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Endothelial Dysfunction in Type 2 Diabetes: Targeting Inflammation

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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 pro-thrombotic, 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 (BH₄) 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 κ B (NF κ B) 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 (TNF α), 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; H₂S; 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; PGH₂, prostaglandin H₂; PGI₂, prostacyclin; ROS, reactive oxygen species; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TGF- β , transforming growth factor- β ; t-PA, tissue plasminogen activator; TXA₂; thromboxane A₂; 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 NF κ B 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 NF κ B

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—TGF β

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; NF κ B, nuclear factor κ B; TGF β , *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- κ B 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-1 β 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)1 α and MIP1 β [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- κ B. 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- κ B activation [64–66]. NF- κ B 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- κ B-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 NF κ B [88]. In two randomized, placebo-controlled trials, fenofibrate treatment reduced the postprandial production of TNF- α , IL-1 β , IL-6, CCL2, and macrophage inflammatory protein-1 α [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-1 β 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.

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References

- [1] Muniyappa R, Sowers JR. Role of insulin resistance in endothelial dysfunction. *Reviews in Endocrine & Metabolic Disorders*. 2013;**14**:5-12
- [2] Sena CM, Pereira AM, Seça R. Endothelial dysfunction—A major mediator of diabetic vascular disease. *Biochimica et Biophysica Acta*. 2013;**1832**:2216-2231
- [3] Roberts AC, Porter KE. Cellular and molecular mechanisms of endothelial dysfunction in diabetes. *Diabetes & Vascular Disease Research*. 2013;**10**:472-482
- [4] Brady EM, Webb DR, Morris DH, Khunti K, Talbot DS, Sattar N, Davies MJ. Investigating endothelial activation and oxidative stress in relation to glycaemic control in a multiethnic population. *Experimental Diabetes Research*. 2012;**2012**:386041
- [5] Cines DB, Pollak ES, Buck CA, Loscalzo J, Zimmerman GA, McEver RP, Pober JS, Wick TM, Konkle BA, Schwartz BS, Barnathan ES, McCrae KR, Hug BA, Schmidt AM, Stern DM. Endothelial cells in physiology and in the pathophysiology of vascular disorders. *Blood*. 1998;**91**:3527-3561
- [6] Lee HY, Youn SW, Cho HJ, Kwon YW, Lee SW, Kim SJ, Park YB, Oh BH, Kim HS. FOXO1 impairs whereas statin protects endothelial function in diabetes through reciprocal regulation of Kruppel-like factor 2. *Cardiovascular Research*. 2013;**97**:143-152
- [7] Omar A, Chatterjee TK, Tang Y, Hui DY, Weintraub NL. Proinflammatory phenotype of perivascular adipocytes. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2014;**34**:1631-1636
- [8] Sena CM, Pereira A, Fernandes R, Letra L, Seça RM. Adiponectin improves endothelial function in mesenteric arteries of rats fed a high-fat diet: Role of perivascular adipose tissue. *British Journal of Pharmacology*. 2017;**174**:3514-3526
- [9] Daniele G, Guardado Mendoza R, Winnier D, Fiorentino TV, Pengou Z, Cornell J, Andreozzi F, Jenkinson C, Cersosimo E, Federici M, Tripathy D, Folli F. The inflammatory status score including IL-6, TNF- α , osteopontin, fractalkine, MCP-1 and adiponectin underlies whole-body insulin resistance and hyperglycemia in type 2 diabetes mellitus. *Acta Diabetologica*. 2014;**51**:123-131
- [10] Kaptoge S, Seshasai SR, Gao P, Freitag DF, Butterworth AS, Borglykke A, Di Angelantonio E, Gudnason V, Rumley A, Lowe GD, Jørgensen T, Danesh J. Inflammatory cytokines and risk of coronary heart disease: New prospective study and updated meta-analysis. *European Heart Journal*. 2014;**35**:578-589
- [11] Lubrano V, Balzan S. Consolidated and emerging inflammatory markers in coronary artery disease. *World Journal of Experimental Medicine*. 2015;**5**:21-32
- [12] Pepys MB, Hirschfield GM. C-reactive protein: A critical update. *The Journal of Clinical Investigation*. 2003;**111**:1805-1812

