The Metabolic Syndrome and Endothelial Dysfunction: Common Highway to Type 2 Diabetes and CVD?

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Due to global lifestyle changes, obesity (the main driver of type 2 diabetes [T2D] and cardiovascular disease [CVD]) is reaching pandemic proportions. The metabolic syndrome, which is regarded as a prediabetic state, is characterized by a concurrence of interrelated cardiovascular risk factors, including abdominal obesity, insulin resistance, hypertension, dyslipidemia, and glucose intolerance. Endothelial dysfunction (ED) is common in the metabolic syndrome and is associated with increased risk for T2D and CVD. This review focuses on the mechanisms linking ED to the metabolic syndrome, T2D, and CVD, and the possible therapies that may improve ED and reduce T2D and CVD risk.

Introduction

Overweight and obesity are reaching pandemic proportions and the projected increase for the coming decades will occur predominantly in the densely populated developing parts of the world [1]. Concomitantly, using modest assumptions about future growth, the number of people with type 2 diabetes (T2D) will increase from 175 million in 2000 to 353 million in 2030, with the biggest increases expected in India (25 to 59 million) and China (14 to 25 million) [1,2]. The excess global mortality attributable to diabetes in the year 2000 was estimated to be 2.9 million deaths, equivalent to 5.2% of all deaths, which is similar in magnitude to numbers reported for HIV and AIDS in the same year [2]. Development of diabetes is related to that of atherosclerotic cardiovascular disease (CVD) [3].

The etiologic interrelationship of T2D with CVD suggests that both arise from a common antecedent, which was described earlier as the metabolic syndrome of insulin resistance [4]. Although the notion of the existence of "a diminished ability of the tissue to utilization of glucose" as the essential lesion in diabetes already existed in the 30s of the past century [5••], the insulin resistance syndrome or syndrome X was first described by Reaven in 1988 [4]. It was defined as insulin resistance, compensatory hyperinsulinemia, varying degrees of glucose tolerance, hypertriglyceridemia, and low plasma high-density lipoprotein (HDL) cholesterol concentration [4]. Ever since, assuming as a premise that insulin resistance increases CVD risk, many experimental data have led to the expansion and modification of this concept [5••]. Thus, in addition to insulin resistance, glucose intolerance, dyslipidemia, central adiposity, hypertension, a procoagulant state, inflammation, hyperuricemia, hyperhomocysteinemia, and endothelial dysfunction (ED) have been added [5••].

Today, for reasons of unification and clinical use, the most used working definition of the metabolic syndrome is that proposed by the National Cholesterol Education Program Adult Treatment Panel III, characterized by central obesity, hypertriglyceridemia, low plasma HDL cholesterol, hypertension, subclinical inflammation, and insulin resistance (Table 1) [6].

The syndrome increases the risk for both T2D and CVD, but the specific unifying mechanisms that underlie these seemingly diverse pathophysiologic effects remain unclear. ED is a mechanism that may unify the etiology of T2D and CVD: vascular ED may contribute to insulin resistance and the development of diabetes, whereas ED is a consistent antecedent of CVD [7–9].

Endothelial Dysfunction

The vascular endothelium, consisting of approximately 10^{14} cells in the human body and when spread as a monolayer, able to cover an area of numerous tennis courts, regulates many different processes, including vascular tone and the interaction of the vessel wall with circulating substances and blood cells [9]. Under physiologic conditions, vascular

Table 1. Evolving concept of the metabolic syndrome: etiology versus classification

Etiologic definitions of the metabolic syndrome		Clinical criteria of the metabolic syndrome
Reaven [4]	**Reaven [5••]**	**NCEP ATP III [6]**
Insulin resistance, compensatory hyperinsulinemia, varying degrees of glucose tolerance	IFG, IGT, or type 2 diabetes Decreased HDLC, HDLC dysfunction, small, dense LDLC particles	Any 3 of the following 5 features: IFG, IGT, or type 2 diabetes Decreased HDLC: male: < 1.03 mmol/L, female: < 1.3 mmol/L
Decreased HDLC Increased triglycerides	Increased triglycerides, postprandial hypertriglyceridemia	Triglycerides ≥ 1.7 mmol/L Waist: male: ≥ 102 cm, female: ≥ 88 cm
	Nonalcoholic fatty liver disease	Blood pressure ≥ 130/85 mm Hg
	Essential hypertension	
	Hypercoagulable state	
	Low-grade inflammatory state	
	Endothelial dysfunction	
	Hyperuricemia	
	Autonomic nervous dysfunction	
	Hyperhomocysteinemia	
	Polycystic ovary syndrome	
	Sleep apnea	

