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Review article

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OXIDATIVE STRESS AND INFLAMMATORY MARKERS IN PREDIABETES AND DIABETES

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Prediabetes is a state of elevated plasma glucose in which the threshold for diabetes has not yet been reached and can predispose to the development of type 2 diabetes and cardiovascular diseases. Insulin resistance and impaired beta-cell function are often already present in prediabetes. Hyperglycemia can upregulate markers of chronic inflammation and contribute to increased reactive oxygen species (ROS) generation, which ultimately cause vascular dysfunction. Conversely, increased oxidative stress and inflammation can lead to insulin resistance and impaired insulin secretion. Proper treatment of hyperglycemia and inhibition of ROS overproduction is crucial for delaying onset of diabetes and for prevention of cardiovascular complications. Thus, it is imperative to determine the mechanisms involved in the progression from prediabetes to diabetes including a clarification of how old and new medications affect oxidative and immune mechanisms of diabetes. In this review, we discuss the relationship between oxidative stress and hyperglycemia along with links between inflammation and prediabetes. Additionally, the effects of hyperglycemic memory, microvesicles, micro-RNA, and epigenetic regulation on inflammation, oxidative state, and glycemic control are highlighted. Adipose tissue and their influence on chronic inflammation are also briefly reviewed. Finally, the role of immune-targeted therapies and anti-diabetic medication on glycemic control and oxidative stress are discussed.

Key words: *prediabetes, diabetes, metabolic syndrome, hyperglycemia, reactive oxygen species, oxidative stress, adipose tissue, inflammation, anti-diabetic drugs*

INTRODUCTION

Metabolic syndrome (MetS) is recognized as a constellation of risk factors which can predispose an individual to the development of cardiovascular diseases (CVDs) and type 2 diabetes (T2DM). These factors include central obesity, hypertension, hypertriglyceridemia, low HDL levels, and abnormal glucose metabolism. Worldwide, 18 million people die each year from CVD with the major predisposing factors being hypertension and diabetes (1). Obesity, often coexisting with T2DM, has reached pandemic proportions. The International Obesity Task Force and WHO estimate that about 1.7 billion people globally could be categorized as overweight or obese (1).

This upsurge in obesity is also closely associated with the growing prevalence of diabetes, which is quickly developing into a major burden on healthcare systems around the world. The International Diabetes Federation estimated that there were 415 million people living with diabetes in 2015, with an expected rise to 642 million by the year 2040 (2). Moreover, about 200 million people globally have impaired glucose tolerance, and this number is expected to rise to 420 million by the year 2025 (1).

Impaired insulin-mediated glucose uptake is the principal abnormality that bridges the metabolic and hemodynamic disturbances found in MetS (3, 4). This state of insulin resistance is associated with prediabetes, which is considered to be a high-risk state for conversion to diabetes. In prediabetes, an individual has an elevated plasma glucose level above the normal range, but below the threshold of clinical diabetes.

Total body glucose disposal is diminished in patients with T2DM, with over 80% of this impairment attributed to muscle insulin resistance (5). In insulin resistant nondiabetic patients, normoglycemia is maintained as long as pancreatic beta-cells are able to increase their production of insulin. Over time, these conditions lead to disease progression. Impaired beta-cell function along with insulin resistance can appear years before the development of diabetes and is already present in the majority of prediabetic patients (6).

Insulin resistance can lead to a myriad of changes, such as increased systemic blood pressure, elevated triglyceride levels, and lowered HDL levels, which are risk factors for macrovascular dysfunction. Furthermore, microangiopathic changes due to increased oxidative stress and inflammation are already present in prediabetic states (7). Thus, proper treatment of hyperglycemia is crucial, not only for delaying onset of diabetes but also for prevention of cardiovascular complications. Although many pathologies are associated with diabetes, most diseases that lead to morbidity and mortality in diabetic patients stem from cardiovascular complications (8). Significant progress has been made in understanding links between metabolism,

immunity and development of cardiovascular pathology in diabetes (7). This includes a better understanding of sex-specific changes in both cardiac and vascular metabolic damage (9, 10), and also a clearer understanding of how old and new medications affect oxidative and immune mechanisms of diabetes. This review will focus on these mechanisms.

THE LINK BETWEEN OXIDATIVE STRESS AND HYPERGLYCEMIA

Hyperglycemia in prediabetes can lead to oxidative stress and the upregulation of proinflammatory factors, which ultimately lead to vascular dysfunction (*Fig. 1*). To prevent the development of comorbidities, it is imperative to determine the mechanisms involved in the progression from prediabetes to diabetes. Oxidative stress leads to impaired glucose uptake in muscle and fat cells and decreases insulin secretion from beta-cells (11, 12). Reduction of systemic oxidative stress through the use of an nicotinamide adenine dinucleotide phosphate (NADPH) oxidase inhibitor improved glucose metabolism in a mouse model (13).

Data from the Framingham Offspring Study showed a positive association between the prevalence of insulin resistance and concentration of an oxidative stress marker, urinary 8-epi-prostaglandin F2α (8-epi-PGF2α) (14). This demonstrates that insulin resistance is associated with oxidative stress in non-diabetics and subgroups with an elevated risk of diabetes such as obesity or impaired fasting glucose (IFG). Moreover, in subjects with IFG, this association was higher when compared to subjects with normal fasting glucose (NFG). This is in line with previous studies correlating 8-epi-PGF2α with increased insulin resistance and impaired glucose tolerance (IGT) in humans (15, 16) and with previous *in vitro* and rodent model data (17).

Focus on oxidative and inflammatory genes is supported by whole gene expression profiling of epicardial adipose tissue from patients with coronary artery disease. Genes involved in oxidative and lipid metabolism, mitochondrial function, nuclear receptor transcriptional activity, antigen presentation, chemokine signaling, and inflammation are altered in cardiovascular disease (18). Thus, their associations to key risk factors such as diabetes need to be better established.

Succinobucol is an antioxidant which is a potential oral antidiabetic agent, as it was shown to have antihyperglycemic activity in preclinical studies. In phase II trials it was demonstrated to have anti-inflammatory properties and positive effects on coronary atherosclerosis (19, 20). While most studies have focused

