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The Cardiovascular Risk Prognostication in Diabetes Mellitus: The Role of Myeloid-related Protein Complex Calprotectin

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Abstract

The low-intense inflammation is discussed as a one of the clue of various faces of pathogenesis of diabetes mellitus (DM) including insulin resistance, mitochondrial dysfunction, lipotoxity, oxidation injury that contributed in cardiovascular (CV) disease and clinical outcomes. However, there are a lot of candidates for on early biological marker that could stratify DM patients at CV risk. The myeloid-related protein 8/14 known as calprotectin is a heterodimeric complex of calcium-binding proteins, which is predominantly expressed in activated human neutrophils, monocytes, adipocytes, and innate immunity cells including macrophages, but not in normal tissue macrophages. Calprotectin may activate of Toll-like receptor 4 as innate amplifier of infection, autoimmunity, and cancer that attenuates some extracellular functions, i.e. antimicrobial, cytostatic, and chemotactic activities. Therefore, calprotectin activates of NADPH oxidase, induces apoptotic caspase-9 and caspase-3 activation, DNA fragmentation, and membrane phosphatidylserine exposure, and increases the activation of nuclear factor-κB by promoting the nuclear translocation of p65 in target cells. Recent clinical studies have shown that calprotectin was found as a marker for activation of granulocytes, mononuclear phagocytes and immune cells that play a pivotal role in tissue damage, it could link important molecular pathological mechanisms of inflammation contributing to endothelial damage. The aim of the review is summarize of knowledge regarding predictive value of calprotectin as surrogate biomarker of CV events in DM patients.

Keywords

Calprotectin, Inflammation, Diabetes mellitus, Cardiovascular disease

Introduction

Diabetes mellitus (DM) remains a one of leading causes of cardiovascular (CV) disease development [1]. It is well known that type 1 and type 2 DM increase CV morbidity and mortality globally through their complications and negative effects on nature evolution of CV disease [2]. Despite both types of DM have different characteristics affected genetics, aged of populations, sex- and family-related particularities, pathophysiology, clinical presentation, complications, prognosis, and require distinguished management [3-6], low-intense inflammation is discussed as a one of the clue of various faces of pathogenesis of DM including insulin resistance, mitochondrial dysfunction, lipotoxicity, oxidation injury, that contributed in CV disease and clinical outcomes [7-9]. Interestingly that insulin resistance and inflammation do not develop at the same time in all tissues in DM [1,10]. In this context, an adipose tissue is considered a one of the tissues where inflammation is established earlier during aging and prior insulin resistance [10,11]. There are evidences regarding a strong link between abundant secretions of several spectrum pro-inflammatory cytokines i.e. tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, monocyte chemoattractant protein 1, and vascular cell adhesion molecule-1 by macrophage infiltrated adipose tissue and insulin resistance [11,12]. Although an exaggerated inflammatory response in DM is associated with CV disease development and other complications related to nature evolution of DM, the “ideal” surrogate biomarker that might predict CV disease and would therefore be useful in routine clinical use is still not identified [10-12]. The one of candidates on early biological marker that could stratify DM patients at CV risk is inflammatory-related myeloid-related protein complex calprotectin. Recent animal and clinical studies have been shown that calprotectin concentration could represent an independent risk factor of type 2 DM, and a potential surrogate marker of inflammation and endothelial dysfunction in both types of DM [13,14]. The aim of the review is to summarize of knowledge regarding predictive value of calprotectin as surrogate biomarker of CV events in DM patients.

Biology and Function of Calprotectin

Calprotectin is calcium and zinc binding heterocomplex protein (known as Myeloid-Related Protein (MRP) complex 8/14, S100A8/A9), which is comprised of two intracellular calcium-binding proteins named S100A8 (MRP8), and S100A9 (also referred to as S100A8/A9 MRP14) [15,16]. Both S100 proteins are abundant in cytosol of phagocytes and exert diverse effects with respect to its intracellular versus extracellular actions as well as its expressions in various cell types. They play critical roles in numerous cellular processes such as motility and danger signalling by interacting and modulating the activity of target proteins.