- [13] Puri R, Nissen SE, Shao M, Elshazly MB, Kataoka Y, Kapadia SR, Tuzcu EM, Nicholls SJ. Non-HDL cholesterol and triglycerides: Implications for coronary atheroma progression and clinical events. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2016;**36**:2220-2228
- [14] Krintus M, Kozinski M, Kubica J, Sypniewska G. Critical appraisal of inflammatory markers in cardiovascular risk stratification. *Critical Reviews in Clinical Laboratory Sciences*. 2014;**51**:263-279
- [15] Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *The New England Journal of Medicine*. 2004;**350**:1387-1397
- [16] Myers GL, Christenson RH, Cushman M, Ballantyne CM, Cooper GR, Pfeiffer CM, Grundy SM, Labarthe DR, Levy D, Rifai N, Wilson PW. National academy of clinical biochemistry laboratory medicine practice guidelines: Emerging biomarkers for primary prevention of cardiovascular disease. *Clinical Chemistry*. 2009;**55**:378-384
- [17] Wallentin L, Hijazi Z, Andersson U, Alexander JH, De Caterina R, Hanna M, Horowitz JD, Hylek EM, Lopes RD, Asberg S, Granger CB, Siegbahn A, ARISTOTLE Investigators. Growth differentiation factor 15, a marker of oxidative stress and inflammation, for risk assessment in patients with atrial fibrillation: Insights from the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial. *Circulation*. 2014;**130**:1847-1858
- [18] Ionita MG, Vink A, Dijke IE, Laman JD, Peeters W, van der Kraak PH, Moll FL, de Vries JP, Pasterkamp G, de Kleijn DP. High levels of myeloid-related protein 14 in human atherosclerotic plaques correlate with the characteristics of rupture-prone lesions. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2009;**29**:1220-1227
- [19] Peng WH, Jian WX, Li HL, Hou L, Wei YD, Li WM, Xu YW. Increased serum myeloid-related protein 8/14 level is associated with atherosclerosis in type 2 diabetic patients. *Cardiovascular Diabetology*. 2011;**10**:41
- [20] Yang HS, Woo JE, Lee SJ, Park SH, Woo JM. Elevated plasma pentraxin 3 levels are associated with development and progression of diabetic retinopathy in Korean patients with type 2 diabetes mellitus. *Investigative Ophthalmology & Visual Science*. 2014;**55**:5989-5997
- [21] Chen M, Nagase M, Fujita T, Narumiya S, Masaki T, Sawamura T. Diabetes enhances lectin-like oxidized LDL receptor-1 (LOX-1) expression in the vascular endothelium: possible role of LOX-1 ligand and AGE. *Biochemical and Biophysical Research Communications*. 2001;**287**:962-968
- [22] Tan KC, Shiu SW, Wong Y, Leng L, Bucala R. Soluble lectin-like oxidized low density lipoprotein receptor-1 in type 2 diabetes mellitus. *Journal of Lipid Research*. 2008;**49**:1438-1444

