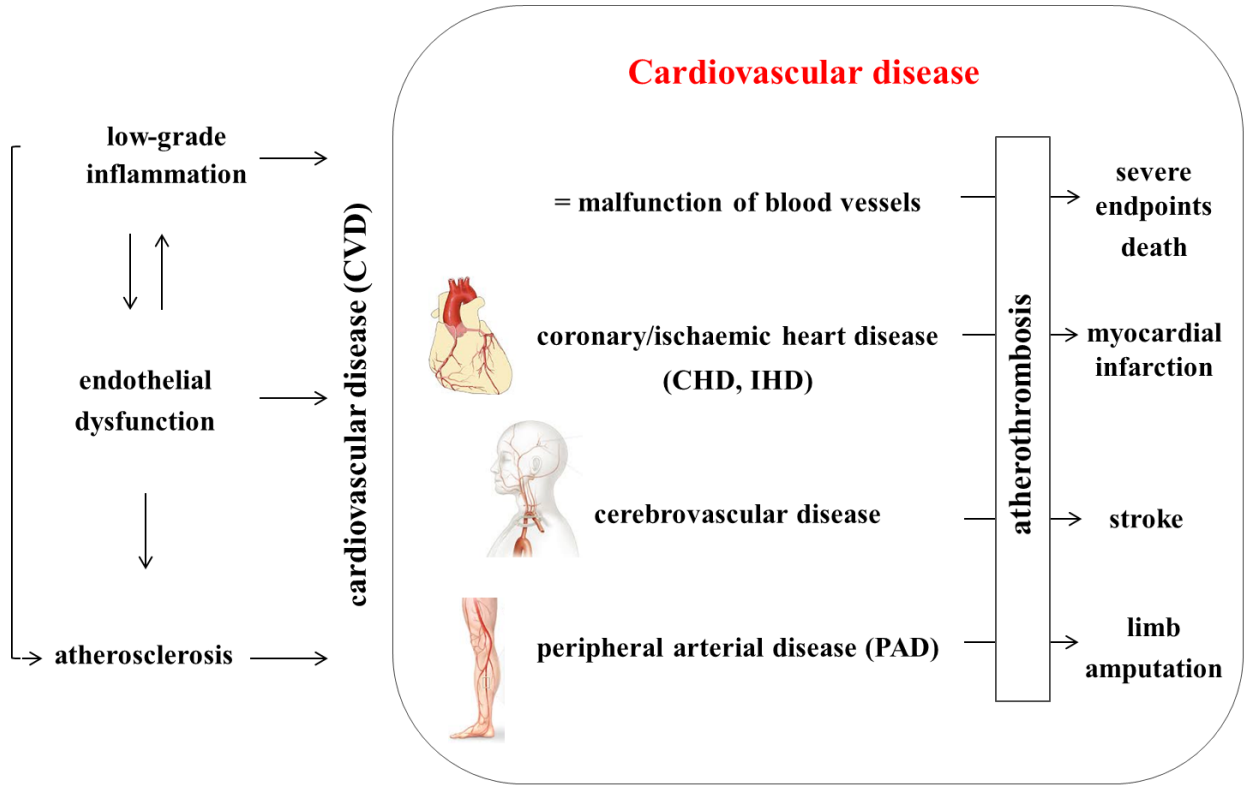

Figure 1. Etiology, manifestations and endpoints of cardiovascular disease (CVD).
Endothelial dysfunction, low-grade inflammation and atherosclerosis lead to the malfunction of blood vessels. CHD constitutes malfunction of vessels supplying the heart muscle; and cerebrovascular disease constitutes to malfunction of the vessels supplying the brain. PAD constitutes to malfunction of the vessels supplying the legs and arms. Myocardial infarction, stroke and limb amputation are advanced clinical endpoints of CVD.

have a large impact not only on western counties especially on low-income countries[44].

As a major mediator of immune responses, complement anaphylatoxin C5a signaling can be an attractive target to tame inflammation without affecting opsonization or the lytic properties of the complement system. Of note, the recent reports on the crosstalk between C5a and cholesterol crystals in the induction of atherosclerotic inflammation provides another interesting mechanistic insight into complement activation in atherosclerosis that needs to be harnessed for the treatment of atherosclerosis[42,47]. The candidacy of C5 as a potential therapeutic target was shown by the ability of C5-inhibitors to attenuate atherosclerosis in experimental models[34,48]. In line with this, a precursor of the recombinant anti-C5 antibody eculizumab, pexelizumab, reduced mortality rate in patients undergoing coronary artery bypass grafting[48,49,50]. In addition, blocking of pro-inflammatory C5aR1 with the small molecule antagonist JPE1375 can limit the atherosclerotic plaque formation in animal model[34]. Several substances which can inhibit C5aR1-medated effects exist, however, they have a short half-life in the circulation limiting their application as a drug[37,51]. Therefore, increasing their half-life and the development of novel drugs are necessary in the future. An important future area of investigation is the role of C5a-C5aRs-mediated effects in the pathogenesis of atherosclerosis among the Mongolian population. To date, comparatively little has been done to investigate the molecular pathogenic mechanisms of atherosclerosis in Mongolians. Nevertheless, targeting complement anaphylatoxins, particularly C5a and its receptors provides new therapeutic option for the treatment of atherosclerosis in Mongolians. Moreover, future studies should investigate more low-grade inflammation markers which can predict CVD complications. In addition, larger population studies are needed to substantiate the role of C5a in atherosclerosis.

Conflict of interest

The author has no conflict of interests.

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