HDLC—high-density lipoprotein cholesterol; IFG—impaired fasting glucose; IGT—impaired glucose tolerance; LDLC—low-density lipoprotein cholesterol; NCEP ATP III—National Cholesterol Education Program Adult Treatment Panel III.

homeostasis is maintained by a balance of endothelium-derived relaxing and contracting factors (Table 2). The production and secretion of nitric oxide (NO) as well as other vasodilators by the endothelium is critical for maintaining this balance away from atherogenesis. NO promotes vasodilation by stimulating cyclic guanosine 3',5'-monophosphate in vascular smooth muscle cells (VSMCs), but NO also inhibits growth and migration of VSMCs, platelet aggregation and thrombogenesis, monocyte adhesion, and inflammation and oxidation, all processes that may damage the vessel wall [9]. Vasoconstrictors such as endothelin and angiotensin II (ATII) promote atherogenesis (Table 2).

Endothelial function can be tested only indirectly, using two main methods. The first involves an "endothelial stress test" or endothelial vasomotor test by evaluating vascular relaxation by stimulus-induced NO release from the endothelium. This can be performed in the coronary circulation by invasive angiography or in the peripheral circulation, most commonly in the forearm, either by intra-arterial infusion of endothelium-dependent vasodilators or by noninvasive measurements of endothelium-dependent flow-mediated dilation using high-resolution ultrasound [9]. The benefits and limitations of these methods have recently been reviewed [10]. The other indirect test to gain information on the status of the endothelium is the measurement of circulating markers derived from the endothelium.

ED is invariably used as one term to designate a condition wherein vasoconstrictors outweigh the effects of vasodilators. However, it is clear that ED should not be regarded as a single defect, but rather should be viewed as a syndrome that exhibits systemic manifestations associated with considerable morbidity and mortality. The concept of ED should be extended beyond conduit vessels into the vascular wall itself and the adventitial vasa vasorum [11], as well as to the bone marrow and the endothelial progenitor cells [12]. Finally, defects in the endothelial glycocalyx, an intraluminal layer consisting of glycosaminoglycans and hyaluronan, which constitutes an important component to the vascular permeability barrier by preventing transvascular leakage of macromolecules, may be added to the concept of ED [13••].

Oxidative stress and inflammation: common mechanisms underlying insulin resistance and ED leading to T2D and CVD?

In target tissues, insulin stimulates two major pathways: the phosphatidylinositol 3-kinase (PI3K) pathways and the mitogen-activated protein kinase (MAPK) pathway. After binding to its receptors, PI3K activation is critical for insulin-mediated glucose uptake into insulin-dependent target tissues, such as skeletal muscle, liver, heart, and adipose tissue [14]. This pathways also regulates insulin-dependent endothelial NO production, by virtue of which insulin may be regarded as a vasodilator [15,16]. Thus, a systemic defect in the PI3K pathway, which is the key defect in insulin resistance, leads to a combined defect in insulin-mediated glucose transport and in insulin-stimulated endothelial vasodilation. Insulin-mediated

vasodilation in isolated rat arteries of the rat cremaster muscle was inhibited in the presence of tumor necrosis factor (TNF)-α, a proinflammatory cytokine among others derived from adipose tissue [17]. The addition of TNF-α resulted in insulin-mediated vasoconstriction and this effect was found dependent of TNF-α–mediated activation of c-Jun N-terminal kinase (JNK), an enzyme involved in insulin sensitivity [18].

Activation of the MAPK pathway renders insulin into a growth factor. In the vasculature, this pathway mediates not only cellular growth but also the ability of endothelial cells, VSMCs, and monocytes to migrate. Also, it mediates the expression of plasminogen activator inhibitor-1 (PAI-1), a prothrombotic and profibrotic factor, by various stimuli. By mediating cell growth, migration, and prothrombotic and proinflammatory processes, the MAPK pathway may be proatherogenic. In contrast to the PI3K pathway, in insulin-resistant states and T2D, activation of the MAPK pathway following insulin administration is not attenuated, thus allowing for some of the detrimental effects of chronic hyperinsulinemia on the vasculature [16,19]. Furthermore, insulin also possesses anti-inflammatory action [20]. Insulin at physiologically relevant concentrations suppressed intranuclear expression of nuclear factor-κB, intracellular adhesion molecule-1, and monocyte chemoattractant protein-1 in human aortic endothelial cells in vitro, and these effects were associated with the ability of insulin to induce NO release and enhance the expression of constitutive NO synthase [20].