- [23] Papapanagiotou A, Siasos G, Kassi E, Gargalionis AN, Papavassiliou AG. Novel inflammatory markers in hyperlipidemia: Clinical implications. *Current Medicinal Chemistry*. 2015;**22**:2727-2743
- [24] Ozturk D, Celik O, Satilmis S, Aslan S, Erturk M, Cakmak HA, Kalkan AK, Ozyilmaz S, Diker V, Gul M. Association between serum galectin-3 levels and coronary atherosclerosis and plaque burden/structure in patients with type 2 diabetes mellitus. *Coronary Artery Disease*. 2015;**26**:396-401
- [25] Pugliese G, Iacobini C, Ricci C, Blasetti Fantauzzi C, Menini S. Galectin-3 in diabetic patients. *Clinical Chemistry and Laboratory Medicine*. 2014;**52**:1413-1423
- [26] Weigert J, Neumeier M, Wanninger J, Bauer S, Farkas S, Scherer MN, Schnitzbauer A, Schäffler A, Aslanidis C, Schölmerich J, Buechler C. Serum galectin-3 is elevated in obesity and negatively correlates with glycosylated hemoglobin in type 2 diabetes. *The Journal of Clinical Endocrinology and Metabolism*. 2010;**95**:1404-1411
- [27] Li P, Liu S, Lu M, Bandyopadhyay G, Oh D, Imamura T, Johnson AMF, Sears D, Shen Z, Cui B, Kong L, Hou S, Liang X, Iovino S, Watkins SM, Ying W, Osborn O, Wollam J, Brenner M, Olefsky JM. Hematopoietic-derived galectin-3 causes cellular and systemic insulin resistance. *Cell*. 2016;**167**:973-984
- [28] Libby P. Inflammation in atherosclerosis. *Nature*. 2002;**420**:868-874
- [29] Wenzel P, Knorr M, Kossmann S, Stratmann J, Hausding M, Schuhmacher S, Karbach SH, Schwenk M, Yogev N, Schulz E, Oelze M, Grabbe S, Jonuleit H, Becker C, Daiber A, Waisman A, Münzel T. Lysozyme M-positive monocytes mediate angiotensin II-induced arterial hypertension and vascular dysfunction. *Circulation*. 2011;**124**:1370-1381
- [30] Nguyen MT, Favelyukis S, Nguyen AK, Reichart D, Scott PA, Jenn A, Liu-Bryan R, Glass CK, Neels JG, Olefsky JM. A subpopulation of macrophages infiltrates hypertrophic adipose tissue and is activated by free fatty acids via toll-like receptors 2 and 4 and JNK-dependent pathways. *The Journal of Biological Chemistry*. 2007;**282**:35279-35292
- [31] Vandanmagsar B, Youm YH, Ravussin A, Galgani JE, Stadler K, Mynatt RL, Ravussin E, Stephens JM, Dixit VD. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. *Nature Medicine*. 2011;**17**:179-188
- [32] Libby P, Tabas I, Fredman G, Fisher EA. Inflammation and its resolution as determinants of acute coronary syndromes. *Circulation Research*. 2014;**114**:1867-1879
- [33] Oliveira-Marques V, Marinho HS, Cyrne L, Antunes F. Role of hydrogen peroxide in NF-kappaB activation: From inducer to modulator. *Antioxidants & Redox Signaling*. 2009;**11**:2223-2243
- [34] Son Y, Kim S, Chung HT, Pae HO. Reactive oxygen species in the activation of MAP kinases. *Methods in Enzymology*. 2013;**528**:27-48

- [35] Janssen-Heininger YMW, Poynter ME, Baeuerle PA. Recent advances towards understanding redox mechanisms in the activation of nuclear factor κ B. *Free Radical Biology and Medicine*. 2000;**28**:1317-1327
- [36] Matsumoto K, Sera Y, Nakamura H, Ueki Y, Miyake S. Serum concentrations of soluble adhesion molecules are related to degree of hyperglycemia and insulin resistance in patients with type 2 diabetes mellitus. *Diabetes Research and Clinical Practice*. 2002;**55**:131-138
- [37] Soskić SS, Dobutović BD, Sudar EM, Obradović MM, Nikolić DM, Djordjevic JD, Radak DJ, Mikhailidis DP, Isenović ER. Regulation of inducible nitric oxide synthase (iNOS) and its potential role in insulin resistance, diabetes and heart failure. *Open Cardiovascular Medicine Journal*. 2011;**5**:153-163
- [38] Montezano AC, Burger D, Paravicini TM, Chignalia AZ, Yusuf H, Almasri M, He Y, Callera GE, He G, Krause KH, Lambeth D, Quinn MT, Touyz RM. Nicotinamide adenine dinucleotide phosphate reduced oxidase 5 (Nox5) regulation by angiotensin II and endothelin-1 is mediated via calcium/calmodulin-dependent, rac-1-independent pathways in human endothelial cells. *Circulation Research*. 2010;**106**:1363-1373
- [39] Ning RB, Zhu J, Chai DJ, Xu CS, Xie H, Lin XY, Zeng JZ, Lin JX. RXR agonists inhibit high glucose-induced upregulation of inflammation by suppressing activation of the NADPH oxidase-nuclear factor-kappaB pathway in human endothelial cells. *Genetics and Molecular Research*. 2013;**12**:6692-6707
- [40] Xia F, Wang C, Jin Y, Liu Q, Meng Q, Liu K, Sun H. Luteolin protects HUVECs from TNF- α -induced oxidative stress and inflammation via its effects on the Nox4/ROS-NF- κ B and MAPK pathways. *Journal of Atherosclerosis and Thrombosis*. 2014;**21**:768-783
- [41] Rathinam VAK, Fitzgerald KA. Inflammasome complexes: Emerging mechanisms and effector functions. *Cell*. 2016;**165**:792-800
- [42] Hansen NW, Hansen AJ, Sams A. The endothelial border to health: Mechanistic evidence of the hyperglycemic culprit of inflammatory disease acceleration. *IUBMB Life*. 2017;**69**:148-161
- [43] Giacco F, Brownlee M. Oxidative stress and diabetic complications. *Circulation Research*. 2010;**107**:1058-1070
- [44] Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature*. 2001;**414**:813-820
- [45] Araki E, Nishikawa T. Oxidative stress: A cause and therapeutic target of diabetic complications. *Journal of Diabetes Investigation*. 2010;**1**:90-96
- [46] Geraldles P, King GL. Activation of protein kinase C isoforms and its impact on diabetic complications. *Circulation Research*. 2010;**106**:1319-1331
- [47] Gower RM, Wu H, Foster GA, Devaraj S, Jialal I, Ballantyne CM, Knowlton AA, Simon SI. CD11c/CD18 expression is upregulated on blood monocytes during hypertriglyceridemia and enhances adhesion to vascular cell adhesion molecule-1. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2011;**31**:160-166

