Chapter 10

Endothelial Dysfunction in Type 2 Diabetes: Targeting Inflammation

Cristina M. Sena, Fernanda Carrilho and Raquel M. Seiça

Additional information is available at the end of the chapter

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Abstract

Several experimental and clinical studies have indicated a prominent role of vascular inflammation in the development of endothelial dysfunction. In endothelial dysfunction, the endothelium loses its physiological features, decrements nitric oxide bioavailability, and shifts towards a vasoconstrictor, pro-thrombotic and pro-inflammatory state. Within arterial wall, the interplay between the pro-inflammatory and pro-oxidant milieus promotes vascular dysfunction, and perivascular adipose tissue seems to play an important role. Inflammation is now considered a key event in vascular dysfunction and the development of vascular disease associated with obesity and type 2 diabetes. This concept is supported by the fact that anti-inflammatory adipokines such as adiponectin protect endothelial function, and interventions resulting in reduced inflammation such as the administration of salicylates prevent vascular dysfunction and cardiovascular events. Thus, the aim of this review is to address the role of inflammation and its mechanisms in endothelial dysfunction associated with diabetes, describing the impact of these conditions on vascular function.

Keywords: type 2 diabetes, endothelial dysfunction, oxidative stress, inflammation, adipokines

1. Introduction

Endothelial dysfunction is one of the major causes for vascular complications, accompanied by oxidative stress and inflammation. In diabetic and obesity/insulin resistance states, the endothelial dysfunction is incremented promoting the development and progression of vascular diseases [1].

Endothelial dysfunction involves reduced endothelium-dependent vasodilatation and a prothrombotic, pro-inflammatory and oxidant milieu [2]. The endothelial nitric oxide (NO) synthase (eNOS), renin-angiotensin-aldosterone and kallikrein-kinin response systems all fail to maintain normal vascular homeostasis in conditions of hyperglycemia, reactive oxidative species (ROS), free fatty acid (FFA) stress, and pro-inflammatory signaling [3, 4].

The aim of this review is to address the role of inflammation and its mechanisms in endothelial dysfunction associated with diabetes, describing the impact of these conditions on vascular function. We searched PubMed and Google Scholar primarily for original research articles published up to 2017 that were focused on the pathophysiology of endothelial dysfunction associated with type 2 diabetes. The main search terms used were "type 2 diabetes," "inflammation and endothelial dysfunction," "insulin resistance," and "therapies". We identified primarily full-text manuscripts written in English. We also searched Clinicaltrials.gov for information on ongoing clinical trials in endothelial dysfunction associated with type 2 diabetes.

2. Endothelial cell function

Vascular endothelium is crucial for the regulation of vascular homeostasis. It is metabolically active through the secretion of vasodilators and vasoconstrictors and acts as an active signal transducer for circulating factors that modify the vessel wall phenotype. The normal paracrine and autocrine functions of endothelial cells include the synthesis of a series of substances that moderate vascular tone, decrease leucocyte migration, control permeability, regulate proliferation and migration of smooth muscle cells, and regulate platelet adhesion and aggregation (**Figure 1**). Endothelium also regulates cellular adhesion, vessel wall inflammation, and angiogenesis.

The mechanisms implicated in the genesis of endothelial dysfunction are of extreme importance in developing adequate strategies to prevent or retard the clinical manifestations of cardiovascular diseases.

2.1. Endothelial dysfunction in diabetes

Dysfunction of vascular endothelium is considered not only as an important factor in the initiation of vascular complications, but also in its progression and clinical sequelae [5]. Endothelial dysfunction is the loss of endothelium physiological properties with a shift toward a vasoconstrictor, prothrombotic, and pro-inflammatory state [2].

