

Endothelial Dysfunction in Diabetes: Pathogenesis, Significance, and Treatment

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Manuscript submitted March 20, 2013; resubmitted April 15, 2013; accepted June 13, 2013

■ Abstract

Type 2 diabetes (T2D) markedly increases the risk of cardiovascular disease. Endothelial dysfunction (ED), an early indicator of diabetic vascular disease, is common in T2D and independently predicts cardiovascular risk. Although the precise pathogenic mechanisms for ED in T2D remain unclear, at inception they probably involve uncoupling of both endothelial nitric oxide synthase activity and mitochondrial oxidative phosphorylation, as well as the activation of vascular nicotinamide adenine dinucleotide phosphate oxidase. The major contributing factors include dyslipoproteinemia, oxidative stress, and inflammation. Therapeutic interventions are designed to target these pathophysiological factors that underlie ED. Therapeutic interventions, including life-

style changes, antiglycemic agents and lipid-regulating therapies, aim to correct hyperglycemia and atherogenic dyslipidemia and to improve ED. However, high residual cardiovascular risk is seen in both research and clinical practice settings. Well-designed studies of endothelial function in appropriately selected volunteers afford a good opportunity to test new therapeutic interventions, paving the way for clinical trials and utilization in the care of the diabetic patient. However, based on the results from a recent clinical trial, niacin should not be added to a statin in individuals with low high-density lipoprotein cholesterol and very well controlled low-density lipoprotein cholesterol.

Keywords: type 2 diabetes • dyslipoproteinemia • lipoprotein • vascular disease

1. Introduction

ype 2 diabetes (T2D) markedly increases the risk of all forms of cardiovascular disease with prospective studies demonstrating a significantly increased incidence of morbidity and mortality [1-3]. Endothelial dysfunction (ED), an early indicator of diabetic vascular disease, is common in T2D and independently predicts cardiovascular risk [4]. The pathogenesis of ED in diabetes is complex. The major contributing pathophysiological factors include dyslipoproteinemia [5], oxidative stress and inflammation [6-8]. Although important, dysglycemia, hypertension and insulin resistance chiefly operate through oxidative stress and pro-inflammatory pathways [6, 9, 10]. Both invasive and non-invasive methods for

assessing endothelial function have generated a wealth of knowledge concerning the pathogenesis and therapeutic regulation of ED in T2D [4, 11, 12]. Treatment strategies necessarily target the pathophysiological factors that underlie ED and range from lifestyle interventions to nutritional supplements and specific pharmacological therapies [12]. We review these areas with a focus on dyslipoproteinemia.

2. Endothelial function

2.1 Normal endothelial function

The endothelium maintains vascular homeostasis through multiple and complex physiological functions, including the release of several vasoac-

tive factors that regulate vascular tone, blood fluidity and coagulation, while limiting smooth muscle cell proliferation and inflammation [11, 13, 14]. Arguably, the most critical endothelium-derived molecule is nitric oxide (NO), although maintenance of endothelial function also involves endothelin-1 (ET-1), angiotensin II, protacyclin, and endothelial-derived hyperpolarizing factor (EDHF) [4].

In response to shear stress or activation of muscarinic receptors, a G-protein signal transduction pathway is activated, stimulating endothelial NO synthase (eNOS) [4]. In a tightly coupled process, this forms NO and citrulline from L-arginine, molecular oxygen and reduced nicotinamide adenine dinucleotide phosphate (NADPH) (**Figure 1A**) [4, 13]. NO released by this process functions via a cyclic guanosine 3', 5'-monophosphate (cGMP) mediated pathway, resulting in vasodilation and inhibition of chemotaxis and platelet aggregation [13, 15].

2.2 Measurement of endothelial function

Endothelial function may be measured by invasive and non-invasive methods (**Table 1**). Indirect measures in the peripheral circulation assess the vasodilatory responses of conduit and resistance arteries to stimuli that increase NO release [4, 11, 15, 16]. In the brachial artery, shear stress is generated by hyperemia following an induced period of local ischemia, and flow-mediated dilatation (FMD), an endothelium-dependent function, is measured using high-resolution ultrasonography or even magnetic resonance imaging (MRI) [16-18]. Venous occlusion strain-gauge plethysmography can be utilized to measure blood flow changes in the forearm microcirculation following hyperemia, or intra-arterial infusion of muscarinic receptor agonists such as acetylcholine [19, 20]. An emerging non-invasive clinical tool to assess peripheral vasodilator response is digital peripheral arterial tonometry (PAT) (Endo-PAT, Itamar Medical) [21, 22].

Endothelial function in coronary arteries may be assessed, in response to intra-arterial infusion of acetylcholine or shear stress stimuli, using quantitative angiography to measure vessel diameter changes [23]. Non-invasive methods such as Doppler echocardiography, positron emission tomography and MRI may be utilized to assess coronary microvascular vasodilatory capacity, but these methods are costly [15].