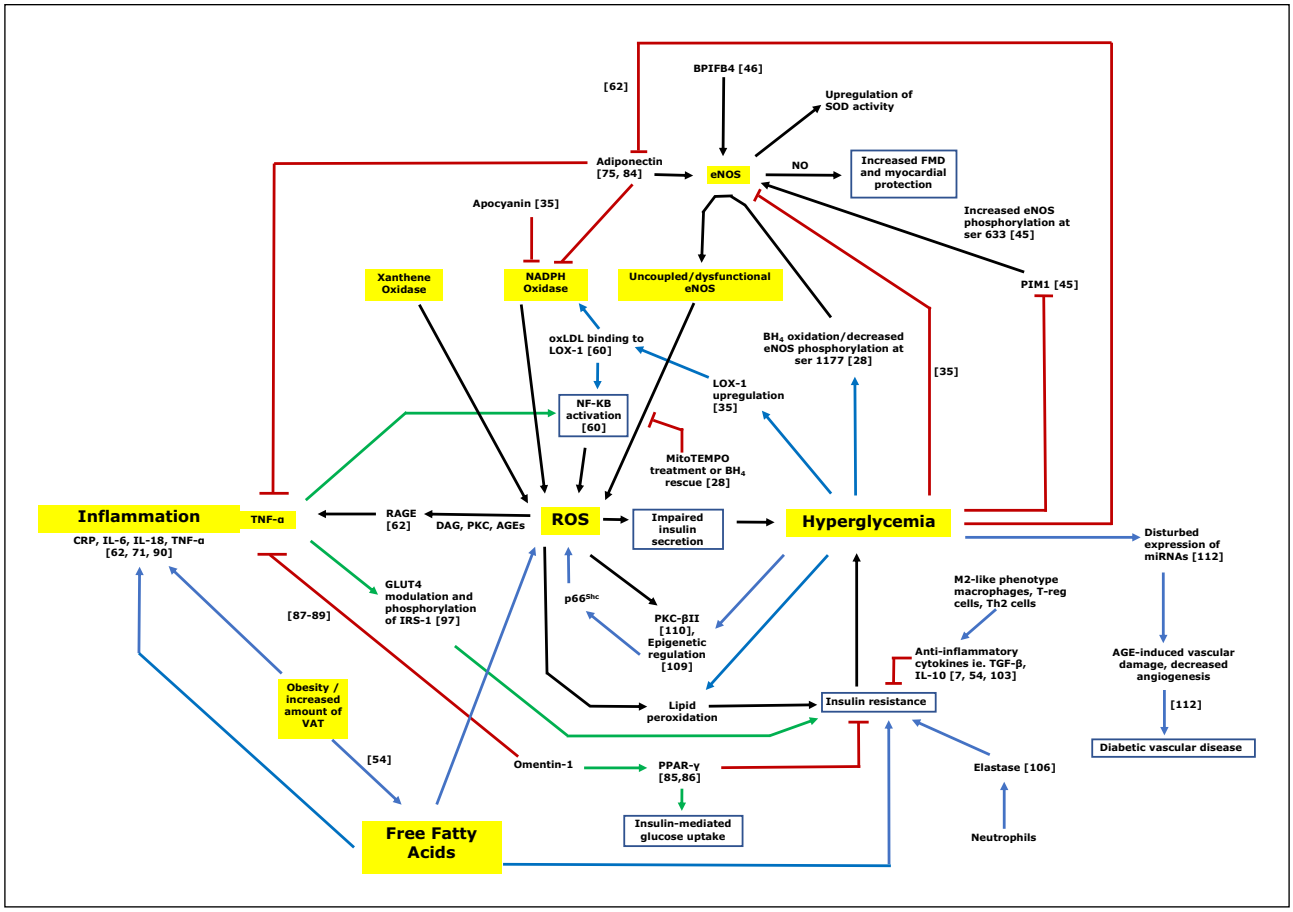

Fig. 1. Major interactions between oxidative stress, inflammation, hyperglycemia, and insulin-resistance. ROS play a central role in the interactions involving inflammation, oxidative stress, and metabolic control. Hyperglycemia, through various mechanisms, leads to increased ROS production and chronic inflammation. Perturbed expression of miRNAs and epigenetic regulation of oxidative stress genes are contributory factors to hyperglycemic memory. Sources of ROS include NADPH oxidase, dysfunctional eNOS, and xanthene oxidase. Excessive production of ROS can feedback and contribute to the pathogenesis of insulin-resistance and impaired insulin secretion. Adipokines such as adiponectin and omentin-1 can influence insulin-resistance through various pathways.

on macroangiopathy, a better understanding microcirculatory dysfunction in cardiovascular pathology (21) is needed in metabolic diseases including obesity and diabetes (22, 23).

Sources of reactive oxygen species in prediabetes

1. Mitochondrial oxidation

Mitochondrial respiration is the major cellular source of reactive oxygen species (ROS), and this production is balanced by clearance through antioxidant systems (superoxide dismutase (SOD), glutathione peroxidase, catalase, *etc*). In hyperglycemic states such as prediabetes and diabetes, ROS can accumulate and lead to non-specific oxidative damage to DNA, proteins, and other molecules (24). Hyperglycemia also leads to increased ROS production through activation of the kinase C (PKC) pathway *via* diacylglycerol (DAG), increased hexosamine pathway flux, increased advanced glycation end (AGE) production, and increased flux in the polyol pathway (24). *Atf3*, an immediate response gene to metabolic and oxidative insults, has been recently identified as an important protective regulator of many of these changes (25).

Mitochondrial oxidative stress is associated with insulin resistance, T2DM, and its complications (17, 26, 27). To examine the effects of a mitochondrial-targeted antioxidant, MitoTEMPO, on markers of oxidative stress, glucose tolerance, and insulin resistance, one study used a high-fat diet (HFD) mouse model (28). Increased acetylation of manganese superoxide dismutase (MnSOD), the main scavenging enzyme in mitochondria, which reduces its activity (29), was observed in the HFD group. Furthermore, markers of mitochondrial oxidative stress and cellular oxidation were elevated in HFD mice (28). Following MitoTEMPO treatment, mitochondrial-induced oxidative stress was reduced. In addition, MitoTEMPO-treated HFD mice had significantly reduced serum glucose and six-hour fasting insulin levels compared with untreated HFD-mice (28). This demonstrated that reduction of mitochondrial oxidative stress leads to improved glucose tolerance and insulin resistance in a mouse model of MetS. Finally, mitochondrial oxidation is closely interlinked with other sources of oxidative stress such as NADPH oxidases (30).

2. Nicotinamide adenine dinucleotide phosphate oxidases

Exposure to hyperglycemia is known to increase intracellular ROS generation, which leads to vascular inflammation, leukocyte adhesion, insulin resistance, protein/macromolecule glycation, and inhibition of NO synthesis. Intracellular superoxide production is increased from various sources such as NADPH oxidase, xanthine oxidase, cyclooxygenase, and uncoupled eNOS (31, 32). Although there are many sources of ROS, NADPH oxidases appear to have a central role their generation. Found in almost all mammalian cells, their physiological role is to produce ROS for functions of innate immunity, redox-signaling cascades, and for the production of certain hormones (33). Dysfunction of NADPH oxidase can lead to dysregulation of other oxidases, leading to increased ROS production (34). Because of their overarching role in ROS generation, this makes NADPH oxidases an attractive target for future therapeutic strategies in the treatment of CVDs.

Upon exposure of human umbilical artery endothelial cells (HUAECs) to hyperglycemia, increased expression of NADPH oxidase subunits Nox2 and p47phox was observed (35). *NOS3*, *NOX1*, *NOX4*, and *CYBA* gene (codes for p22-phox subunit) expression was upregulated by hyperglycemia in human microvascular endothelial cells (HMVEC), but not in human umbilical vein endothelial cells (HUVEC) (36). This shows that elevated glucose can induce different responses in NOS and NOX in different cell types.