The mechanisms underlying the development of endothelial dysfunction in type 2 diabetes are complex and include oxidative stress, inflammation, and chronic alterations in the hemodynamic balance. Several contributors to endothelial activation and dysregulation have been described: decreased tetrahydrobiopterin (BH_4) bioavailability and eNOS uncoupling, increased arginase, increased ROS production, decreased NO bioavailability, increased asymmetric dimethyl arginine, increased glycation and expression of receptor for advanced glycation end products (RAGE), nuclear factor κB (NFκB) activation, suppression of Kruppel-like Factor 2 [6], and phenotypic changes in perivascular adipose tissue leading to low grade inflammation and reduced adiponectin secretion [7, 8].

2.2. Inflammation

A state of subclinical systemic inflammation is characteristically present in obesity/insulin resistance and type 2 diabetes. The inflammation can be monitored by inflammatory markers such as high sensitivity C-reactive protein (hsCRP) and the inflammatory score derived from the pro-inflammatory plasma cytokines, interleukin (IL)-6, tumor necrosis factor α (TNFα), osteopontin, fractalkine, chemokine (C-C motif) ligand 2 (CCL2) and anti-inflammatory adiponectin, that inversely relate to insulin sensitivity (**Table 1**). The inflammatory score independently predicted fasting plasma glucose and insulin resistance in type 2 diabetic patients with high sensibility and specificity [9–12]. Moreover, other inflammatory biomarkers [i.e., growth differentiation factor-15 (GDF15), myeloid-related protein 8/14, pentraxin 3, lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1)] have been considered surrogate markers of cardiovascular disease and atherosclerosis in type 2 diabetes patients [13–16].

GDF15 is a member of the transforming growth factor beta family, secreted from cells such as adipocytes and myocytes in response to cellular ischemia and oxidative stress both present in diabetes. GDF15 is a marker of oxidative stress and inflammation and provides independent prognostic information on cardiovascular events [17].