Circulating biomarkers may be measured as indirect indices of endothelial cell damage, activa-

Abbreviations:

ACCORD - Action to Control Cardiovascular Risk in Diabetes
ADMA - asymmetric dimethylarginine
AGE - advanced glycation end-product
Ach - acetylcholine
AIM-HIGH - Atherothrombosis Intervention in Metabolic Syndrome with Low HDL-cholesterol/High Triglyceride and Impact on Global Health Outcomes
ApoB - apolipoprotein B
BH₄ - tetrahydrobiopterin
CAD - coronary artery disease
CETP - cholesteryl ester transfer protein
cGMP - cyclic guanosine 3',5'-monophosphate
CHD - coronary heart disease
CoQ₁₀ - coenzyme Q₁₀
CRP - C-reactive protein
CVD - cardiovascular disease
DHA - docosahexaenoic acid
DPP4 - dipeptidyl peptidase 4
ecSOD - extracellular superoxide dismutase
ED - endothelial dysfunction
EDHF - endothelial-derived hyperpolarizing factor
EMP - endothelial-derived microparticle
ET-1 - endothelin-1
eNOS - endothelial nitric oxide synthase
EPA - eicosapentaenoic acid
ER niacin - extended release niacin
FABF - forearm blood flow
FIELD - Fenofibrate Intervention and Event Lowering in Diabetes study
FMD - flow-mediated dilatation
glcNAc - N-acetylglucosamine
GLP - glucagon-like peptide
GLUT4 - glucose transporter
HDL - high-density lipoprotein
HPS2-THRIVE - Heart Protection Study 2 and the Treatment of HDL to Reduce the Incidence of Vascular Events
hs-CRP - high-sensitivity C-reactive protein
ICAM-1 - intercellular adhesion molecule 1
IRS-1 - insulin receptor substrate 1
LDL - low-density lipoprotein
L-NMMA - L-nitro-mono-methyl arginine
Lp(a) - lipoprotein (a)
LpB - apolipoprotein B
LpC - apolipoprotein C
Lp-PLA₂ - lipoprotein-associated phospholipase A₂
MDA - malondialdehyde
MRI - magnetic resonance imaging
NADPH - nicotinamide adenine dinucleotide phosphate
NO - nitric oxide
NOS - nitric oxide synthase
O₂⁻ - superoxide
PAT - peripheral arterial tonometry
PCSK9 - proprotein convertase subtilisin/kexin type 9
PKC - protein kinase C
PPARα - Peroxisome proliferator-activated receptor alpha
ROS - reactive oxygen species
SGLT2 - type 2 sodium-glucose cotransporter inhibitors
SNP - single nucleotide polymorphism
T2D - type 2 diabetes
VCAM-I - vascular cellular adhesion molecule 1
vWF - von Willebrand factor

Table 1. Methods of assessing endothelial function

Coronary circulation	Peripheral circulation	Circulating biomarkers
QCA	Ultrasonography: FMD	ADMA, NO
PET	Plethysmography: FAFB	ET-1
MRI	Endo-PAT	hs-CRP
Echocardiography		vWF
		PAI-1
	Vasodilatory stimuli	ICAM, VCAM
	Acetylcholine	Selectins
	Shear stress	EP cells
	Nitrates	EMPs
	NOS inhibitors	SNPs

Legend: QCA - quantitative coronary angiography, PET - positron emission tomography, MRI - magnetic resonance imaging, FMD - flow-mediated dilation, FAFB - forearm blood flow, Endo-PAT - non-invasive peripheral artery tonometry, NOS - nitric oxide synthase, ADMA - asymmetric dimethylarginine, NO - nitric oxide, ET-1 - endothelin-1, hs-CRP - high-sensitivity C-reactive protein, vWF - von Willebrand factor, PAI-1 - plasminogen activator inhibitor 1, ICAM - intercellular adhesion molecule, VCAM - vascular cell adhesion molecule, EP cells - endothelial progenitor cell, EMP - endothelial-derived microparticle, SNP - single nucleotide polymorphisms.

tion and inflammation (**Table 1**) [24-30]. Impaired mobilization or depletion of endothelial progenitor cells derived from bone marrow are involved in the pathogenesis of ED, and their circulating levels can also be used as a marker of ED [31-34]. A relationship between decreased levels of progenitor cells and increased levels of cell-derived microparticles has been demonstrated in T2D [33]. Endothelial-derived microparticles (EMPs) are small membrane-shed vesicles derived from endothelial cell surfaces under conditions of cellular activation or injury/apoptosis [33, 35]. Thus, circulating EMPs may be potential markers of ED and there may be potential value in utilizing the EMP/progenitor cell ratio [33, 35]. Reduced vascular extracellular superoxide dismutase (ecSOD) activity, the major antioxidant enzyme system of the vessel wall, was closely associated with NO-mediated vasodilation in patients with coronary artery disease, suggesting that reduced ecSOD activity contributes to the reduced bioavailability of NO and ED [36]. However, its utility as a surrogate marker of ED in the clinical setting is limited as its measurement requires the intravenous injection of heparin. Relationships between ED and single nucleotide polymorphisms (SNPs) in the eNOS-3 gene have been demonstrated in conduit arteries but not resistance arteries [37].