Treatment of obese mice with apocynin, an NADPH oxidase inhibitor, reduced lipid peroxidation and H_2O_2 generation in white adipose tissue (WAT) (13). Additionally, plasma levels of adiponectin increased, while plasma glucose, insulin, and triglyceride levels were all significantly reduced. This is clear demonstration that inhibition of NADPH oxidase leads to reduced lipid peroxidation, ROS synthesis, oxidative stress in WAT, and improved glucose/lipid metabolism (13). This is in agreement with older studies which showed that oxidative stress impairs insulin secretion from pancreatic beta-cells and glucose uptake in muscle and adipose tissue (11, 12). Thus, reduction of oxidative stress can lead to improved glucose metabolism.

3. Endothelial nitric oxide synthase

Endothelial nitric oxide synthase (eNOS) is an enzyme which has cardioprotective properties, mainly through its production of nitric oxide (NO) in the vascular endothelium. Although NO is known mostly for its role in regulating vascular tone, it also possesses antioxidant activity through its upregulation of superoxide dismutase (SOD) (37). In certain disease states, oxidation of tetrahydrobiopterin (BH4) occurs, a cofactor for eNOS, which leads to eNOS uncoupling. In these situations, dysregulated eNOS contributes to increased oxidative stress through the generation ROS instead of NO (34, 38, 39). Exposure of HUAECs to hyperglycemia attenuated eNOS activity and total nitrate levels (35).

It is also known that eNOS exerts important protective effects on the myocardium (40). Thus, dysfunctional eNOS will promote diabetic cardiomyopathy, and this association is a hallmark of myocardial dysfunction in diabetes (41). Hyperglycemic mice induced through the use of a high-fat diet (HFD) had increased mitochondrial superoxide and cardiac levels of H_2O_2 (28). Upon treatment with MitoTEMPO and BH4, these were reversed. This indicates that mitochondria and uncoupled eNOS are the major sources of ROS in a MetS mouse model. In addition, decreased eNOS phosphorylation at Ser-1177, which diminishes its activity, was seen in HFD-mice (28). This suggests that eNOS activity is itself downregulated in hyperglycemic conditions. Hyperglycemia also significantly blunted the flow-mediated dilation response to endogenous NO stimulation (42). This effect was reversed in hyperinsulinemia or by an exogenous NO donor (nitroglycerin administration), showing that hyperglycemia acts through an endogenous NO mechanism to impair endothelial function (42).

Several new aspects of eNOS regulation have recently been uncovered. This includes epigenetic regulation (43, 44) and novel regulatory functions of serine threonine kinases. Pim1 is a serine/threonine kinase acting upstream of eNOS to phosphorylate it at Ser-633, thereby increasing its activity and production of NO (45). Exposing cultured HUVECs to hyperglycemia decreased eNOS activity and NO production through the impairment of Pim1 expression (45). Pim1 could prove to be another therapeutic target in the treatment of diabetic vascular complications in the future. Because of this, it would be valuable to determine if upregulation of Pim1 can improve endothelial function through anti-oxidative effects in prediabetic or diabetic subjects. Bactericidal/permeability-increasing fold-containing-family-B-member-4 (BPIFB4) is another interesting molecule which may be important in prediabetes and diabetes and has recently been shown to upregulate eNOS function through Ca^{2+} mobilization and PKCα activation (46). Additionally, when eNOS was inhibited, BPIFB4 still enhanced endothelial activity *via* an EDHF-mediated pathway.

Biomarkers of oxidative stress in prediabetes

Previously, oxidative stress was thought to be a simple imbalance between the synthesis and scavenging of ROS. This is not entirely the case, as the current understanding is that increased oxidative stress also involves the dysfunction of ROS-producing enzymes (34). Moreover, many clinical trials using scavenger antioxidants have failed to demonstrate benefits in human subjects, even though studies using animal and *in vitro* models have shown an improvement in endothelial function. Increased oxidative stress has a central role in the pathogenesis of many diseases such as atherosclerosis, vascular inflammation, and endothelial dysfunction and is thought to play a role in the progression of prediabetes to diabetes (8). Thus, it is important to detect changes in oxidative stress early enough to prevent disease progression.

The role of oxidative stress and its relationship to endothelial dysfunction in diabetes has been widely studied (47-51). Moreover, there are already detectable features of hyperglycemia-associated complications and changes in general redox-status and inflammatory state even before diabetes is diagnosed. Consequently, recent efforts have focused on the role of oxidative stress and inflammation in prediabetes (13, 14, 28, 36, 42, 52). Evidence shows that obesity, especially that involving visceral adipose tissue (VAT), has a major role in contributing to systemic oxidative stress and inflammation in humans, and these can lead to insulin resistance (17, 53, 54).

1. Glutathione

Antioxidant markers could be useful in prediabetes screening. One such marker, glutathione, can exist in two forms, reduced (GSH) and oxidized (GSSG). The reduced form, Glutathione (GSH), is an antioxidant and the main scavenger of free radicals in RBCs, which helps prevent cellular damage by neutralizing ROS. It acts by donating a reducing equivalent, such as $H^+ + e^-$, to other molecules such as ROS. In the process, GSH is oxidized into glutathione disulfide (GSSG). A commonly used marker of increased oxidative stress is the GSH/GSSG ratio (55). Subjects with prediabetes had a significantly decreased GSH/GSSG ratio in comparison to controls, which indicates that an impaired redox status is already present and detectable before clinical manifestations of diabetes appear (56).

2. 8-hydroxy-2'-deoxyguanosine

Levels of GSH are dependent on diabetes progression (52). Although erythrocyte GSH levels were similar in IFG and normoglycemic subjects, serum levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a biomarker for oxidative DNA damage and endothelial dysfunction, were significantly higher in the IFG group (52). Furthermore, a significant positive correlation was seen between serum 8-OHdG and the atherogenic index of plasma, which indicates a relationship between atherosclerotic risk and oxidative stress. Preclinical atherosclerosis was associated with increased 8-OHdG in subjects with IFG, even though these subjects had normal cholesterol and no significant lipid peroxidation (52).

3. Lectin-like oxLDL receptor

Lectin-like oxLDL receptor (LOX-1) is a receptor for oxidized LDL found mainly on endothelial cells, however, it is also seen on vascular smooth muscle cells and macrophages (57, 58). Normally, *LOX-1* is expressed at low levels in healthy adults. Its upregulation in the pathogenesis of atherosclerosis as well as diabetes has already been documented (47, 57, 59). Upregulation of LOX-1 signaling pathways is involved in vascular smooth muscle cell (VSMC) proliferation and foam cell formation when taken up by macrophages. Upon binding of oxidized LDL to LOX-1, multiple downstream events are activated, including activation of membrane-bound NADPH oxidase, and activation of the NF-κB pathway (60). In cultured HUAECs, it was observed that high glucose increased *LOX-1* mRNA levels, accompanied by an augmented uptake of oxLDL (35). Apocynin, an inhibitor of NADPH oxidase, reversed these effects, demonstrating its antioxidant and cardioprotective properties.