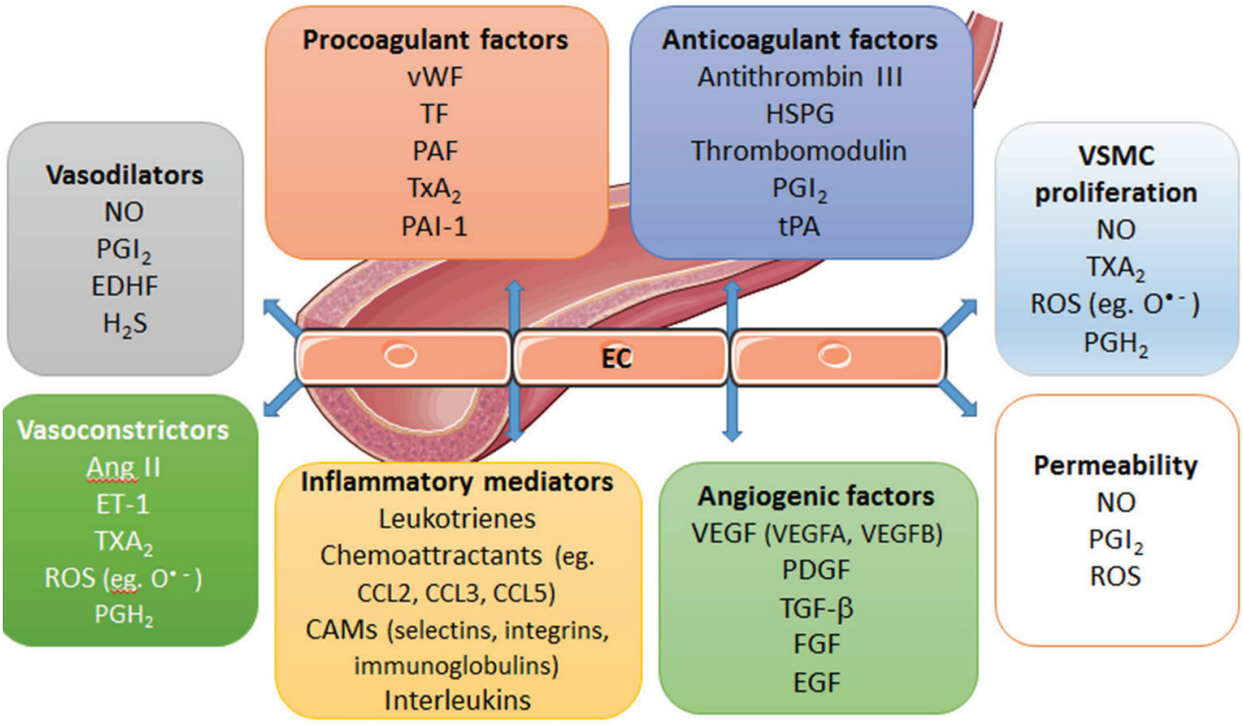

Figure 1. Major functions of endothelial cells: regulation of vascular tone, control of VSMC proliferation, inflammation, permeability, angiogenesis, metabolism and hemostasis. Ang II, angiotensin II; CAMs, cell adhesion molecules; CCL; chemokine (C-C motif) ligand; EC, endothelial cell; EDHF, endothelium derived hyperbolizing factor; EGF, epidermal growth factor; ET1, endothelin-1; FGF, fibroblast growth factor; H_2S; hydrogen sulfide; HSPG, heparan sulfate proteoglycans; ICAM, intercellular adhesion molecule; NO, nitric oxide; PAF, platelet-activating factor; PAI-1, Plasminogen activator inhibitor-1; PDGF, platelet-derived growth factor; PGH_2, prostaglandin H_2; PGI_2, prostacyclin; ROS, reactive oxygen species; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TGF-β, transforming growth factor-β; t-PA, tissue plasminogen activator; TXA_2; thromboxane A_2; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cells; vWF, von Willebrand factor.

Myeloid-related protein 8/14 is a heterodimer consisting of two proteins that bind calcium and calgranulin A and B, which play an important role in the signaling pathways of calcium and in the interaction between the cytoskeleton and the membrane [18]. Myeloid-related protein 8/14 is synthesized by activated monocytes and neutrophils and is a pro-inflammatory protein expressed in atherosclerotic plaques associated with atherosclerosis in diabetic patients [19].

Pentraxin 3 is an acute-phase reactant produced by the peripheral tissues at sites of local inflammation and reflects impaired vascular endothelial function [20].

LOX-1 is a *lectin-like receptor* for *oxidized low-density* lipoproteins (ox-LDL), mainly expressed in endothelial cells, macrophages, smooth muscle cells, and monocytes. This receptor is upregulated by ox-LDL itself and by angiotensin II, endothelin, cytokines, and shear stress. The LOX-1 expressed on the cell surface can be proteolytically cleaved and released in a soluble form (sLOX-1) in the circulation under pathological conditions such as hyperlipidemia and type 2 diabetes [21, 22].

Additionally, galectin-3 might also be an independent marker of vascular remodeling and endothelial dysfunction accompanied by inflammation, proliferation, and atherosclerosis in both normal and diabetic individuals [23, 24]. Galectin-3 is a multifunctional protein that belongs to a family of β-galactoside binding proteins and widely distributes in the heart, brain, visceral **adipose tissue,** and blood vessels. Galectin-3 is able to bind the advanced glycation end products (AGEs) and advanced lipoxidation end products that accumulate in target organs and exert their toxic effects by triggering pro-inflammatory and pro-oxidant pathways [25]. Galectin-3 levels are increased in subjects with obesity and type 2 diabetes [26], and animal studies have suggested that galectin-3 may be involved in the onset and progression of these metabolic disorders by acting primarily at the adipose tissue level. A recent study by Olefsky and co-workers has shown that galectin-3 provides a crucial mechanistic link between inflammation and insulin resistance and that pharmacological inhibition of galectin-3 can increase insulin sensitivity [27].