3. Endothelial dysfunction

3.1 Pathogenesis of endothelial dysfunction

Endothelial dysfunction reflects an imbalance in the endothelial-derived vasoactive substances

that promote vasodilation, importantly NO bioavailability, and vasoconstriction. Decreased bioavailability of NO involves either decreased NO synthesis or increased NO degradation, or both, due to enhanced endothelial production of reactive oxygen species (ROS) [15, 38]. With increased oxidative stress, tetrahydrobiopterin (BH₄), a cofactor that tightly regulates NO production, is oxidized resulting in the uncoupling of eNOS and reduced NO production [39-41]. The absence of BH₄ perpetuates a cycle of vascular oxidative stress through the transfer of electrons to molecular oxygen, forming oxidant species such as superoxide and peroxynitrite, which further consumes NO and increases oxidative stress (**Figure 1B**) [15, 39, 40]. Elevated levels of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of eNOS through competition with L-arginine, may further reduce NO production [15].

Endothelial dysfunction may also involve altered levels of vasoconstrictors, such as endothelin-1 and angiotensin II, and other vasodilators such as endothelial-derived hyperpolarizing factor (EDHF) and prostacyclin [15, 38].

3.2 Predictive value of endothelial dysfunction

Several studies in a diverse range of subjects have shown that ED measured by the aforementioned techniques in different vascular beds is predictive of clinical events [42-54]. The principal studies are shown in **Table 2**. Two recent meta-analyses concluded that FMD is predictive of cardiovascular events and may provide independent prognostic information that is at least equal to the

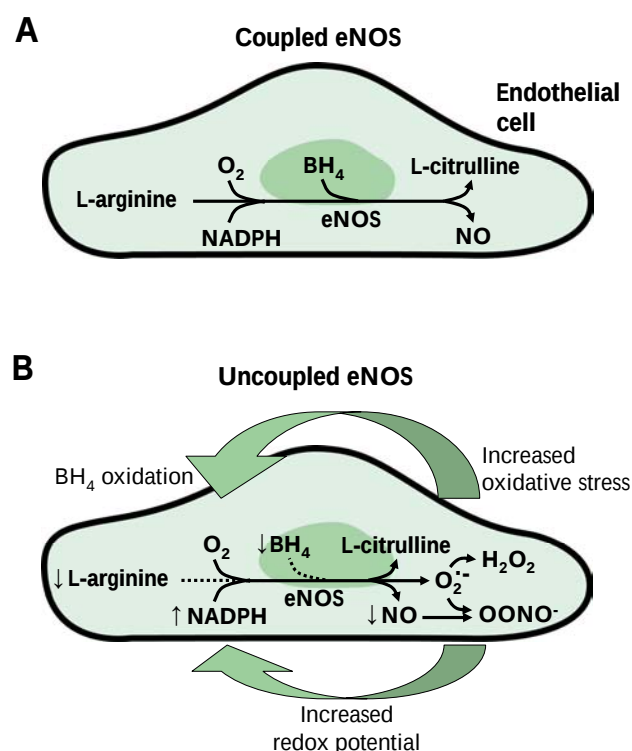


Figure 1. A: Nitric oxide (NO) is produced from L-arginine and molecular oxygen (O₂) by endothelial nitric oxide synthase (eNOS) in a tightly 'coupled' process involving tetrahydrobiopterin (BH₄) and nicotinamide adenine dinucleotide phosphate (NADPH). **B:** In diabetes, increased redox imbalance (due to increased NADH/NADPH) and decreased availability of BH₄ (due to oxidation) leads to 'uncoupling' of NO production. This results in transfer of electrons to O₂ to form superoxide (O₂⁻). Superoxide in turn reacts with and consumes NO, forming the oxidant species peroxynitrite (OONO⁻). Hence, oxidative stress and endothelial dysfunction are further increased [39, 41]. *Abbreviations:* NADH - reduced nicotinamide adenine dinucleotide, H₂O₂ - hydrogen peroxide.

information gained from conventional cardiovascular risk factors; however, future research is required to confirm FMD's efficacy in the assessment of cardiovascular risk [55, 56].

Studies in type 2 diabetic patients have demonstrated endothelial dysfunction to be predictive of cardiovascular outcomes. Coronary endothelial dysfunction, as assessed by the cold-pressor test, was predictive of long-term cardiovascular events in type 2 diabetic patients with normal coronary arteriography [52]. In type 2 diabetic patients without known coronary artery disease (CAD), normal endothelial function, assessed by myocardial perfusion imaging, had a 93% negative predic-

tive value in excluding CAD [43]. In patients with newly diagnosed CAD and impaired brachial artery FMD (43% with diabetes), persistently impaired FMD following 6 months of optimized lifestyle changes and pharmacotherapy was an independent predictor of future cardiovascular events [47]. Impaired endothelial-dependent vasodilation in forearm resistance arteries, but not the brachial artery, was associated with a 5 year risk of major cardiovascular events in a community based study of 1016 older adults (72% with diabetes) [54].