- [48] Kizub IV, Klymenko KI, Soloviev AI. Protein kinase C in enhanced vascular tone in diabetes mellitus. *International Journal of Cardiology*. 2014;**174**:230-242
- [49] Rezzonico R, Imbert V, Chicheportiche R, Dayer JM. Ligation of CD11b and CD11c $\beta 2$ integrins by antibodies or soluble CD23 induces macrophage inflammatory protein 1 α (MIP-1 α) and MIP-1 β production in primary human monocytes through a pathway dependent on nuclear factor- κ B. *Blood*. 2001;**97**:2932-2940
- [50] Geng S, Chen K, Yuan R, Peng L, Maitra U, Diao N, Chen C, Zhang Y, Hu Y, Qi CF, Pierce S, Ling W, Xiong H, Li L. The persistence of low-grade inflammatory monocytes contributes to aggravated atherosclerosis. *Nature Communications*. 2016;**7**:13436
- [51] Dasu MR, Devaraj S, Zhao L, Hwang DH, Jialal I. High glucose induces toll-like receptor expression in human monocytes: Mechanism of activation. *Diabetes*. 2008;**57**:3090-3098
- [52] Thallas-Bonke V, Thorpe SR, Coughlan MT, Fukami K, Yap FY, Sourris KC, Penfold SA, Bach LA, Cooper ME, Forbes JM. Inhibition of NADPH oxidase prevents advanced glycation end product-mediated damage in diabetic nephropathy through a protein kinase C- α -dependent pathway. *Diabetes*. 2008;**57**:460-469
- [53] Chen JX, Stinnett A. Critical role of the NADPH oxidase subunit p47phox on vascular TLR expression and neointimal lesion formation in high-fat diet-induced obesity. *Laboratory Investigation*. 2008;**88**:1316-1328
- [54] Sena CM, Matafome P, Louro T, Nunes E, Fernandes R, Seica RM. Metformin restores endothelial function in aorta of diabetic rats. *British Journal of Pharmacology*. 2011;**163**:424-437
- [55] Thallas-Bonke V, Coughlan MT, Tan AL, Harcourt BE, Morgan PE, Davies MJ, Bach LA, Cooper ME, Forbes JM. Targeting the AGE-RAGE axis improves renal function in the context of a healthy diet low in advanced glycation end-product content. *Nephrology*. 2013;**18**:47-56
- [56] Kellow NJ, Savage GS. Dietary advanced glycation end-product restriction for the attenuation of insulin resistance, oxidative stress and endothelial dysfunction: a systematic review. *European Journal of Clinical Nutrition*. 2013;**67**:239-248
- [57] Pereira AM, Fernandes R, Crisóstomo J, Seica RM, Sena CM. The Sulforaphane and pyridoxamine supplementation normalize endothelial dysfunction associated with type 2 diabetes. *Scientific Reports*. 2017;**7**:14357
- [58] Tomino Y, Hagiwara S, Gohda T. AGE-RAGE interaction and oxidative stress in obesity-related renal dysfunction. *Kidney International*. 2011;**80**:133-135
- [59] De Vries MA, Klop B, Janssen HW, Njo TL, Westerman EM, Cabezas MC. Postprandial inflammation: Targeting glucose and lipids. *Advances in Experimental Medicine and Biology*. 2014;**824**:161-170
- [60] Ott C, Jacobs K, Haucke E, Navarrete Santos A, Grune T, Simm A. Role of advanced glycation end products in cellular signaling. *Redox Biology*. 2014;**2**:411-429
- [61] Chen Y, Wang L, Pitzer AL, Li X, Li PL, Zhang Y. Contribution of redox-dependent activation of endothelial NLRP3 inflammasomes to hyperglycemia-induced endothelial dysfunction. *Journal of Molecular Medicine (Berlin)*. 2016;**94**:1335-1347