Advanced glycation end-products

Advanced glycation end-products (AGEs) are proteins or lipids which are formed through non-enzymatic glycation as a result of being exposed to hyperglycemic conditions. They are believed to have an important role in cardiovascular complications in diabetes (61). AGEs bind to and activate RAGE (receptor for AGE), which then initiates a proinflammatory response. This acts *via* heterodimerization with TLR-4, which stimulates the production of pro-IL-1B, pro-IL-18, and NLRP-3 (62). In this context, soluble RAGE has been postulated as a valuable biomarker of these molecular events (63). Although initially described in pulmonary hypertension, future studies involving soluble RAGE in diabetes and prediabetes will identify further links to inflammatory and oxidative stress mechanisms in humans (63).

Reactive oxygen species neutralizers and others

Nuclear factor erythroid 2-related factor-2 (Nrf2) is a transcription factor which acts as the main regulator of the antioxidant response. Nrf2 levels are normally low and the protein is kept in the cytoplasm. During periods of oxidative stress, Nrf2 translocates into the nucleus (64). Through activation of this signaling pathway, expression of genes involved in the removal of ROS contributes to the cellular defense against oxidative stress. Nrf2 activation also regulates genes that have a role in the immune and inflammatory responses. In mouse models, Nrf2 activation protected pancreatic beta-cells from damage, prevented diabetic development, and increased insulin sensitivity (65, 66).

Nrf2 levels from nuclear extracts of peripheral blood mononuclear cells (PBMC) were lower in prediabetic and diabetic patients (67). This is interesting, as the reverse is expected, since oxidative stress in diabetic patients should enhance Nrf2 levels. These findings indicate that the Nrf2 response in prediabetic and diabetic subjects is impaired. In diabetic patients, total antioxidant status and GSH levels were lower, while increased lipid peroxidation and SOD activity were observed (67). Hence, the low levels of Nrf2 seen in prediabetic and diabetic patients lead to oxidative stress and redox status imbalance. In the future, Nrf2 could emerge as a potential target for therapy in the prevention of further complications due to oxidative stress in prediabetic patients.

In HMVECs exposed to hyperglycemia, there was an overall upregulation of ROS-neutralizing and peroxide-clearance enzymes such as SOD1, glutathione peroxidase-1, thioredoxin reductase-1 and 2 (36). Uncoupling protein 1 (UCP1) is a protein that uncouples the electron transport chain from oxidative phosphorylation, which leads to decreased ROS generation in mitochondria. Gene expression of both *UCP1* and *NFE2L2* (which encodes for Nrf2) were upregulated in HMVEC in response to hyperglycemia (36). In HUVEC, levels of these enzymes either stayed the same or were downregulated. Superoxide production increased in HUVEC and HMVEC, but

H_2O_2 levels increased only in HUVEC in response to hyperglycemia. This demonstrates a differential change in gene expression profiles, and superoxide and H_2O_2 levels between different endothelial cell types during hyperglycemia.

INFLAMMATION IN PREDIABETES

Inflammation is an essential player in both endothelial and cardiac pathology in prediabetes and diabetes. In the vessels, endothelial signaling regulates recruitment of leukocytes (68) and this mechanism is also important for metabolic cardiomyopathy, while smooth muscle cells play a role in more chronic stages of vascular remodeling and calcification/stiffening (69, 70). In diabetic or obese patients, there is chronic low-grade inflammation which is reflected by high levels of cytokines such os TNF-α and other inflammatory markers such as CRP and TNF-α (71). Furthermore, this inflammatory state is thought to be the mechanism by which metabolic disorders are associated with the development of CVD and heart failure in patients with MetS (62).

The context of cardiac myocyte metabolic changes in diabetes and prediabetes is controversial, as it has been recently reported that cardiac metabolic adaptations in diabetic db/db mice seem to prevent pressure overload-induced heart failure (72). At the same time, complex metabolic changes promote metabolic cardiomyopathy (24). Because of this, both vascular and cardiac inflammation and its role in the development of prediabetes is currently a topic of interest. Various pro- and anti-inflammatory markers have been associated with the progression of prediabetes to diabetes, a few of which include adiponectin, extracellular newly identified-RAGE (EN-RAGE), IL-6, IL-13, CRP, IL-18, IL-1 receptor antagonist, and neopterin (73). Moreover, lipid-responsive/specific CD1d restricted immune cells (74), which play an important role in atherosclerosis, are gaining significant attention in diabetes as part of the immunometabolic network (7).

Adipose tissue and free fatty acids

White adipose tissue (WAT) is used mainly for lipid storage and exists as visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). VAT is generally more metabolically active than SAT, containing more immune cells in normal and pathological states. Aside from energy storage purposes, adipose tissue can also function as an endocrine organ, being involved in many metabolic and inflammatory responses (75). Another factor, underappreciated so far, includes increased sympathetic outflow in metabolic conditions. Adipose tissue is highly innervated and this innervation is essential for regulation of its inflammatory and adipokine releasing properties (76).

When the physiological functions of adipose tissues are perturbed, such as in obesity, there is increased production of proinflammatory mediators and release of free fatty acids (FFA), which can lead to the development of metabolic disorders such as insulin resistance (54). The mechanisms of induction of inflammatory responses in adipose tissue have been expertly reviewed elsewhere (77-80), however, from a hormone metabolism point of view it is important to emphasize the role of the mineralocorticoid receptor (MR) in this process (81). Additionally, increased levels of FFAs have been proposed as key activators of inflammation and metabolic signaling in obesity (82). FFAs activate TLR-4 in adipocytes and macrophages, this leads to upregulation of NF-κB signaling and increased expression of inflammatory cytokines such as TNF-α and IL-6 (83). This suggests that inflammation of adipose tissue is the cause of impaired insulin function and not the other way around.

1. Adiponectin

Adiponectin is considered as an anti-inflammatory adipokine, which can inhibit TNF-α-induced activation of NF-κB signaling and endothelial adhesion molecule expression. It has been shown to inhibit NADPH-oxidase activity in humans, increase 5'adenosine monophosphate-activated protein kinase (AMPK)-mediated eNOS phosphorylation in cell culture models, and improve eNOS coupling and NO availability in human vasculature (75, 84). Levels of adiponectin are reduced in hyperglycemic states and this dysregulation is thought to contribute to increased inflammation and impaired insulin sensitivity in prediabetic patients (62).