3.3 Endothelial dysfunction in type 2 diabetes

Endothelial dysfunction has been demonstrated in T2D, in both the peripheral and coronary circulation [57-63]. Elevated levels of circulating biomarkers, indirect indices of endothelial cell damage, activation and inflammation, are found in type 2 diabetic patients. These include the soluble adhesion molecules E-selectin, vascular cellular adhesion molecule (VCAM) 1 and intercellular adhesion molecule (ICAM) 1, indices of vascular inflammation [4, 29, 30, 64]. Similarly, increased levels von Willebrand factor (vWF), a measure of endothelial cell damage and activation are reported [4, 30, 64]. Microalbuminuria, an independent predictor of ED, may indicate widespread vascular dysfunction in diabetes [4, 65].

There is a growing body of evidence elucidating the pathogenetic mechanisms underlying the development of ED in T2D. At inception, they probably involve uncoupling of both eNOS activity (**Figure 1B**) and mitochondrial oxidative phosphorylation (**Figure 2**), as well as the activation of vascular NADPH oxidase [12, 39, 66]. These three mechanisms essentially result in the uncoupling of eNOS production, increased generation of superoxide (O₂⁻) radicals and overproduction of peroxynitrite [39]. The main factors that combine to cause these biochemical disturbances are dyslipoproteinemia [5], oxidative stress [5, 66], and inflammation [6-8, 66]. Other clinical factors also play a role, contributing either individually or synergistically to ED in T2D. These include hypertension [67], visceral obesity [68], insulin resistance [6, 69, 70], postprandial hyperlipidemia [71-73], fasting and postprandial hyperglycemia [74-76], and elevated levels of ADMA [38, 77].

Evidence suggests a reciprocal relationship between insulin resistance and ED [6]. The impact of insulin resistance in T2D operates at an insulin signaling level in the vascular endothelium, adipose tissue and skeletal muscle [6]. Impaired insulin receptor substrate-1 (IRS-1) and phos-

Table 2. Principal studies evaluating endothelial dysfunction as a predictor of cardiovascular events

Study (year)	n	Patient Population	Arterial Bed	Technique(s)	Endpoints	Mean Follow-up (months)	Endothelial Dysfunction as an Independent Predictor	Estimated RR of CV events
Chan <i>et al.</i> (2003) [42]	152	Patients with CAD	Brachial Carotid	FMD IMT	CAD, CVD	34	Yes	4.7*
Papaioannou <i>et al.</i> (2006) [43]	75	T2D patients without CAD	Brachial	FMD, NMD MPI	CAD	60	No association	na
Muesan <i>et al.</i> (2008) [44]	172	Patients with uncomplicated hypertension (28% diabetes)	Brachial	FMD	CV events	109	Yes	2.5 [§]
Rossi <i>et al.</i> (2008) [45]	2,264	Post-menopausal women without CV Disease and not using HRT	Brachial	FMD	CV events	45	Yes	1.0, 1.33, 4.42, higher to lower FMD tertile
Yeboah <i>et al.</i> (2009) [46]	3026	Population based cohort of without known CVD	Brachial	FMD	CV event	60	Yes	na
Kitta <i>et al.</i> (2009) [47]	251	Patients with CAD and optimized therapy (40% with diabetes)	Brachial	FMD	CVD	36	Yes	1.8 [§]
Al Suwaidi <i>et al.</i> (2000) [48]	157	Patients with mild CAD	Coronary	Acetylcholine, adenosine, and nitroglycerin responses	CAD	28	na	na
Schachinger <i>et al.</i> (2000) [49]	147	Patients with chest pain or SVD	Coronary	Acetylcholine response, CPT, FMD, NMD	CAD, CVD, PVD	80	Yes	na
Halcox <i>et al.</i> (2002) [50]	308	Patients with and without CAD	Coronary	Acetylcholine response	CAD, CVD	46	Yes	1.4
Nitenberg <i>et al.</i> (2004) [51]	72	T2D patients without CAD	Coronary	CPT	CAD, CVD	45	Yes	2.8
Nitenberg <i>et al.</i> (2005) [52]	124	Patients with HT or T2D and normal coronary arteries	Coronary	CPT	CAD, CVD	112	Yes	4.9
Perticone <i>et al.</i> (2001) [53]	225	Patients with untreated hypertension	Forearm	FABF	CAD, CVD, PVD	32	Yes	2.1
Lind <i>et al.</i> (2011) [54]	1016	Community based study of older adults (>70 years), 72% with diabetes	Forearm, brachial, radial, carotid	Acetylcholine and sodium nitroprusside, FMD, PWA, IMT	CV disease (MI or stroke)	60	Yes, forearm EDV only	na