Inflammation plays a crucial role in the etiology of vascular disease in diabetic states (**Figure 2**). The causes that trigger inflammation are pleiotropic and include most of the features that characterize type 2 diabetes. Arterial hypertension is also a low-grade inflammatory disease [28, 29] often present in diabetes along with hyperinsulinemia, insulin resistance, dyslipidemia, and obesity (**Figure 2**). Chronic exposure to glucotoxicity and lipotoxicity in diabetes induces a pro-inflammatory phenotype in macrophages residing or invading the adipose tissue and the vasculature [30, 31]. The dysfunctional endothelium may enhance leukocyte adhesion and the recruitment of inflammatory cells to the arterial wall, primarily through CCL2, a chemokine that promotes the attraction of immune cells to the sites of inflammation, thereby promoting lipid deposition and facilitating the atherosclerotic plaque formation [28, 32]. In addition, it is well known that the pro-inflammatory transcription factors NFκB and activator protein-1 and kinases such as c-Jun N-terminal kinase, p38 mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK) are regulated by the cellular redox state [33, 34]. Proatherogenic factors in obesity and diabetes such as oxidized

Pro-inflammatory cytokines
TNF-α; Interleukins IL-1, IL-6, IL-8, IL-22
Local inflammation
iNOS
Cyclooxygenases—COX
Transcription factors as NFκB
Adhesion molecules
Intercellular adhesion molecule-1—ICAM-1
Vascular cellular adhesion molecule-1—VCAM-1
E-selectin
Chemokines
CCL2 (MCP-1)
CX3CL1 (fractalkine)
CCL5 (RANTES)
Toll-like receptors
Toll like receptor—TLR2
Toll like receptor—TLR4
Pro-fibrotic factors
Transforming growth factor—TGFβ
Connective tissue growth factor—CTGF

CCL2, chemokine (C-C motif) ligand 2; CCL5, chemokine (C-C motif) ligand 5; COX, cyclooxygenases; CTGF, connective tissue growth factor; CX3CL1, fractalkine; IL- Interleukin; iNOS, inducible nitric oxide synthase; ICAM-1, intercellular adhesion molecule-1; NFκB, nuclear factor κB; TGFβ, *transforming growth factor* β; TLR, toll like receptor; TNF-α; tumor necrosis factor α; VCAM-1, vascular cellular adhesion molecule-1.

Table 1. Inflammatory components of diabetic complications.

lipids, angiotensin II, and hyperglycemia increase the activity of NF-κB and MAPKs in endothelial cells and promote the activation of pro-inflammatory cytokines (e.g., IL-6), chemokines (e.g., CCL2, IL-8) [35], the expression of adhesion molecules [intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1)] [36] and activation of inducible nitric oxide synthase (iNOS) [37], growth factors, and enzymes [38–40]. The subsequent increment in intracellular ROS production and the activation of the pro-inflammatory signaling complexes—the inflammasomes (including nucleotide binding and oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome) is responsible for the activation of interleukins such as IL-1β and IL-18, triggering inflammation [41]. The NLRP3 inflammasomes of the innate immune system induce a microinflammatory state stimulating various pro-inflammatory cytokines involved in the pathogenesis of diabetes and its complications.