2. Omentin-1

Omentin-1 is another adipokine which is highly expressed in VAT, although receptors for this protein are currently unknown. Omentin-1 stimulates insulin-mediated glucose uptake in human adipocytes and is negatively correlated with obesity and insulin resistance, and this reduction of insulin resistance is thought to act through upregulation of PPAR-γ activity (85). Moreover, omentin-1 was found to decrease NF-κB activation, production of TNF-α and IL-6, and inhibit lipopolysaccharide (LPS)-induced inflammation and oxLDL-induced foam cell formation in macrophages (86). The downregulation of NF-κB signaling also acts to shift macrophage differentiation towards the M2-like phenotype. In a transgenic mouse model expressing the human omentin gene in adipose tissue, there was a significant decrease in both macrophage accumulation and mRNA expression of proinflammatory mediators such as TNF-α, IL-6, and monocyte chemoattractant protein (MCP)-1 (87). Additionally, exposing endothelial cells to omentin reduced TNF-α-stimulated NF-κB activation. Interestingly, the level of circulating omentin-1 increases after treatment with metformin, or glucagon-like peptide-1 (GLP-1) analog (exenatide) through improved insulin sensitivity (88). In the future, omentin might be a valuable therapeutic target in the treatment of prediabetes and CVDs.

Inflammatory markers

The C5a protein acts as a potent inflammatory mediator and is increased in a variety of inflammatory diseases such as rheumatoid arthritis (RA), inflammatory bowel disease, SLE, and psoriasis. Importantly, C5a is involved in coagulation *via* the induction of adhesion molecule expression and tissue factor activity in endothelial cells (56). A recent study found that there was a consistent trend of increased inflammatory markers such as CRP, IL-6, and C5a in prediabetic patients (56). This leads to increased coagulation activity in the prediabetic state, which potentiates future cardiovascular complications. Furthermore, this is in line with data from The Women's Health Study, a randomized clinical trial initiated in 1992, which showed that elevated baseline plasma levels of CRP and IL-6 predict the development of T2DM (89).

In prediabetic and diabetic patients there was clear enhancement of the inflammatory response, as demonstrated by the measurement of inflammatory markers such as WBC, granulocytes, monocytes, CRP, IL-18, IL-1 receptor antagonist (IL-1RA), and neopterin (90). As glycemic status progressed from normoglycemic to prediabetes to T2DM, the inflammatory and immune biomarker profile varied with this progression (90). This is potentially useful since it allows differentiation between early preclinical and clinical phases of the disease, its complications, and progression.

Levels of atherogenic vascular adhesion molecules (VCAM, ICAM, and E-selectin), pro-thrombotic factors (plasminogen

activator inhibitor-1 and P-selectin), and IL-6 response all increased in acute-moderate hyperglycemia (42). This demonstrates that there is activation of potent systemic cytokines and increases in proinflammatory and proatherogenic markers in non-diabetic overweight and obese subjects. Conversely, exposure to acute-high physiological insulin levels reversed these effects, which matches observations from a previous study (49).

1. Cytokines in prediabetes

IL-6 is a proinflammatory cytokine produced in a number of tissues such as activated leukocytes, endothelial cells, and adipocytes (91, 92). It has been shown to induce hyperglycemia and compensatory hyperinsulinemia in murine models and humans (93, 94). Conversely, hyperglycemia can directly stimulate upregulation of cytokines, chemokines, and adhesion molecules, modulating various pathways which converge towards NF-κB signaling (83). For example, expression of high-mobility group box 1 (HMGB1) was upregulated in isolated cardiomyocytes and macrophages exposed to hyperglycemia, which led to increased activation of MAPK and NF-κB signaling pathways and ultimately to increased TNF-α and IL-6 secretion (95).

TNF-α is a proinflammatory cytokine which increases insulin resistance *via* modulation of glucose transporter type 4 (GLUT 4) and phosphorylation of insulin receptor substrate-1 (IRS-1) (96). TNF-α affects lipid metabolism and was previously known as cachectin due to its significant role in the pathogenesis of cachexia in various diseases (97). In fact, patients being treated for psoriasis or RA with a TNF-α inhibitor often gain weight (98). In patients suffering from psoriasis, treatment with etanercept results in the reduction of lipid peroxidation and oxidative stress. Moreover, an increase in plasma total antioxidant capacity and paraoxonase-1 (PON-1) activity, an anti-inflammatory enzyme associated with HDL, was observed during treatment (99). Crosstalk between TNF-α-regulated pathways is potentially both pro- and anti-inflammatory, with CKII-SIRT1-SM22α being induced by TNF-α (100). This reinforces the expression of SM22α, which limits the inflammatory response in VSMCs, and has been demonstrated both *in vivo* and *in vitro* (100).

Infiltration of adipose tissue by immune cells has an important role in insulin resistance and prediabetes. M1-like phenotype macrophages are considered to be proinflammatory, while M2-like phenotype macrophages secrete anti-inflammatory cytokines such as TGF-β and IL-10, which act to decrease inflammation in adipose tissue and improve insulin sensitivity (7). In a mouse model, macrophage infiltration of adipose tissue was higher in mice with insulin resistance than controls (101). It was also observed that VAT infiltration by macrophages led to increased serum insulin levels. T regulatory cells, considered to be anti-inflammatory, are also present in healthy adipose tissue and recent studies suggest that they express the insulin receptor and secrete TGF-β and IL-10 (7). In states of insulin overload, the ability of T regulatory cells to suppress inflammatory responses is diminished. Th2 cells in the region also release anti-inflammatory cytokines including IL-4, IL-5, IL-13, IL-10 (54, 102).

2. C-reactive protein

C-reactive protein (CRP) is the main downstream mediator of the acute phase response and is derived from IL-6-dependent hepatic biosynthesis. It is one of the most well-studied epidemiological biomarkers of inflammation in prediabetes, diabetes, and its associated CVDs (56, 73, 89, 103). Its major roles include regulation of platelet activation, enhancement of leukocyte activity, and complement fixation. CRP was found to be strongly elevated in prediabetic compared to normoglycemic individuals (90). However, there was only a modest increase in CRP when comparing diabetic to prediabetic subjects. This illustrates that even in prediabetes, early low-level inflammation is present which is reflected by the rise in CRP levels.

3. Fibrinogen

Fibrinogen is another acute-phase protein which is heavily involved in the systemic response to inflammation. Its actions include contributing to blood viscosity, platelet aggregation, modulation of coagulation activation, and enhancement of atherosclerotic plaque progression (104). Similar to CRP, there was a strong increase in fibrinogen when comparing prediabetic and normoglycemic patients (90). However, diabetic subjects had only a slight increase in fibrinogen levels when compared with prediabetic subjects. Besides having a principal role in the progression of CVD, fibrinogen levels strongly associated with prediabetes independently from cardiovascular risk factors, indicating that it could be involved in the pathogenesis of prediabetes and diabetes (90).

Neutrophils

Neutrophils constitute more than 90% of granulocytes and are typically involved in maintaining a chronic inflammatory state. A study in mice showed that secreted elastase from neutrophils, which normally has an important role during the early stages of inflammatory responses, is involved in the development of insulin resistance (105). Through multiple mechanisms such as reduced insulin signaling, imbalanced lipid metabolism, and an increase in glucose production, the secreted neutrophil elastase led to increased cellular insulin resistance and could have a role in the progression from normoglycemia to prediabetes. This may be essential for vascular remodeling in the context of neutrophil involvement (106).