Legend: * Approximation for patients with high IMT plaque burden. [§] Estimated for patients with impaired FMD compared with those with preserved FMD. [§] Estimated for patients with persistently impaired FMD compared with those with improved FMD. *Abbreviations:* RR – relative risk, CV – cardiovascular, T2D – type 2 diabetes mellitus, CAD – coronary artery disease, EDV – endothelial-dependent vasodilation, FMD – flow-mediated dilation of the brachial artery, NMD – nitroglycerin-mediated dilation, MPI – myocardial perfusion imaging, na – not assessed, HT – hypertension, CPT – cold-pressor test, CVD – cerebrovascular disease, IMT – intima medial thickness, FABF – forearm blood flow, PVD – peripheral vascular disease, PWA – pulse wave-based method, SVD – single vessel disease. References [42-54].

phatidylinositol (PI) 3-kinase in the insulin signaling pathway cause a decreased production of both eNOS and NO resulting in ED on the one hand, and a decreased glucose transporter (GLUT4) translocation in skeletal muscle and adipose tissue leading to peripheral insulin resistance on the other hand [6]. Elevated free fatty acid levels are observed in insulin resistant states, including

T2D, obesity and dyslipoproteinemia [5]. This increased fatty acid availability uncouples mitochondrial function in endothelial cells, generating ROS by increasing advanced glycation end-products (AGES), protein kinase C (PKC) and N-acetylglucosamine (glcNAC), impairing eNOS activity and inducing ED [6]. Inflammation, lipotoxicity and glucotoxicity are all increased in diabetes

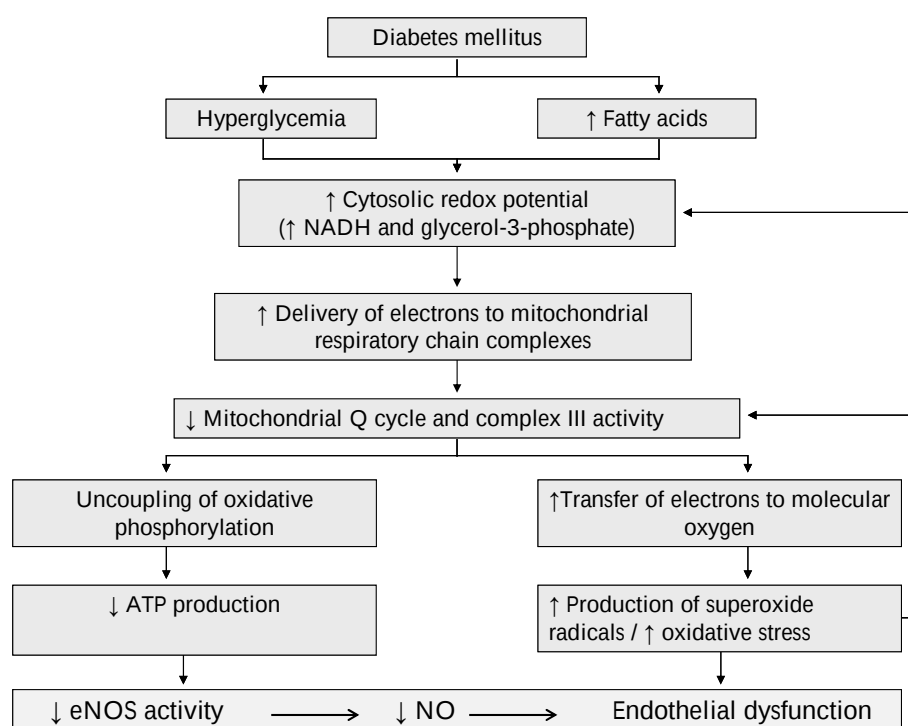


Figure 2. Mechanism whereby hyperglycemia and elevated fatty acids induce uncoupling of mitochondrial oxidative phosphorylation and increased oxidative stress in diabetes. Abbreviations: ATP - adenosine triphosphate, NADH - reduced nicotinamide adenine dinucleotide [12].

and collectively contribute to insulin resistance and ED [6, 66]. **Figure 3** suggests that the pathogenesis of ED in T2D has oxidative stress as the central pathway for a wide spectrum of risk factors [4].

4. Therapeutic regulation of endothelial dysfunction in type 2 diabetes

Strategies for treating ED in T2D will necessarily target the pathophysiological factors that underlie vasculopathy, such as dyslipidemia, increased oxidative stress, inflammation, visceral obesity, insulin resistance, hyperglycemia, and hypertension [8, 78]. Treatment options range from lifestyle interventions to nutritional supplements and specific pharmacological therapies. We review treatment options, focusing on dyslipoproteinemia.

4.1 Lifestyle interventions

Lifestyle programs aimed at achieving weight loss improve many of the metabolic abnormalities in T2D that contribute to ED, such as hyperglyce-

mia, insulin resistance, visceral obesity, hypertension and dyslipidemia. Weight loss in subjects with the metabolic syndrome improves lipoprotein dysregulation that is associated with obesity [79-82]. Following 4 years of follow-up in the Look AHEAD (Action for Health in Diabetes) study, intensive lifestyle intervention was associated with greater weight loss and improvements in physical fitness [83]. Improvements in glycemic control, blood pressure, triglycerides and HDL-cholesterol were also demonstrated [83]. In type 2 diabetic patients, a reduction in insulin resistance and fat mass following prolonged aerobic exercise resulted in improvements in lipoprotein metabolism [84].