Most of the risk factors that are related to atherosclerosis and CVD morbidity and mortality, including traditional and nontraditional risk factors, were also found to be associated with ED [9,16]. Many of these risk factors, including hyperlipidemia, hypertension, diabetes, insulin resistance, and smoking, are associated with overproduction of reactive oxygen species (ROS) or increased oxidative stress [21,22,23••,24–33]. Additional abnormalities, typically present in individuals with the metabolic syndrome, that have been acknowledged to contribute to ED and CVD risk, are an increased flux of nonesterified fatty acids (NEFAs), due to unsuppressed lipolysis, and circulating proinflammatory cytokines derived from abundant visceral fat accumulation [24–26]. Also, nonalcoholic fatty liver disease, which is now considered as another feature of the metabolic syndrome, was found to be associated with ED [27]. Another intriguing possibility that perivascular fat, which is associated with central fat but does not necessarily produce low-grade acute-phase response, may play a role in influencing ED and insulin action through "vasocrine" signaling, was recently proposed [28].

Because metabolic syndrome, T2D, and CVD seem interrelated, it was put forward that ED due to substantial decrease of NO bioactivity caused by oxidative stress may be the key unifying defect (Fig. 1).

Table 2. Physiologic functions of the vascular endothelium

Maintenance of vascular tone
Nitric oxide
Prostaglandins (prostacyclin, thromboxane A_2)
Endothelial hyperpolarizing factor
Endothelin-1
Angiotensin II
C-type natriuretic peptide
Balancing blood fluidity and thrombosis
Nitric oxide
Glycocalyx
Tissue plasminogen activator
Heparins
Thrombomodulin
Prostaglandins
Plasminogen activator inhibitor-1
Tissue factor
von Willebrand's factor
Control of the vascular inflammatory process
Monocyte chemotactic factor-1
Adhesion molecule expression
Interleukins 1, 6, and 18
Tumor necrosis factor
Regulating angiogenesis
Vascular endothelial growth factor
(Circulating) endothelial progenitor cells

However, maintenance of normal blood glucose levels involves not only the insulin responsiveness of skeletal muscle and liver but also the ability of the pancreatic β cell to adapt its glucose-stimulated insulin secretion to the body's changing demand for insulin. Defects in the former are responsible for insulin resistance, and defects in the latter are responsible for progression to hyperglycemia. Emerging evidence supports the potentially unifying hypothesis that both these prominent features of T2D are caused by mitochondrial dysfunction and oxidative stress [29,30]. Mitochondrial dysfunction and oxidative stress were also demonstrated recently to occur within endothelial cells as a consequence insulin resistance [31]. In aortic endothelial cells, increased NEFA oxidation caused increased superoxide production by the mitochondrial electron transport chain. NEFA-induced superoxide production activated a variety of proinflammatory signals and inactivated two important antiatherogenic enzymes, prostacyclin synthase and endothelial nitric oxide synthase (eNOS) [31]. Several studies have shown the associations of ED with incident T2D [32,33]; however, the role of ED in

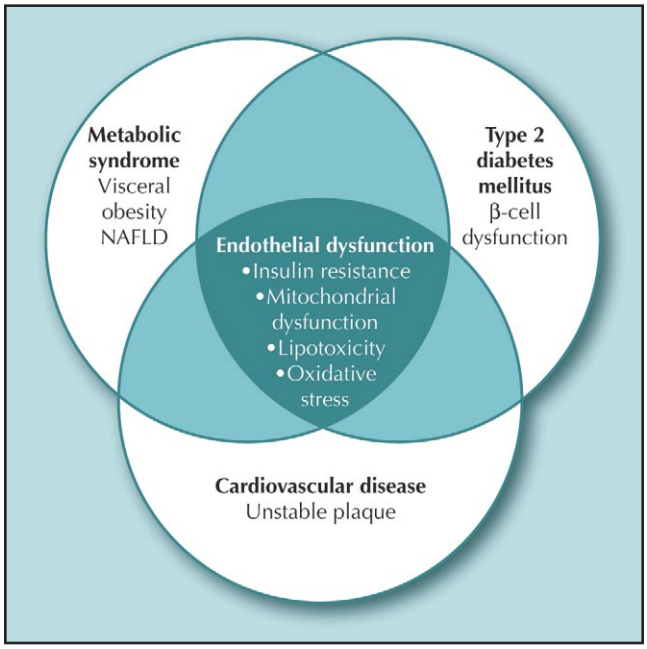

Figure 1. The interrelationship between endothelial dysfunction, metabolic syndrome, type 2 diabetes, and cardiovascular disease. NAFLD—nonalcoholic fatty liver disease.

the pathogenesis of T2D, independently of other diabetes risk factors including obesity, insulin resistance, and inflammation, was demonstrated only recently in the Framingham Offspring Study [34].