The abundant expression of calprotectin (MRP8/14) in activated human neutrophils, monocytes, adipocytes, and innate immunity cells including macrophages, indicate an exclusive role in immunity [17-19]. The expression of this factor is down-regulated during maturation to macrophages and, however, calprotectin is absent in

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peripheral blood lymphocytes and monocytes in healthy volunteers [20,21]. Therefore, the calprotectin in neutrophils and monocytes is the receptor of RAGE [21].

Calprotectin contained in the cytosol fraction of these cells and released immediately after host-pathogen interaction and cytokine stimulation [22]. Therefore, it is essential to discriminate between intracellular and extracellular interaction partners. It was found in biological fluids in not only infections, but in autoimmune and rheumatic diseases, inflammatory bowel diseases, acute and chronic rejection of renal allografts, obesity, metabolic syndrome, cancer, sepsis, and other acute and chronic inflammatory conditions [19,23-26].

The main biological effect of calprotectin is an endogenous activation of Toll-like receptor 4 (TLR) as innate amplifier of infection, autoimmunity, and cancer that attenuates some extracellular functions, e.g. antimicrobial, cytostatic, and chemotactic activities [27,28]. Therefore, there is evidence that calprotectin activates of NADPH oxidase, induces apoptotic caspase-9 and caspase-3 activation, DNA fragmentation, and membrane phosphatidylserine exposure, increases the activation of nuclear factor-κB (NF-κB) by promoting the nuclear translocation of p65 in target cells [29], subsequently inducing expression of the pro-inflammatory cytokines IL-6, IL-8, TNF-alpha, and COX2 [30]. As result, calprotectin may induce plasma membrane damage via caspase-dependent as well as -independent mechanisms and trigs apoptosis and necrosis [29]. Therefore, calprotectin may induce ATM TLR4/MyD88 and NLRP3 inflammasome-dependent IL-1β production. Finally, IL-1β interacted with the IL-1 receptor on bone marrow myeloid progenitors to stimulate the production of monocytes and neutrophils [30]. All these findings suggest that calprotectin might have proposed for the diagnosis of inflammatory conditions. Despite a lot of number of known functions for calprotectin have proposed, the exactly biological function of this factor remains still not fully understood [31,32].

Calprotectin, Endothelial Dysfunction and Atherosclerosis

Although calprotectin was found as a nonspecific marker for activation of granulocytes, mononuclear phagocytes and immune cells that play a pivotal role in tissue damage, it could link important molecular pathological mechanisms of inflammation contributing to endothelial damage [33,34]. Moreover, calprotectin may specifically released during interaction of activated monocytes with TNF-stimulated endothelial cells [35] and induce a thrombogenic response in human microvascular endothelial cells [36]. These effects realize by increasing the transcription of pro-inflammatory chemokines and adhesion cell molecules and therefore by decreasing the expression of cell junction proteins and molecules involved in monolayer integrity [35,36]. Overall, calprotectin is able to regulate endothelial cell survival via a various signaling mechanism involving membrane-to-nucleus cascade Raf-MEK-ERK via TLR4 and CD11B/CD18 cooperation [37], which play a key role in endothelial dysfunction and atherosclerosis development. Indeed, characteristics of rupture-prone lesions of plaque, inflammatory biomarkers and platelet aggregation correlate well with elevated level of calprotectin [38].

Interestingly that calprotectin may exert a biological effect by binding and affecting various target proteins. There are several additional targets for this heterocomplex protein including p53, a nuclear Dbf2 related kinase, neuromodulin, protein kinase C, the advanced glycation end products (RAGE) receptor. Calprotectin appears to be receptor for RAGE [39], which plays a crucial role during the development of many human diseases (such as diabetes, CV disease), and regulates a number of cell processes of pivotal importance like inflammation, apoptosis, proliferation and autophagy. Accordingly, there is a growing interest of unravelling the intracellular signalling pathways mediating by calprotectin through RAGE [40].