Dietary restriction, weight loss, and increased physical activity have been shown to improve conduit and resistance artery ED in overweight and obese non-diabetic subjects with and without CAD [85-88]. In obese, but otherwise healthy subjects, brachial artery FMD improved with a 6-week low-fat diet but was blunted with a low-carbohydrate diet despite similar degrees of weight loss, suggesting that greater vascular benefit is conferred by a low-fat diet [85]. In obese non-diabetic subjects, improvement in brachial artery FMD following a 6-week low-fat weight loss diet, but not a high-fat weight loss diet, was associated with decreased visceral fat mass and an improved adipokine profile, specifically increased adiponectin and decreased leptin and resistin [89]. Improvement in resistance artery endothelial function following weight loss was mediated by increased NO bioavailability and associated with reductions in abdominal visceral fat [86]. In patients with CAD, greater weight reduction following exercise training was associated with a greater increase in FMD, suggesting a dose response effect [87]. Physical activity also improved plasma markers of

endothelial function and oxidative stress in adolescents with the metabolic syndrome [90].

In type 2 diabetic patients, weight loss and increased physical activity have been shown to improve endothelial function [91-93]. An uncontrolled study in obese subjects with insulin resistance syndrome (33% with T2D) demonstrated an improvement in brachial artery FMD and reductions in markers of endothelial activation and coagulation following 6 months of caloric restriction and regular supervised exercise and a 7% mean reduction in body weight [91]. Insulin sensitivity and glycemic control improved and significant increases in HDL-cholesterol levels were demonstrated. In multiple regression analysis, percentage improvement in FMD was strongly associated with percentage weight reduction [91]. A randomized, crossover study of combined aerobic and resistance exercise training for eight weeks demonstrated increased brachial artery FMD and acetylcholine (ACh)-stimulated forearm blood flow (FABF) in T2D subjects [92]. Although glycemic control also improved, reductions in HbA_{1c} and fasting glucose were not correlated with changes in endothelial function [92]. A recent study compared the effects of aerobic exercise, resistance training or usual activities (control group) on endothelial function in women with T2D [93]. Brachial artery FMD was significantly increased by aerobic exercise but not with resistance training or usual activities. Within group weight loss was significantly improved in both the aerobic exercise and resistance training groups but was not correlated with per cent change in FMD. Compared with resistance training and usual activities, aerobic exercise significantly improved HbA_{1c}, but it was not correlated to per cent change in FMD [93]. In a pooled data analysis, the benefits of short-term exercise in sub-

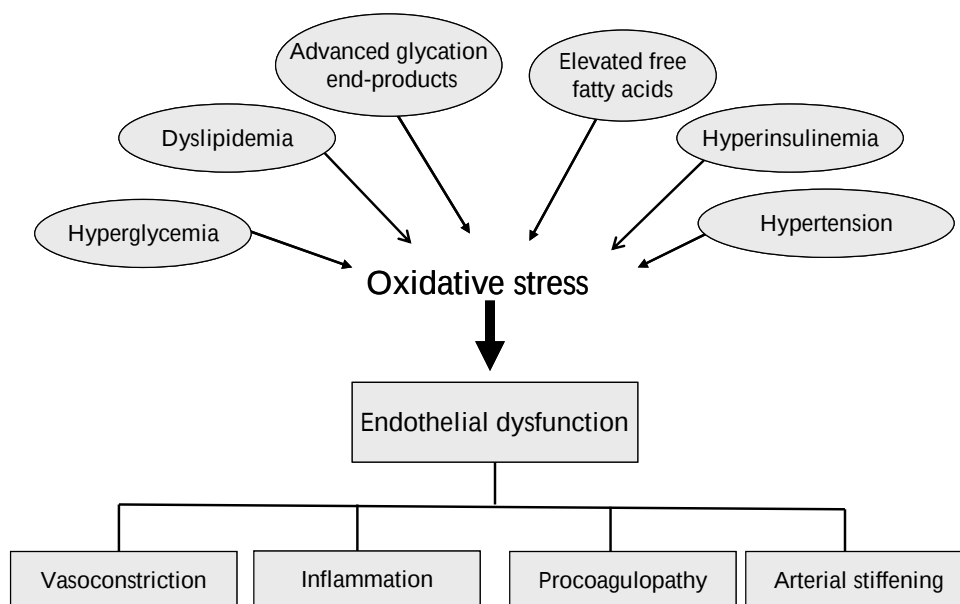


Figure 3. Pathogenesis and consequences of endothelial dysfunction in type 2 diabetes mellitus. Oxidative stress contributes to endothelial dysfunction by activating protein kinase C, polyol, hexosamine, and NF kappa B pathways, as well as increasing asymmetric dimethylarginine and advanced glycation end-products [4].

jects with vascular dysfunction were not necessarily dependent on improvement in associated cardiovascular risk factors [94], suggesting that repeated exercise may also act directly on the vasculature via a shear stress-related mechanism, possibly involving endothelial nitric oxide synthase (eNOS) upregulation or reduced NO degradation by free radicals [95].