In individuals with the metabolic syndrome, insulin resistance and central obesity lead to increased lipolysis with high flux of NEFA from adipose tissue and elevated production of triglyceride-rich lipoprotein (TRL) particles. In the postprandial state, insulin fails to suppress hepatic triglyceride output and gluconeogenesis, leading to a prolonged and exaggerated postprandial dysmetabolic state, which becomes complicated by hyperglycemia once β-cell failure occurs [35]. Four main molecular mechanisms underlying the hyperglycemia-induced vascular damage have recently been reviewed [36••], all of which are the result of intracellular hyperglycemia. These include increased polyol pathway influx, increased advanced glycation end-product formation, activation of protein kinase C isoforms, and increased hexosamine pathway flux. These seemingly different mechanisms are the result of a single process (ie, overproduction of superoxide by the mitochondrial electron-transport chain). This hyperglycemia-induced oxidative stress ultimately results in modification of intracellular proteins resulting in an altered function, DNA damage, activation of the transcription factor nuclear factor-κB, causing abnormal changes in gene expression, decreased production of NO, and increased expression of cytokines, growth factors, and procoagulant and proinflammatory molecules [36••]. Conversely, due to the augmented (postprandial) lipid load in the presence of impaired glucose utilization, nonadipose tissues, including the liver and skeletal muscle, but also the myocardium and endothelial cells, accumulate triglycerides [37]. This excessive deposition of triglycerides enlarges the intracellular pool of fatty acyl-coenzyme A, thereby providing substrate for nonoxidative metabolic pathways leading to oxidative stress, cellular dysfunction, and apoptosis (lipotoxicity). Furthermore, the large amount of TRLs and their prolonged residence time in the circulation leads to increased exchange of the core lipid cholesteryl ester for triglycerides between TRLs and low-density lipoprotein (LDL) and HDL particles mediated by cholesteryl ester transfer protein. Thus, LDL and HDL particles become enriched with triglycerides, rendering them more susceptible to hydrolysis by hepatic lipase, leading to the generation of smaller, denser LDL particles—which are more prone to oxidation—and lower HDL concentrations [35]. High triglycerides, small, dense LDL, and low HDL are considered the atherogenic lipid profile. Collectively, the postprandial metabolic abnormalities encountered in people with the metabolic syndrome and T2D lead to oxidative stress, inflammation, and ED [38,39]. Therefore, already decades ago, the postprandial state was associated with an increased risk of CVD [35,40]. Provided the fact that in our 24-hour Western economy, food is available at all times, subjects with the metabolic syndrome and patients with T2D may be in a proatherogenic postprandial state around the clock.

Central adiposity, adipokines, and inflammation

In addition to its role as a storage depot for lipids, the adipose cell produces and secretes a number of hormones, collectively termed adipo(cyto)kines [41,42]. Visceral adipose tissue, which is abundant in individuals with the metabolic syndrome, seems to be metabolically more active because it is more resistant to suppression of lipolysis by insulin and contributes to a larger extent to adipokine production than adipocytes from gluteal-femoral subcutaneous regions [24]. More recently, it was demonstrated that adipose tissue–resident macrophages may also significantly contribute to systemic inflammation [43].

Adipocytes produce and secrete adipokines for the regulation of their own growth, differentiation, metabolism, and vascularization [41]. However, these substances also affect metabolism, inflammation, and growth of many other tissues. Today, the number of adipokines is substantial, and new substances are still being discovered [44]. The most studied include leptin, TNF-α, PAI-1, interleukin-6 (IL-6), and adiponectin.