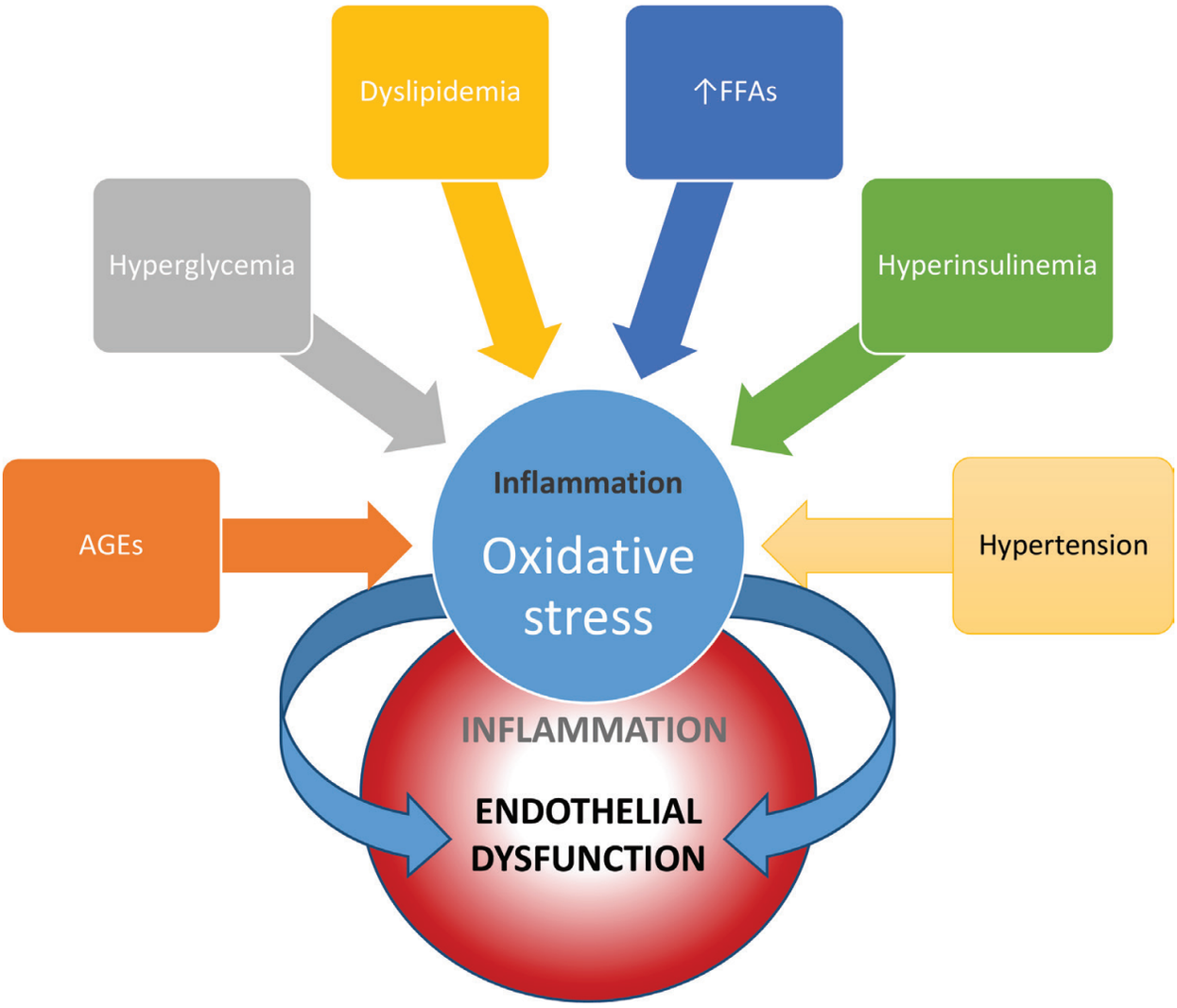

Figure 2. Risk factors for endothelial dysfunction associated with type 2 diabetes. Major role for oxidative stress and inflammation. AGEs, advanced glycation end products; FFAs, free fatty acids.

2.2.1. Hyperglycemia-induced inflammation

In diabetes, hyperglycemia can induce inflammation via different mechanisms [42]. The metabolic defects underlying diabetes cause mitochondrial superoxide overproduction in endothelial cells of blood vessels. This increased superoxide production leads to the activation of five major pathways involved in the pathogenesis of complications: polyol pathway flux, increased formation of advanced glycation end products (AGEs), increased expression of the receptor for AGEs and its activating ligands, activation of protein kinase C (PKC) isoforms and overactivity of the hexosamine pathway [43].