Recent studies suggest that calprotectin correlates positively with platelet aggregation, endothelial cell activation, as well as other biological markers of endothelial dysfunction i.e. serum thromboxane B2 [39,41,42]. Moreover, there is a large of body evidence that elevated calprotectin may predict clinical outcomes in patients with stable coronary artery disease, acute coronary syndrome, acute myocardial dysfunction [43-45].

Croce et al. [46] demonstrated that S100a9-deficiency reduced atherosclerosis in apolipoprotein E-deficient (ApoE-/-) mice through reduced arterial macrophage accumulation. Because of the abundance of calprotectin in myeloid cells compared to non-myeloid cells, myeloid-derived calprotectin was therefore believed to mediate the effects of whole-body calprotectin-deficiency. However, Averill et al. [47] have tested this hypothesis by transplantation of low-density lipoprotein receptor-deficient (Ldlr-/-) mice with bone marrow from S100a9-/- mice or wild type littermate controls followed by feeding a high-fat diet for 20 weeks. The authors reported that bone marrow S100A9-deficiency reduced neither atherosclerotic lesions, arterial wall macrophage, nor neutrophil accumulation. Nevertheless, the increased plasma levels of S100A8/A9 predict cardiovascular CV events in humans, and deletion of these proteins partly protects Apoe(-)(/)(-) mice from atherosclerosis [48]. Taken together, it has been suggested that S100A8/A9 might exert a more important role in non-myeloid cells than previously recognized. Hirata et al. [49] have exhibited that asymptomatic atherosclerosis in diabetics associates strongly with elevated level of calprotectin. Thus, calprotectin may be considered as a very sensitive inflammation-related biological marker of endothelial dysfunction and asymptomatic atherosclerosis, although clear mechanism of calprotectin-induced endothelial dysfunction was not shown and require more investigations.

Calprotectin in Diabetes Mellitus

As an inflammation-associated biomarker, which binds toll-like receptor 4 and associates with the RAGE, calprotectin (S100A8/A9) complex is candidate to be a predictor of diabetes-related complications and CV events in subjects with dysmetabolic diseases, while the results of the clinical studies are limited. Recent clinical studies have shown that increased calprotectin level was associated with type 2 DM, obesity and metabolic syndrome (MetS) [50-53]. Pedersen et al. [13] reported that type 2 DM patients had higher concentrations of plasma calprotectin, which were associated with obesity, MetS status, autonomic neuropathy, peripheral artery disease, and myocardial infarction. However, elevated calprotectin level was not found an independent predictor of CV disease development and progression, as well as manifestation of type 2 DM in general population [54]. Tabur et al. [55] found elevated serum level of calprotectin in individuals with diabetic-induced peripheral neuropathy. Therefore, there was detected a moderate positive correlation between calprotectin levels and high sensitive C-reactive protein and HbA1c. Peng et al. [56] reported that increased calprotectin level is closely associated with atherosclerosis in type 2 DM. Interestingly the increased levels of calprotectin in obesity and obesity-associated type 2 diabetes was found in positive association with low-grading inflammation [57]. However, exposure antidiabetic agent, i.e. pioglitazone, even without changing body mass index might lead to decrease of calprotectin level and improve of endothelial function [58]. There is evidence that insulin resistance and microalbuminuria might be mediated by calprotectin [59,60]. Theoretically, the serum level of calprotectin should decrease in response of therapeutic care as it was found in patients with autoimmune diseases, malignancy, and sepsis. In this context, calprotectin as biomarker of inflammation and endothelial damage with probably predictive value might be considered not only "blinded whiteness" of CV risk, but as a target of DM therapy.

Conclusion

In conclusion, one can propose that calprotectin could identify DM patients at high CV risk. Moreover, calprotectin might be useful for biomarker-guided therapy among DM individuals with high CV risk. This could provide a rationale for monitoring calprotectin in

DM patients, although this assumption requires to be discussed and confirmed the results of future clinical studies.

Conflict of Interest

None declared

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