The association between cigarette smoking and cardiovascular events is supported by a large body of epidemiological evidence [96]. Cigarette smoking is also associated with the premature development of vascular complications in patients with T2D [97]. Cigarette smoke increases inflammation, thrombosis and oxidation of low-density lipoprotein (LDL)-cholesterol, with experimental and clinical evidence supporting the notion that increased oxidative stress results in vascular dysfunction [96]. Both active and passive cigarette smoking are associated with a dose-related impairment of endothelial function [98-100]. Evidence also suggests that endothelial function may improve with smoking cessation [98]. A large prospective randomized, placebo-controlled study investigated the effects of five smoking cessation pharmacotherapies on brachial artery FMD in 1504 current smokers [101]. Smoking intensity

Table 3. Randomized controlled trials investigating the therapeutic regulation of endothelial function in patients with type 2 diabetes mellitus: lipid-regulating monotherapies

Study (year)	n	Treatment	Treatment duration (months)	Endpoint	Treatment effect
Statins					
Ceriello <i>et al.</i> (2005) [109]	20	Atorvastatin /irbesartan/placebo	1 wk	FMD	+
Tsunekawa <i>et al.</i> (2001) [110]	27	Cerivastatin/placebo	3 days	FMD	+
Tan <i>et al.</i> (2002) [111]	80	Atorvastatin/placebo	6	FMD	+
Ceriello <i>et al.</i> (2002) [112]	30	Simvastatin/placebo	3-6 d + 3	FMD	+
Adel <i>et al.</i> (2010) [113]	60	Atorvastatin/placebo	4 wk	FMD	+
Dalla <i>et al.</i> (2003) [114]	25	Atorvastatin/placebo	12	VCAM-I and E-selectin	+
Rawlings <i>et al.</i> (2009) [115]	30	Rosuvastatin/atorvastatin	1	FMD	+
Brunetti <i>et al.</i> (2007) [116]	22	Atorvastatin/rosuvastatin	3	FMD	+
Economides <i>et al.</i> (2004) [117]	40	Atorvastatin/placebo	3	FMD	ns
Beishuizen <i>et al.</i> (2005) [118]	250	Cerivastatin replaced by simvastatin	24	FMD	ns
van Venrooij <i>et al.</i> (2002) [119]	133	Atorvastatin 10mg/atorvastatin 80mg	7.5	FMD	ns
Balletshofer <i>et al.</i> (2005) [120]	103	Cerivastatin/placebo	3	FMD	ns
Tantikosoom <i>et al.</i> (2005) [121]	42	Atorvastatin/placebo	7.5	FMD	ns
Tousoulis <i>et al.</i> (2007) [122]	41	Atorvastatin/vitamin C/no treatment	1	FABF response to post-ischemic hyperemia	+ *
Tran <i>et al.</i> (2005) [123]	11	Cerivastatin/placebo	2	FABF response to ACh and L-NMMA	ns
Fibrates					
Playford <i>et al.</i> (2002) [138]	40	Fenofibrate/placebo	3	FMD	+
Playford <i>et al.</i> (2003) [139]	20	Fenofibrate/placebo	3	FABF response to ACh, BK, SNP	ns
Evans <i>et al.</i> (2000) [141]	20	Ciprofibrate/placebo	3	FMD	+
Avogaro <i>et al.</i> (2001) [142]	10	Gemfibrozil/placebo	3	FMD	+
Fegan <i>et al.</i> (2005) [143]	10	Fenofibrate/placebo	3	Blood flow responses to iontophoresis of ACh	ns
Hiukka <i>et al.</i> (2008) [144]	170	Fenofibrate/placebo	60	IMT, AIX, biomarkers of endothelial activation	ns
Niacin					
No studies identified in T2D patients					
Omega-3 fatty acids					
McVeigh <i>et al.</i> (1993) [153]	23	Fish oil/placebo	1.5	FABF response to ACh	+
Woodman <i>et al.</i> (2003) [154]	51	EPA/DHA/placebo	1.5	FMD	ns
Wong <i>et al.</i> (2010) [155]	97	Fish oil/olive oil	3	FMD	ns
Stirban <i>et al.</i> (2010) [156]	34	EPA/DHA or placebo	6 wk	FMD, microvascular function (RH of the hand)	+
West <i>et al.</i> (2005) [157]	18	MUFA ± omega-3 FA	3 test meals over 3wk	FMD	+

Legend: + indicates improved endothelial function. ++ indicates combination therapy improved FMD more than monotherapy alone. ± = with or without. * + in atorvastatin only. *Abbreviations:* FMD – flow-mediated dilation of the brachial artery, ACh – acetylcholine, FABF – forearm blood flow, ns – no significant effect, SNP – sodium nitroprusside, BK – bradykinin, L-NMMA – L-nitro-mono-methyl arginine, EPA – eicosapentenoic acid, DHA – docosahexenoic acid, T2D – type 2 diabetes mellitus, AIX – augmentation index, IMT – intima-media thickness, MUFA – monounsaturated fatty acids, omega-3 FA – omega-3 fatty acids, CoQ₁₀ – coenzyme Q₁₀, VCAM-I – vascular cell adhesion molecules 1, RH – reactive hyperemia. References [109-123, 138-144, 153-157].