Leptin, the product of the *ob* gene, is involved in energy homeostasis, but also has direct vascular effects that seem to be both beneficial (vasodilation) and potentially deleterious (prothrombotic, proinflammatory) [42]. Multiple interactions exist between insulin and leptin: insulin was shown to enhance leptin-dependent vasodilation by increasing endothelial NO release and by potentiating Akt and eNOS phosphorylation. Conversely, leptin increases insulin sensitivity in rats and may improve

vascular responses to insulin [42]. The cross-talk between insulin and leptin, in particular at the vascular endothelium, requires more research. TNF-α interferes with insulin signaling, at the level of tyrosine phosphorylation of both the insulin receptor and insulin receptor substrate-1, thereby inducing insulin resistance. TNF-α also aggravates the insulin resistance associated–metabolic derangements and was found to increase PAI-1 expression [41]. Concentrations of PAI-1 are elevated beginning at the stage of impaired glucose tolerance and continuing through the development of the metabolic syndrome and T2D. PAI-1, which is in part derived from endothelial cells, is associated with increased risk of diabetes [34], and of CVD morbidity and mortality [45].

We and others have observed an association between visceral fat accumulation and vascular dysfunction in patients with T2D [46]. However, this association was fully explained by proinflammatory markers, in part derived from adipocytes, in particular IL-6. Circulating IL-6 levels are an independent predictor of myocardial infarction in healthy men [47].

Several adipocytokines, in particular IL-6, stimulate the acute-phase response, including hepatic C-reactive protein (CRP) production. CRP is the best studied marker of inflammation, which was found to be associated with increased CVD morbidity and mortality in various populations [48].

Adiponectin is an endogenous insulin-sensitizing factor, and it circulates at lower levels in obese, insulin-resistant humans and in humans with T2D. Adiponectin normalizes lipid abnormalities, through AMP-activated protein kinase (AMPK) signaling, and causes weight loss in rodent models of obesity and insulin resistance by generating a negative energy balance. Several lines of evidence also indicate an anti-inflammatory and antiatherogenic role for adiponectin [44].

Do therapies have effects beyond improvement of the individual CVD risk factors?

If ED contributes to the pathogenesis of T2D and CVD, then reversing ED will reduce the risk. Although this assumption has not been tested directly, numerous studies have evaluated (short-term) lifestyle and pharmacologic interventions to improve ED, and many of these same interventions are known to target features of the metabolic syndrome and/or classical risk factors and reduce CVD risk. However, at present, it is not clear whether these therapies have effects beyond improving the individual CVD risk factors, including overweight, hyperlipidemia, hypertension, and hyperglycemia.

Lifestyle intervention

Lifestyle interventions (ie, exercise and diet) resulting in weight loss were shown to reduce circulating inflammatory markers and/or improve ED in high-risk populations [49]. Moreover, lifestyle interventions prevented or delayed the onset of T2D in a high-risk population [50].

Antioxidants and vitamins

The use of antioxidants and vitamins, although promising in short-term studies assessing surrogate end points [51], has so far not yielded the expected benefit in long-term prospective trials [52,53]. Of note are the two recently published trials reporting no beneficial effect of plasma homocysteine lowering by combined intervention of folic acid and vitamins B_{12} and B_6 on CVD morbidity in a total of 8000 high-risk individuals [54,55]. These findings may have come as a surprise to many because hyperhomocysteinemia was shown to be associated with ED and CVD events and mortality in multiple studies.

Blood glucose–lowering agents

Although not consistently, blood glucose–lowering drugs, including sulfonylurea, metformin, and insulin, were shown to ameliorate ED [51]. This effect may be mainly due to their glucose-lowering actions and the concomitant alleviation of oxidative stress [36••]. Based on the results from the UKPDS (United Kingdom Prospective Diabetes Study), metformin is currently the drug of choice for overweight patients with T2D [56]. Only recently, the mechanism of action of this compound was discovered (ie, stimulation of the AMPK signaling cascade), thereby increasing NEFA oxidation, inhibiting hepatic gluconeogenesis, and stimulating skeletal muscle glucose uptake [57]. In vitro, activation of AMPK by metformin reduced the hyperglycemia-induced production of ROS, by induction of manganese superoxide dismutase and by promoting mitochondrial biogenesis [58]. Metformin also stimulated eNOS and NO bioactivity in endothelial cells [59]. In spite of these favorable effects in vitro, the effects of metformin on inflammation and (markers of) ED in humans are controversial [60,61]. Finally, metformin given to subjects with impaired glucose tolerance reduced the 3-year incidence of T2D by 31% (95% CI, 17% to 43%, $P < 0.001$) [62].