Anti-inflammatory markers

Studies have shown that not only proinflammatory markers are elevated during disease progression. IL-1RA, TGF-β1, and GDF-15 are all anti-inflammatory proteins which are increased in T2DM (107). IL-1RA increased more in subjects with prediabetes than IL-18 (90). Since anti-inflammatory markers are elevated in patients with prediabetes, it seems that this might be an attempt by the body to counteract increased proinflammatory activity. However, this anti-inflammatory activity appears to be negligible, as the elevation is insufficient to prevent disease progression to diabetes.

Epigenetics and hyperglycemic memory

Recently, studies have investigated how epigenetics can regulate translation of ROS-generating or proinflammatory genes in the setting of hyperglycemia (7). These investigations are also linked to the concept of hyperglycemic memory, whereby complications caused by hyperglycemic stress persist even after normalization of glucose level has occurred (108). In human endothelial cells, hyperglycemia upregulated the activity of a mitochondrial enzyme, $p66^{Shc}$, through phosphorylation by protein kinase C-βII (PKC-βII) (109). Additionally, expression of the *p66^{Shc}* gene was epigenetically regulated, with overexpression of *p66^{Shc} via* promoter region CpG demethylation and acetylation of histone 3. These studies also demonstrated that $p66^{Sch}$-derived ROS generation sustained

upregulation of PKC-βII, producing a vicious cycle of persistent mitochondrial ROS production (109, 110). Upregulated $p66^{Shc}$ activity continued, even after returning the cells to normoglycemic levels. Through the use of *$p66^{Shc}$* siRNA gene silencing (in addition to insulin treatment), endothelial function was rescued by a reduction in ROS production, PKC-βII activity, and restoration of eNOS activity (110).

MicroRNAs (miRNAs) are small non-coding RNA molecules involved in post-transcriptional regulation of gene expression and are thought to have a key role in the pathogenesis of hyperglycemia-induced cardiovascular dysfunction (111). Various studies have shown that hyperglycemia-induced disturbances in expression of microRNAs (such as miR-320, miR-221, miR-222, miR-503, and miR-126) can lead to decreased angiogenesis, cause AGE-induced vascular damage, and perturb endothelial progenitor cell migration, all of which contribute to diabetic vascular disease (111). Furthermore, miRNA profiling showed that a number of miRNAs are dysregulated in diabetic mice, participating in hyperglycemic memory and contributing to the pathogenesis of diabetic cardiomyopathy (112). Finally, a study in a large population-based cohort used plasma miRNA profiling to demonstrate that certain miRNAs may serve as potential biomarkers of T2DM (113). The role of miRNAs in metabolic and cardiovascular dysfunction have previously been detailed elsewhere (7, 114-117).

Microvesicles

Microvesicles (MVs), also known as microparticles, are small particles secreted by cells, containing various molecules such as lipids, cytokines, growth factors, microRNA, and mitochondria (118-120). They are delivered into the plasma from blood and endothelial cells in physiological conditions, but also in response to inflammation, activation of coagulation, or shear stress (118, 121). In T2DM patients, the level of circulating microparticles increases and correlates negatively with flow-mediated dilation, while correlating positively with brachial ankle pulse wave velocity (122).

Endothelial microparticles, generated from human coronary artery endothelial cells (HCAEC) which were exposed to high glucose concentration, had increased NADPH oxidase activity and ROS levels in comparison to microparticles delivered from cells in normoglycemic conditions. Moreover, these microparticles promoted ROS production and inflammation in endothelial cells (31).

MVs secreted by M1-like phenotype adipose tissue macrophages regulate NF-κB activation, which decreases insulin signal transduction and glucose uptake in adipocytes contributing to obesity-related insulin resistance (123). Liraglutide, a GLP-1 analog, decreased endoplasmic reticulum stress-induced production of MVs by macrophages and reduced atherosclerotic development in T2DM rats (124).

Estrogen and oxidative stress in diabetes

It has been shown that exogenous estrogen lowers a woman's risk of cardiovascular disease (125). Furthermore, pancreatic islet β-cells are protected against oxidative injury and proinflammatory cytokine-induced apoptosis through the induction of estrogen receptor-α expression (126, 127). A recent study, which used a model of hyperglycemia-induced persistent oxidative stress, showed that activation of the estrogen receptor-β diminishes generation of ROS, which leads to improved wound-healing in T2DM rats (128). Additionally, estrogen-replacement therapy leads to decreased free radical generation and enhanced insulin sensitivity (129). Thus, estrogens could be an attractive therapeutic agent in T2DM postmenopausal women, however, their potential side-effects must be taken into account. Future studies are required to better understand their potential benefit.

IMMUNE-TARGETED THERAPIES

Reducing cardiovascular risk is a major goal in the treatment of patients with prediabetes and diabetes (130). Since there is a mutual relationship between systemic inflammation and several metabolic parameters, interest in the effects of immunomodulatory agents on classical CVD risk factors is increasing (131-134). Furthermore, drugs used in conventional therapies are also being investigated for their ability to reduce systemic inflammation. These include anti-hypertensive drugs, statins, anti-platelets, and antihyperglycemic agents (135). Several clinical studies have been performed to investigate the effects of immunotargeted treatments on inflammation, insulin resistance, and glucose control (131).

Interleukin antagonists

Anakinra is an IL-1 receptor antagonist that was shown to reduce levels of hs-CRP and effectively improve glycemic control in T2DM patients (136). Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor and was shown to improve insulin sensitivity in RA patients (137). Since IL-6 has been shown to be involved in obesity-associated inflammation, which is linked with insulin-resistance, it will be an interesting target for treatment in the future (138, 139). IL-1β antagonists have a more defined action on metabolic profile, including antihyperglycemic effects, which acts *via* increased B-cell secretory function. Gevokizumab is a recombinant human monoclonal antibody which has been demonstrated to neutralize IL-1β and reduce inflammatory biomarkers in diabetic patients (140). Canakinumab is an engineered human monoclonal antibody targeting IL-1β. Data from the CANTOS study shows that canakinumab reduces the risk of major recurrent cardiovascular events and further studies have been planned that will address its effects on glycemic levels in diabetic patients (141, 142). These studies will also investigate its actions on insulin resistance, which is known to stimulate an increase in CRP levels. It was previously observed that canakinumab had no significant effect on glucose control, however, in that group, baseline HbA1c value was already optimal (143). LY2189102 is a neutralizing IL-1β antibody which significantly reduced inflammatory biomarkers such as hs-CRP and IL-6, while also modestly reducing HbA1c and fasting glucose levels in T2DM patients (144).