- [62] Hiramatsu K, Arimori S. Increased superoxide production by mononuclear cells of patients with hypertriglyceridemia and diabetes. *Diabetes*. 1988;**37**:832-837
- [63] Van Oostrom AJ, Rabelink TJ, Verseyden C, Sijmonsma TP, Plokker HW, De Jaegere PP, Cabezas MC. Activation of leukocytes by postprandial lipemia in healthy volunteers. *Atherosclerosis*. 2004;**177**:175-182
- [64] Bentley C, Hathaway N, Widdows J, Bejta F, De Pascale C, Avella M, Wheeler-Jones CP, Botham KM, Lawson C. Influence of chylomicron remnants on human monocyte activation in vitro. *Nutrition, Metabolism, and Cardiovascular Diseases*. 2011;**21**:871-878
- [65] Pirillo A, Norata GD, Catapano AL. LOX-1, OxLDL, and atherosclerosis. *Mediators of Inflammation*. 2013:152786
- [66] Shi Y, Cosentino F, Camici GG, Akhmedov A, Vanhoutte PM, Tanner FC, Lüscher TF. Oxidized low-density lipoprotein activates p66Shc via lectin-like oxidized low-density lipoprotein receptor-1, protein kinase C-beta, and c-Jun N-terminal kinase in human endothelial cells. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2011;**31**:2090-2097
- [67] Timar R, Timar B, Degeratu D, Serafinceanu C, Oancea C. Metabolic syndrome, adiponectin and proinflammatory status in patients with type1 diabetes mellitus. *The Journal of International Medical Research*. 2014;**42**:1131-1138
- [68] Freitas Lima LC, Braga VA, do Socorro de França Silva M, Cruz JC, Sousa Santos SH, de Oliveira Monteiro MM, Balarini CM. Adipokines, diabetes and atherosclerosis: An inflammatory association. *Frontiers in Physiology*. 2015;**6**:304
- [69] Moore KJ, Sheedy FJ, Fisher EA. Macrophages in atherosclerosis: A dynamic balance. *Nature Reviews Immunology*. 2013;**13**:709-721
- [70] Valacchi G, Sticozzi C, Lim Y, Pecorelli A. Scavenger receptor class B type I: A multifunctional receptor. *Annals of the New York Academy of Sciences*. 2011;**1229**:E1-E7
- [71] Lee MK, Moore XL, Fu Y, Al-Sharea A, Dragoljevic D, Fernandez-Rajo MA, Parton R, Sviridov D, Murphy AJ, Chin-Dusting JP. High-density lipoprotein inhibits human M1 macrophage polarization through redistribution of caveolin-1. *British Journal of Pharmacology*. 2016;**173**:741-751
- [72] Koh KK, Park SM, Quon MJ. Leptin and cardiovascular disease: response to therapeutic interventions. *Circulation*. 2008;**117**:3238-3249
- [73] Zhang J, Xia L, Zhang F, Zhu D, Xin C, Wang H, Zhang F, Guo X, Lee Y, Zhang L, Wang S, Guo X, Huang C, Gao F, Liu Y, Tao L. A novel mechanism of diabetic vascular endothelial dysfunction: Hypoadiponectinemia-induced NLRP3 inflammasome activation. *Biochimica et Biophysica Acta*. 2017;**1863**:1556-1567
- [74] Ohashi K, Parker JL, Ouchi N, Higuchi A, Vita JA, Gokce N, Pedersen AA, Kalthoff C, Tullin S, Sams A, Summer R, Walsh K. Adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype. *The Journal of Biological Chemistry*. 2010;**285**:6153-6160