Thiazolidinediones

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that act as transcription factors controlling the expression of target genes that in turn regulate many cellular functions [63]. The isoform PPAR-γ is a key regulator of adipocyte differentiation but is also involved in the regulation of lipoprotein metabolism, coordinating the uptake of oxidized LDL and the processing of cholesterol in macrophages. In patients with T2D, PPAR-γ agonists (or thiazolidinediones [TZDs]), such as pioglitazone and rosiglitazone, ameliorate insulin resistance, among others by decreasing lipotoxicity and stimulating growth of small insulin-sensitive adipocytes, lower blood glucose,

and improve diabetic dyslipidemia [63]. TZDs also inhibit cytokine production and the expression of adhesion molecules and metalloproteinases and improve ED [63–65]. In the recently published PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study, a randomized controlled trial in 5238 patients with T2D with macrovascular disease, pioglitazone, added to their regular medications, after a mean follow-up of 34.5 months significantly reduced the main secondary end point (ie, the composite of all-cause mortality, nonfatal myocardial infarction, and stroke) by 16% (95% CI, 2% to 28%, $P = 0.027$) [66••]. Interestingly, TZD treatment was also shown to decrease the incidence of T2D in high-risk Hispanic women with previous gestational diabetes, among others by preserving pancreatic β-cell function [67]. Results of large prospective studies, respectively investigating the effect of TZDs on incident T2D (DREAM [Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication]) and progression of β-cell dysfunction (ADOPT [A Diabetes Outcome Progression Trial]) in high-risk populations, will become available in the course of 2006 [68,69].

Statins

The most important action of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) is their ability to lower low-density lipoprotein cholesterol (LDLC). Statins have been proved highly effective in reducing CVD event risk, both in primary and secondary prevention trials. Although their beneficial effect is by some authors attributed solely to their lipid-lowering potency [70], others claim that the magnitude of risk reduction associated with statins is greater than that predicted on the basis of LDLC lowering alone [48]. Thus, independently of their LDLC-lowering action, statins may exert numerous pleiotropic effects (ie, improve ED, increase vascular NO bioavailability, reduce oxidant stress, and improve endothelial progenitor cell function), all of which have largely been proposed on the basis of experimental studies.

A recent study suggested the existence of pleiotropic effects of statins in humans, by showing improvement of ED by simvastatin alone compared with the cholesterol absorption inhibitor ezetimibe, given at a dose that lowered LDLC to a similar extent in patients with chronic heart failure [71]. Simvastatin treatment improved ED independently of LDLC lowering, at least in part by reducing oxidant stress. However, the ability of statins to improve ED could not be demonstrated by others [72]. It was proposed that the additional ability of statins to significantly lower CRP on top of their LDLC-reducing action may have substantial benefit over statins with mere lipid-lowering potency [48].

Inhibitors of the renin-angiotensin system

Large-scale outcome trials have demonstrated that angiotensin-converting enzyme (ACE) inhibitors reduce CVD events in patients with coronary artery disease and diabetes, independent of blood pressure reduction [73]. ACE inhibitors and angiotensin receptor blockers also improve ED, by attenuating the ATII-mediated stimulation of ROS production, by inhibiting the breakdown of bradykinin, a substance that stimulated NO production, and by reducing endothelial inflammation [74]. Secondary analyses of various prospective trials have shown that inhibition of the renin-angiotensin system (RAS) prevents the incidence of diabetes [75]. The various mechanisms underlying this association include improvement of insulin sensitivity by RAS inhibition, stimulation of adipocyte differentiation by interfering with local RAS and thereby improving adipocyte triglyceride storage capacity, and finally RAS inhibition may have favorable effects on lipid and glucose handling [75,76]. Recently, beneficial effects of RAS inhibition were found on pancreatic islet morphology and function by their ability to counteract ATII-induced islet vasoconstriction and fibrosis [77].

Conclusions

ED resulting from oxidative stress, mitochondrial dysfunction, and inflammation seems common to the etiology of metabolic syndrome, T2D, and CVD. Current available therapies target individual risk factors and components of the metabolic syndrome, thereby reducing the risk of T2D and CVD. Several of these therapies also seem to ameliorate ED by mechanisms unrelated to the improvement of the separate CVD risk factors. Lifestyle interventions, metformin, statins, TZDs, and drugs interfering with the RAS all seem to additionally reduce vascular oxidative stress and inflammation and are currently the mainstay of the therapeutic ammunition to combat obesity-related diseases.

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