Tumor necrosis factor-α antagonists

Increased insulin resistance is often seen in RA patients and this is thought to be caused in part by the presence of high-grade systemic inflammation (145). Many phase IV studies show that TNF-α blockers consistently decrease levels of CRP and have a protective effect against cardiovascular events in RA patients. However, since there is a large inflammatory component in RA, this result might be due to RA disease control rather than an inherent reduction in cardiovascular risk (145). Sources of TNF-α which should be targeted are currently a topic of interest. While B cells are not considered a primary source in metabolic pathologies, B cell-specific depletion of TNF-α inhibits atherosclerosis and plaque vulnerability (146).

In a recent study involving non-diabetic patients suffering from psoriasis, treatment with adalimumab, a monoclonal antibody inhibiting TNF-α, increased insulin sensitivity (147).

In this group of patients, insulin sensitivity prior to adalimumab treatment negatively correlated with CRP level. Furthermore, in studies involving RA patients, adalimumab and infliximab significantly improved insulin sensitivity (96, 137, 145). Etanercept improved insulin sensitivity in RA subjects (137), however, in patients with psoriasis or T2DM, there was no such effect (148, 149).

ANTI-INFLAMMATORY ACTIVITY OF ANTI-DIABETIC DRUGS

Aside from reducing blood glucose levels, a number of antihyperglycemic agents are known to possess anti-inflammatory activity (150). However, it is important to differentiate between anti-inflammatory effects due to improved glucose control and anti-inflammatory effects due to the intrinsic actions of the antihyperglycemic drug. Insulin sensitizers such as thiazolidinediones (PPAR-γ agonist) and metformin (AMPK activator) have greater anti-inflammatory activity than insulin secretagogues, such as sulphonylureas or glinides (151). Of these, thiazolidinediones have been the most effective in lowering tissue and serum inflammation. Alpha-glucosidase inhibitors have a modest effect on inflammatory markers, while dipeptidyl peptidase (DPP)-4 inhibitors and GLP-1 agonists exert pleiotropic effects and are more effective in this regard. In fact, the possible effects of DPP-4 inhibitors extends into all diseases linked to mitochondrial oxidative stress. For example, a recent experimental study has shown that it improved mitochondrial biogenesis in mice with heart failure *via* activation of GLP-1 receptor signaling (152). Recent clinical trials have shown that SGLT2 inhibitors reduce cardiovascular

Table 1. Anti-diabetic drugs and their effects on inflammation and oxidative stress.

Antihyperglycemic agent	Effects on inflammation and oxidative stress
GLP-1 agonists	
Exendin-4	- Reduction of LPS-induced inflammation in adipocytes and adipose tissue macrophages (186)
Liraglutide	- CRP reduction in T2DM patients (187)
Exenatide	- CRP reduction in T2DM patients (188)
Biguanides	
Metformin	- CRP reduction in IGT and T2DM patients (166, 167) - Reduction of various proinflammatory cytokines from monocytes and lymphocytes in IGT patients (168)
Thiazolidinediones	
Rosiglitazone	- Reduced inflammatory markers and superoxide anion production, inhibition of ubiquitin-proteasome activity in atherosclerotic plaques of T2DM patients [180]
Pioglitazone	- Reduced adipose tissue macrophage accumulation and activity, decreased secretion of chemoattractants and proinflammatory cytokines in neutrophils, macrophages and dendritic cells in T2DM patients (189) - Decreased IL-6, IL-1B and metabolic activity of VAT in obese subjects and IGT/T2DM subjects (190, 191) - Decreased coronary artery inflammation in IGT and T2DM subjects, independent of glucose-lowering effects (192)
Sulphonylureas	
Glibenclamide (glyburide)	- Reduced cytokine production from neutrophils in T2DM patients (171) - In T2DM patients, inflammatory cytokines after treatment with glyburide was significantly lower than in insulin-treated group (172)
Glinides	
Repaglinide	- Reduced levels of PAI-1, hsCRP, and 8-OHdG in Japanese T2DM patients (176)
Mitiglinide	- Reduced levels of oxidative stress and inflammatory markers IL-6, IL-18 and TNF-α in T2DM patients (193)
DPP-4 inhibitors	
Sitagliptin	- Reduction of CRP, TNF-α, TLR-4, TLR-2, IKKβ, CCR-2 in T2DM patients (194, 195) - Significantly improved inflammatory state and endothelial function in patients with coronary artery disease and T2DM, independent of its hypoglycemic activity (196)
Linagliptin	- Reduction of prostaglandin E2, hsCRP, and IL-6 levels in T2DM patients undergoing hemodialysis (197)
Alpha-glucosidase inhibitors	
Miglitol	- Improved flow-mediated dilation and reduced CRP in patients with T2DM and coronary heart disease (182)
SGLT2 antagonists	
Empagliflozin	- Reduction in cardiovascular death and all-cause mortality in patients with established CVD and T2DM (153)
Dapagliflozin	- Improved flow-mediated dilation and decreased oxidative stress as measured by levels of urine 8-OHdG and plasma 8-iso PGF2α in T2DM subjects (154, 155)

Selected studies in human models involving various antihyperglycemic drugs.

and all-cause mortality in diabetic patients with cardiovascular diseases (153) and reduce levels of oxidative stress (154-156). Selected studies examining the anti-inflammatory effects of antihyperglycemic drugs are listed in *Table 1*.

Glucagon-like peptide-1 receptor agonists

Drugs of this class, which include liraglutide and exenatide, reduce glycemic levels through the activation of GLP-1 receptors in pancreatic acinar cells, which stimulates secretion of insulin and suppression of glucagon secretion. Demonstrated to have anti-inflammatory effects in various cell types such as HUVECs, glomerular endothelial cells, monocytes and macrophages, GLP-1 receptor agonists are thought to exert their anti-inflammatory action through inhibition of the IκB kinase beta/NF-κB and JNK pathways (150). These properties are also exhibited on the level of vascular pathology dependent on inflammation and vascular smooth muscle cell proliferation, as GLP-1 vascular delivery prevents neointimal formation in diabetic mice (157). Novel mechanisms of this process are being unraveled, including a recent study on the role of semaphorin-3, which may act as a novel therapeutic target (158).

Endogenous GLP-1 is biologically active for only a short period, on the order of 1 – 2 minutes, since it is rapidly cleaved and inactivated by DPP-4 (159). Its cleavage product, GLP-1(9-36)^{amide}, acts independently of the GLP-1 receptor and is less insulinotropic than GLP-1. In human arterial endothelial cells, GLP-1(9-36)^{amide} has been shown to prevent increased superoxide production by mitochondria following exposure to high glucose or high levels of FFAs (160, 161). Additionally, evidence suggests that GLP-1(9-36)^{amide} exerts atheroprotective effects in advanced inflammatory conditions, acting through NF-κB-dependent pathways (162). Thus, GLP-1(9-36)^{amide} should prove to be an interesting target for future studies related to oxidative stress.