Hyperglycemia leads to increased reduction of glucose to sorbitol by aldose reductase with nicotinamide adenine dinucleotide phosphate (NADPH) consumption [44]. The cellular antioxidant capacity relies on the energy provided by NADPH to the glutathione and thioredoxin antioxidant systems. Thus, NADPH decrement will result in reduced antioxidant capacity and increased oxidative stress [44].

In endothelial cells, vascular smooth muscle cells, monocytes and macrophages, the intracellular synthesis of diacylglycerol is increased in hyperglycemia, leading to the activation of the PKC pathway [45, 46]. In monocytes, there is a subsequent release of the integrins CD11b, CD11c, and CD14 [47, 48]. CD11b or CD11c receptor occupation on the surface of human monocytes stimulates cell-specific pro-inflammatory pathways such as secretion of IL-8, macrophage inflammatory protein (MIP)1α and MIP1β [49]. CD14 + CD16+ monocytes are also linked with pro-inflammatory conditions [50].

Hyperglycemia also upregulates toll-like receptor (TLR) activity through an increment in ROS augmenting inflammation. In human monocytes, Dasu and colleagues [51] reported that high glucose induces TLR2 and TLR4 expression through PKC activation, by stimulating NADPH oxidase (NOX). Several other studies have demonstrated that under hyperglycemic conditions, reducing ROS and specifically NOX activity reduced TLR expression and activity [52, 53].

AGEs are generated in vivo as a normal consequence of metabolism, but their formation is accelerated under conditions of hyperglycemia, hyperlipidemia, and increased oxidative stress [54–57]. AGEs are highly reactive and can trigger inflammation by generating particularly TNF-α and IL-6 [58]. In addition, AGEs activate their receptors/binding sites (RAGE and lactoferrin-like polypeptide complex) in endothelial cells, monocytes, and macrophages leading to the activation of MAPK and NF-κB. AGEs also enhance the formation of oxidized low-density lipoprotein (oxLDL) and during hyperglycemia the expression of LOX-1 on monocytes and macrophages increases. These processes further facilitate the uptake of oxLDL by macrophages, thus increasing inflammation [59, 60].

Another important mechanism to cause hyperglycemia-induced endothelial dysfunction is the redox-dependent activation of endothelial NLRP3 inflammasomes [61]. Endothelial tight junction disruption in diabetes requires NLRP3 inflammasomes. High glucose activates NLRP3 inflammasome in endothelial cells via ROS production. Reducing ROS production abolished high glucose-induced inflammasome activation, tight junction disruption, and endothelial hyperpermeability in endothelial cells. The clinical potential of targeting inflammasome signaling axis for prevention of the early onset of diabetic vasculopathy is evident [61].

2.2.2. Lipids-induced inflammation

Lipids also induce a state of inflammation. In diabetes, lipids increment the inflammatory process by promoting oxidative stress and leukocyte activation and ultimately foster endothelial dysfunction and atherosclerosis progression. The ingestion of high fat diets results in increased leukocyte activation, which is reflected by an increase of surface expression of CD11b, CD11c and CD14 on monocytes and CD11b, CD66b and CD62L on neutrophils [47, 62, 63]. These results suggest a pro-inflammatory effect of dietary lipids on circulating inflammatory cells with detrimental effects on the vessel wall. After a meal, the remnants of triglyceride-rich lipoproteins and *oxLDL* are taken up by circulating leukocytes, macrophages, endothelial cells, and smooth muscle cells, activating the PKC pathway and resulting in *NF-κB* activation [64–66]. NF-κB promotes the transcription of various inflammatory genes, including genes encoding for cytokines, chemokines, and adhesion molecules [59]. In addition, FFA and cholesterol induce inflammation by activating TLR pathways and, subsequently,

NF-κB-mediated release of a broad range of cytokines and chemokines in different tissues [30, 31]. Cytokines released are involved in initiating and promoting a pro-inflammatory status, contributing to insulin resistance [67].