- [75] Ouchi N, Higuchi A, Ohashi K, Oshima Y, Gokce N, Shibata R, Akasaki Y, Shimono A, Walsh K. Sfrp5 is an anti-inflammatory adipokine that modulates metabolic dysfunction in obesity. *Science*. 2010;**329**:454-457
- [76] Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. *Annual Review of Immunology*. 2011;**29**:415-445
- [77] Riek AE, Oh J, Sprague JE, Timpson A, de las Fuentes L, Bernal-Mizrachi L, Schechtman KB, Bernal-Mizrachi C. Vitamin D suppression of endoplasmic reticulum stress promotes an antiatherogenic monocyte/macrophage phenotype in type 2 diabetic patients. *The Journal of Biological Chemistry* 2012;**287**:38482-38494
- [78] Anandabaskar N, Selvarajan S, Dkhar SA, Kamalanathan SK, Tamilarasu K, Bobby Z. Effect of vitamin D supplementation on vascular functions and oxidative stress in type 2 diabetic patients with vitamin D deficiency. *Indian Journal of Endocrinology and Metabolism*. 2017;**21**:555-563
- [79] Karbach S, Wenzel P, Waisman A, Munzel T, Daiber A. eNOS uncoupling in cardiovascular diseases-the role of oxidative stress and inflammation. *Current Pharmaceutical Design*. 2014;**20**:3579-3594
- [80] Steven S, Munzel T, Daiber A. Exploiting the pleiotropic antioxidant effects of established drugs in cardiovascular disease. *International Journal of Molecular Sciences*. 2015;**16**:18185-18223
- [81] Goldfine AB, Shoelson SE. Therapeutic approaches targeting inflammation for diabetes and associated cardiovascular risk. *The Journal of Clinical Investigation*. 2017;**127**:83-93
- [82] Berk KA, Oudshoorn TP, Verhoeven AJM, Mulder MT, Roks AJM, Dik WA, Timman R, Sijbrands EJG. Diet-induced weight loss and markers of endothelial dysfunction and inflammation in treated patients with type 2 diabetes. *Clinical Nutrition ESPEN*. 2016;**15**:101-106
- [83] Paul A, Calleja L, Camps J, Osada J, Vilella E, Ferré N, Mayayo E, Joven J. The continuous administration of aspirin attenuates atherosclerosis in apolipoprotein E-deficient mice. *Life Sciences*. 2000;**68**:457-465
- [84] Rius B, López-Vicario C, González-Pérez A, Morán-Salvador E, García-Alonso V, Clària J, Titos E. Resolution of inflammation in obesity-induced liver disease. *Frontiers in Immunology*. 2012;**3**:257
- [85] Rogge MM. The role of impaired mitochondrial lipid oxidation in obesity. *Biological Research for Nursing*. 2009;**10**:356-373
- [86] Mirza MS. Obesity, visceral fat and NAFLD: Querying the role of adipokines in the progression of nonalcoholic fatty liver disease. *ISRN Gastroenterology*. 2011;**11**:592404
- [87] Tous M, Ferré N, Rull A, Marsillach J, Coll B, Alonso-Villaverde C, Camps J, Joven J. Dietary cholesterol and differential monocyte chemoattractant protein-1 gene expression in aorta and liver of apo E-deficient mice. *Biochemical and Biophysical Research Communications*. 2006;**340**:1078-1084