Metformin

This is the first line oral treatment for patients with T2DM. The glucose-reducing effect of metformin is thought to be mediated through activation of AMPK, ultimately leading to suppression of hepatic gluconeogenesis. Along with its antihyperglycemic effects and its ability to improve insulin resistance (163), metformin is thought to possess anti-inflammatory activity (150), and might inhibit NF-κB activation in macrophages, leading to a reduction in the proinflammatory cytokines IL-1B, IL-6, and TNF-α (164). Other potential pathways of anti-inflammatory activity include inhibition of NF-κB through the phosphatidylinositol-3-kinase (PI3K)-Akt pathway in human vascular smooth muscle cells and inhibition of AGEs (150). Although several studies have demonstrated that metformin reduces inflammatory biomarkers, others have shown this not to be the case (165-168). Thus, the potential anti-inflammatory effects of metformin should be further studied to clarify these discrepancies.

Sulfonylureas

Sulfonylureas are one of the groups of drugs recommended when metformin is contraindicated, however they have the potential to induce hypoglycemia and weight gain (169). A commonly used drug from this class is glibenclamide, which works by inhibiting ATP-sensitive potassium channels in pancreatic beta cells, leading to insulin release. Recent studies have suggested that glibenclamide possesses anti-inflammatory activity (170-173). Possible mechanisms include inhibition of the IL-4/IL-13 signaling pathways and reduced NLRP3 inflammasome activation, leading to decreased production of TNF-α, IL-1B, and ROS (174, 175).

Glinides

These drugs act via a similar mechanism as sulfonylureas, in that they bind to ATP-dependent potassium channels on pancreatic beta cells, leading to insulin secretion. However, they have a weaker binding affinity and dissociate faster from the sulfonylurea receptor 1 (SUR1) binding site. In a study involving Japanese T2DM patients, repaglinide reduced markers of inflammation and oxidative stress (176).

Thiazolidinediones (PPAR-γ agonists)

This class of antidiabetic drugs works by activating PPAR-γ, which stimulates increased storage of FFAs in adipocytes. Because of this, cells utilize more carbohydrates for their energy requirements, thus decreasing circulating glucose levels (177). PPAR-γ is mainly expressed in adipose tissue and has been demonstrated to reduce markers of inflammation in a variety of tissues (178, 179). The ability of thiazolidinediones to activate glucocorticoid nuclear translocation appears to be independent of PPAR-γ and partially explains their anti-inflammatory activity (178). In addition, rosiglitazone decreased inflammatory activity, likely *via* downregulation of NF-κB-mediated pathways, which led to atherosclerotic plaque stabilization in T2DM patients (180).

Alpha-glucosidase inhibitors

This class of medication, including acarbose and miglitol, reversibly inhibits alpha-glucosidases, specifically in the brush border of the small intestine. As a consequence, there is reduced hydrolysis of complex carbohydrates into monosaccharides and delayed absorption of glucose from the gut (181). There are several conflicting reports on the effects of alpha-glucosidase inhibitors on inflammatory markers, however, it appears that they modestly reduce CRP levels in T2DM patients (182).

Sodium-glucose cotransporter 2 inhibitors (gliflozins)

This novel class of drugs inhibit sodium-glucose cotransporter 2 (SGLT2), the major cotransporter responsible for reabsorption of glucose in the kidney. This causes more glucose to be eliminated in the urine, reducing plasma glucose levels in T2DM patients (153, 183). The EMPA-REG OUTCOME trial showed that empagliflozin significantly reduced cardiovascular death and all-cause mortality in patients with established CVD and T2DM (153). Although some recent evidence suggests that SGLT2 inhibitors may provide beneficial effects on the renal and cardiovascular system, it is unclear whether they can slow atherosclerotic progression in T2DM patients (184, 185). Because of this, the EMBLEM trial, a prospective multicenter clinical trial in Japan, was designed to assess the effect of empagliflozin on endothelial function and is currently ongoing (as of publication of this review) (185). In clinical trials involving T2DM patients, dapagliflozin significantly improved flow-mediated dilation and lowered levels of urine 8-OHdG and plasma 8-iso PGF2α, indicating a decreased level of oxidative stress (154, 155).

Conclusions

Early diagnosis and treatment of hyperglycemia in prediabetic patients are needed, as impaired pancreatic beta-cell function along with insulin resistance is already present years

before the development of T2DM. Because of the high risk of morbidity and mortality due to CVDs associated with diabetes, it is imperative that treatment plans are initiated early enough to prevent such complications from developing. Oxidative stress and inflammation during prediabetes could be useful targets for clinicians in the future to prevent progression of prediabetes to T2DM. Targeted immunotherapies and antihyperglycemic medication could one day play an important role in improving the inflammatory state in patients with prediabetes and diabetes.

Abbreviations: 8-epi-PGF2a, 8-epi-prostaglandin F2α; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; AGE, advanced glycation end products; AMPK, 5'adenosine monophosphate-activated protein kinase; ATF3, activating transcription factor 3; BPIFB4, bactericidal/permeability-increasing fold-containing-family-B-member-4; CRP, C-reactive protein; CVD, cardiovascular disease; CYBA, cytochrome B-245 alpha chain; DAG, diacylglycerol; DPP, dipeptidyl peptidase; EDHF, endothelium-derived hyperpolarizing factor; eNOS, endothelial nitric oxide synthase; EN-RAGE, extracellular newly identified receptor for advanced glycation end-products binding protein; FFA, free fatty acids; FMD, flow-mediated dilation; GDF, growth/differentiation factor; GLP, glucagon-like peptide; GSH, glutathione; GSSG, glutathione disulfide; HDL, high density lipoprotein; HFD, high fat diet; HMGB, high-mobility group box; HMVEC, human microvascular endothelial cells; hs-CRP, high sensitivity CRP; HUAEC, human umbilical artery endothelial cells; HUVEC, human umbilical vein endothelial cells; ICAM, intercellular adhesion molecule; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IKKβ, inhibitory-κB kinase; IL, interleukin; IRS, insulin receptor substrate; JNK, c-Jun N-terminal kinase; LDL, low density lipoprotein; LOX-1, lectin-like oxidized LDL receptor-1; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP, monocyte chemoattractant protein; MetS, metabolic syndrome; miRNA, microRNA; MR, mineralocorticoid receptor; NADPH, nicotinamide adenine dinucleotide phosphate; NFG, normal fasting glucose; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP-3, nucleotide-binding domain, leucine-rich-containing family pyrin domain-containing-3; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; PBMC, peripheral blood mononuclear cells; PI3K-Akt, phosphatidylinositol-3-kinase; PKC, protein kinase C; PON, paraoxonase; PPAR, peroxisome proliferator-activated receptors; RA, rheumatoid arthritis; RAGE, receptor for AGE; ROS, reactive oxygen species; SAT, subcutaneous adipose tissue; SLE, systemic lupus erythematosus; SOD, superoxide dismutase; SUR1, sulfonylyrea receptor 1; T2DM, type 2 diabetes mellitus; TGF, transforming growth factor; TLR, Toll-like receptor; TNF, tumor necrosis factor; UCP1, uncoupling protein 1; VAT, visceral adipose tissue; VCAM, vascular cell adhesion protein; VSMC, vascular smooth muscle cells; WAT, white adipose tissue.

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