However, the use of anti-inflammatory therapies to treat these conditions is still controversial and often the results are inferior to the expected. On the other hand, indirect approaches regulating adipokines secretion or signaling seem to be promising [68].

2.2.3. Macrophage polarization

Macrophages are essential factors that contribute to the expression of inflammatory mediators and altered metabolism playing a critical role during the pathogenesis of atherosclerosis [69]. Polarized macrophages toward M1 phenotype aggravate atherosclerosis. The polarized macrophages not only exhibit increased inflammatory profile as observed in the expression of CCL2 and CCL5 but also change cholesterol homeostasis. The scavenger receptor class B type I (SR-B1) plays an important role in mediating the uptake of high-density lipoproteins (HDL)-derived cholesterol and cholesteryl ester in the liver and steroidogenic tissues, and its expression is reduced by M1 macrophages [70]. In addition, HDL prevents the induction of human macrophages into an M1 phenotype by preventing the accumulation of caveolin-1 to the cell membrane [71].

Adipokines play an important role particularly in the context of obesity and diabetes. Some have a direct vascular effect such as leptin and adiponectin [8, 72]. Increasing attention has been paid to the direct vascular effects of adipokines, especially adiponectin. Adiponectin is the most abundant adipokine secreted by adipose cells, which may couple the regulation of insulin sensitivity with energy metabolism as well as regulation of vascular function [8]. We have recently shown that adiponectin normalized endothelial cell function by a mechanism that involved increased eNOS phosphorylation and decreased perivascular adipose tissue inflammation [8]. In addition, hypoadiponectinemia-induced NLRP3 inflammasome was recently suggested as a novel mechanism of diabetic vascular endothelial dysfunction [73].

Some adipokines mediate the polarization of pro-inflammatory M1 and anti-inflammatory M2 macrophages and the influence of inflammation in the diabetic milieu. For instance, adiponectin and secreted frizzled-related protein 5 are both adipokines that have anti-inflammatory properties and that can stimulate M2 polarization [74, 75]. Both M1 and M2 macrophage phenotypes interchange dynamically depending on the environment. Depending on the stimulus, macrophages become polarized, which allows macrophages to critically contribute to tissue homeostasis, as they promote initiation and resolution of inflammatory responses. As a consequence, deregulation of the tissue macrophage polarization balance is an etiological agent of chronic inflammation present in obesity and insulin resistance [76].

In addition, it was previously reported that vitamin D promotes an antiatherogenic monocyte/macrophage phenotype in patients with diabetes [77]. Higher serum 25(OH)D levels correlated positively with a beneficial M2/M1 ratio, suggesting antiatherogenic properties [78]. Moreover, reversibility of the proatherogenic macrophage phenotype by vitamin D supplementation highlights vitamin D sufficiency as a potential therapeutic target to reduce inflammation and diabetic complications [77].

2.3. Therapeutic approaches

Human and animal studies have shown a correlation between inflammatory conditions and endothelial dysfunction [79, 80]. In clinical situations, none of the approaches to specifically and directly treat inflammation to prevent cardiovascular events or reduce atherosclerosis in human individuals were successful, although high-sensitivity C-reactive protein is shown to have a strong relationship with recurrent events of cardiovascular diseases in several clinical trials. Randomized placebo-controlled clinical trials evaluating anti-inflammatory agents are being conducted to clarify whether targeting the inflammation itself will reduce cardiovascular events and risks [81].