- [88] Rosenson RS, Huskin AL, Wolff DA, Helenowski IB, Rademaker AW. Fenofibrate reduces fasting and postprandial inflammatory responses among hypertriglyceridemia patients with the metabolic syndrome. *Atherosclerosis*. 2008;**198**:381-388
- [89] Okopin B, Krysiak R, Herman ZS. Effects of short-term fenofibrate treatment on circulating markers of inflammation and hemostasis in patients with impaired glucose tolerance. *The Journal of Clinical Endocrinology and Metabolism*. 2006;**91**:1770-1778
- [90] Camps J, Marsillach J, Joven J. The paraoxonases: Role in human diseases and methodological difficulties in measurement. *Critical Reviews in Clinical Laboratory Sciences*. 2009;**46**:83-106
- [91] Reddy ST, Devarajan A, Bourquard N, Shih D, Fogelman AM. Is it just paraoxonase 1 or are other members of the paraoxonase gene family implicated in atherosclerosis? *Current Opinion in Lipidology*. 2008;**19**:405-408
- [92] Kratzer A, Giral H, Landmesser U. High-density lipoproteins as modulators of endothelial cell functions: Alterations in patients with coronary artery disease. *Cardiovascular Research*. 2014;**103**:350-361
- [93] Chistiakov DA, Melnichenko AA, Orekhov AN, Bobryshev YV. Paraoxonase and atherosclerosis-related cardiovascular diseases. *Biochimie*. 2017;**132**:19-27
- [94] Zhao Q. Dual targeting of CCR2 and CCR5: therapeutic potential for immunologic and cardiovascular diseases. *Journal of Leukocyte Biology*. 2010;**88**:41-55
- [95] Everett BM, Pradhan AD, Solomon DH, Paynter N, MacFadyen J, Zaharris E, Gupta M, Clearfield M, Libby P, Hasan AAK, Glynn RJ, Ridker PM. Rationale and design of the cardiovascular inflammation reduction trial: A test of the inflammatory hypothesis of atherothrombosis. *American Heart Journal*. 2013;**166**:199-207
- [96] Moreira DM, Lueneberg ME, da Silva RL, Fattah T, Mascia Gottschall CA. Rationale and design of the TETHYS trial: The effects of methotrexate therapy on myocardial infarction with ST-segment elevation. *Cardiology*. 2013;**126**:167-170
- [97] Rissanen A, Howard CP, Botha J, Thuren T, Global Investigators. Effect of anti-IL-1 antibody (canakinumab) on insulin secretion rates in impaired glucose tolerance or type 2 diabetes: Results of a randomized, placebo-controlled trial. *Diabetes, Obesity & Metabolism*. 2012;**14**:1088-1096
- [98] Ridker PM, Howard CP, Walter V, Everett B, Libby P, Hensen J, Thuren T, CANTOS Pilot Investigative Group. Effects of interleukin-1 inhibition with canakinumab on hemoglobin A1c, lipids, C-reactive protein, interleukin-6, and fibrinogen: A phase IIb randomized, placebo-controlled trial. *Circulation*. 2012;**126**:2739-2748
- [99] Goldfine AB, Jablonski KA, Shoelson SE, Creager M. Targeting inflammation using salsalate in patients with type 2 diabetes: Effects on flow-mediated dilation (TINSAL-FMD). *Diabetes Care*. 2013;**36**:4132-4139

- [100] Nohria A, Kinlay S, Buck JS, Redline W, Copeland-Halperin R, Kim S, Beckman JA. The effect of salsalate therapy on endothelial function in a broad range of subjects. *Journal of the American Heart Association*. 2014;**3**:e000609
- [101] Larsen CM, Faulenbach M, Vaag A, Ehlers JA, Donath MY, Mandrup-Poulsen T. Sustained effects of interleukin-1 receptor antagonist treatment in type 2 diabetes. *Diabetes Care*. 2009;**32**:1663-1668
- [102] van Asseldonk EJ, Stienstra R, Koenen TB, Joosten LA, Netea MG, Tack CJ. Treatment with Anakinra improves disposition index but not insulin sensitivity in nondiabetic subjects with the metabolic syndrome: A randomized, double-blind, placebo-controlled study. *The Journal of Clinical Endocrinology and Metabolism*. 2011;**96**:2119-2126
- [103] Timper K, Hruz P, Beglinger C, Donath MY. Infliximab in the treatment of Crohn disease and type 1 diabetes. *Diabetes Care*. 2013;**36**:e90-e91
- [104] Meuwese MC, Mooij HL, Nieuwdorp M, van Lith B, Marck R, Vink H, Kastelein JJ, Stroes ES. Partial recovery of the endothelial glycocalyx upon rosuvastatin therapy in patients with heterozygous familial hypercholesterolemia. *Journal of Lipid Research*. 2009;**50**:148-153
- [105] Drake-Holland AJ, Noble MI. Update on the important new drug target in cardiovascular medicine—The vascular glycocalyx. *Cardiovascular & Hematological Disorders Drug Targets*. 2012;**12**:76-81
- [106] Tarbell JM, Cancel LM. The glycocalyx and its significance in human medicine. *Journal of Internal Medicine*. 2016;**280**:97-113
- [107] Van Teeffelen JW, Brands J, Stroes ES, Vink H. Endothelial glycocalyx: Sweet shield of blood vessels. *Trends in Cardiovascular Medicine*. 2007;**17**:101-105
- [108] Van Hout GP, Bosch L, Ellenbroek GH, de Haan JJ, Van Solinge WW, Cooper MA, Arslan F, de Jager SC, Robertson AA, Pasterkamp G, Hoefer IE. The selective NLRP3-inflammasome inhibitor MCC950 reduces infarct size and preserves cardiac function in a pig model of myocardial infarction. *European Heart Journal*. 2017;**38**:828-836