Diet-induced weight loss reduced the levels of biomarkers of endothelial dysfunction and inflammation in overweight and obese patients with type 2 diabetes independent of medication use and duration [82]. In addition, anti-inflammatory drugs, such as salicylates, have been shown to reverse insulin resistance and other related conditions that result from circulating cytokines which cause and maintain insulin resistance [83–87]. Fibrates seem to inhibit NFκB [88]. In two randomized, placebo-controlled trials, fenofibrate treatment reduced the postprandial production of TNF-α, IL-1β, IL-6, CCL2, and macrophage inflammatory protein-1α [88, 89]. Larger and longer trials are necessary to understand the effects of fibrates. In addition, expression of paraoxonase genes (PON 1, 2, 3) negatively correlates with a number of inflammatory diseases including atherosclerosis [90]. In contrast to PON1, mainly in the circulation, PON2 and PON3 are predominantly localized to intracellular compartments (although small amounts of hPON3 is also associated with HDL) and modulate cellular oxidative stress generated both by intracellular mechanisms and in response to extracellular stimuli [91]. PON1 protects LDL against oxidation and preserves function of HDL [91]. Recent evidence suggests that paraoxonase-1 may exert its anti-inflammatory, anti-oxidative functions leading to HDL-mediated eNOS activation in endothelial cells via inhibition of myeloperoxidase activity of inflammatory HDL [92]. There are several studies suggesting that paraoxonases have been and continue to be target/candidates for developing therapeutic interventions for inflammatory diseases [93].

Emerging anti-inflammatory approaches to vascular protection could be for instance: 5-lipoxygenase inhibitors, 5-lipoxygenase activating protein inhibitors, anti-cell adhesion molecules, SIRT activators, CCR2 and CCR5 antagonists [94], antibodies against TNF-α, and low doses of methotrexate [81].

Large-scale clinical trials are underway to investigate whether anti-inflammatory treatment improves cardiovascular outcomes, for example, methotrexate therapy (TETHYS trial and CIRT trial) [95, 96] and blockade of the cytokine IL-1β with canakinumab for the management of cardiovascular disease (CANTOS trial) [97, 98]. Additionally, randomized, placebo-controlled, double-masked clinical trials of salsalate [99, 100], IL1Ra [101, 102] and anti-TNF-α [103] are being used to determine whether these anti-inflammatory approaches modify disease risk in type 2 diabetes and atherosclerotic cardiovascular disease.

Another novel anti-inflammatory therapy could be based on the normalization of the glycocalyx function [104–106]. The endothelial glycocalyx is now recognized to be a gatekeeper of the vascular wall regulating many aspects of endothelial function including its permeability

and integrity. A disturbed glycocalyx is associated with higher susceptibility to triggers of atherosclerosis and leukocyte/platelet adhesion [105–107].

In addition, it was recently described that inhibition of NLRP3 inflammasome with MCC950 has potential benefits reducing infarct size and preserving cardiac function in a pig model of myocardial infarction [108].

Understanding mediators of the resolution of inflammation deserves further development in order to reduce the progression of vascular complications associated with diabetes [32].

3. Conclusions

Inflammation is suggested to play a crucial role in the interaction between metabolic abnormalities and vascular dysfunction, which occur in diabetes. Indeed, elevated levels of circulating inflammatory markers are observed in patients with diabetes and obesity, promoting endothelial dysfunction. In the diabetic milieu, hyperglycemia and hyperlipidemia promote various intracellular and extracellular events and affect different cells in the vascular wall, leading to endothelial dysfunction. Obesity and type 2 diabetes also promote alterations in several pro-inflammatory cytokines, chemokines, and adipokines that will have an impact on vascular function. Knowing these mechanisms in detail will enable us to find new therapeutic targets for preventing or ameliorating the inflammation and subsequent vascular complications in diabetes.

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Conflict of interest

No conflict of interest.

Author details

Cristina M. Sena[1]*, Fernanda Carrilho[2] and Raquel M. Seiça[1]

*Address all correspondence to: csena@ci.uc.pt

1 Physiology, IBILI, Faculty of Medicine, University of Coimbra, Portugal

2 Santarém Hospital, Portugal

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