Table 4. Randomized controlled trials investigating the therapeutic regulation of endothelial function in patients with type 2 diabetes mellitus: lipid-regulating combination therapies

Study (year)	n	Treatment	Treatment duration (months)	Endpoint	Treatment effect
Hamilton <i>et al.</i> (2010) [209]	15	Statin + fenofibrate / statin + placebo	3	FMD + forearm microcirculatory function	+
Fegan <i>et al.</i> (2005) [143]	11	Cerivastatin + fenofibrate	3	Skin blood flow response to iontophoresis and skin maximum hyperemia	ns
Lee <i>et al.</i> (2009) [220]	71**	Statin + niacin / statin / placebo	12	Carotid MRI, aortic distensibility, MRI brachial artery FMD	****
Hamilton <i>et al.</i> (2010) [221]	15	Statin + niacin / statin alone	5	Small artery vasodilation and compliance	+
Koh <i>et al.</i> (2005) [226]	50	Simvastatin + ramipril	2	FMD	++
Ceriello <i>et al.</i> (2005) [109]	20	Atorvastatin + irbesartan	1 wk	FMD	++
Hamilton <i>et al.</i> (2009) [235]	23	Statin + CoQ ₁₀ / statin + placebo	3	FMD	+
Playford <i>et al.</i> (2003) [139]	20	Fenofibrate + CoQ ₁₀	3	FABF response to ACh, BK, SNP	+
Luescher <i>et al.</i> (2011) [241]	476†	Dalcetrapib + statin / placebo + statin	9	FMD	ns

Legend: ** only 65% of the patients T2D. *** + in Carotid MRI only. † only 45% of patients T2D. + indicates improved endothelial function. ++ indicates combination therapy improved FMD more than monotherapy alone. *Abbreviations:* FMD – flow-mediated dilation of the brachial artery, ACh – acetylcholine, FABF – forearm blood flow, ns – no significant effect, SNP – sodium nitroprusside, BK – bradykinin, L-NMMA – L-nitro-mono-methyl arginine, EPA – eicosapentenoic acid, DHA – docosahexenoic acid, T2D – type 2 diabetes mellitus, AIX – augmentation index, IMT – intima-media thickness, MRI – magnetic resonance imaging, MUFA – monounsaturated fatty acids, omega-3 FA – omega-3 fatty acids, CoQ₁₀ – coenzyme Q₁₀, VCAM-I – vascular cell adhesion molecules 1, RH – reactive hyperemia. References [109, 139, 143, 209, 220, 221, 226, 235, 241].

was demonstrated to be independently associated with ED [101]. Despite weight gain, endothelial function significantly improved in subjects who quit and remained abstinent at one year, but remained impaired in those who continued to smoke [101]. Studies assessing the effects of smoking cessation in patients with T2D are warranted.

4.2 Lipid-regulating therapy

Lipid regulating therapies target to a greater or lesser degree various aspects of dyslipoproteinemia. Evidence suggests that these therapies correct ED through both lipid lowering and direct effects on the vasculature. The results of selected intervention studies utilizing lipid regulating therapy are reviewed below and summarized in **Tables 3 and 4**.

Hydroxymethylglutaryl (HMG)-CoA reductase inhibitors (statins). Large clinical studies in a wide range of population subgroups, including subjects with diabetes, have shown statins to reduce cardiovascular mortality [102]. Apart from their main effect in lowering LDL-cholesterol, statins may also have direct anti-inflammatory and antioxidant effects on the vasculature [78]. Although statins improve endothelial function in non-diabetic

subjects with dyslipidemia [103, 104], evidence in T2D subjects is inconsistent and contradictory. In uncontrolled studies in T2D subjects, neither serotonin-stimulated FABF nor brachial artery FMD improved with statin therapy [105-108]. In one trial, improvement in endothelial function was demonstrated in a subgroup that attained optimal LDL-lowering [108], but another showed no benefit despite intensive lipid-lowering [106].

A number of randomized, placebo-controlled studies have shown beneficial effects of statins on ED in T2D subjects [109-112]. Improvement in endothelial function occurred within days of treatment, prior to any plasma lipid changes and was correlated with a reduction in oxidative stress, inflammation and endothelial cell activation [109-112]. In normocholesterolemic T2D patients without evidence of CAD, 4 weeks of low dose atorvastatin significantly improved brachial artery FMD compared with placebo [113]. In a placebo-controlled study in T2D patients, atorvastatin was associated with a reduction in vascular cell adhesion molecules (VCAM-I) and E-selectin, suggesting an improvement in endothelial function that was independent of the lipid-regulating effects of atorvastatin [114]. Inhibition of Rho/Rho kinase pathway activity by rosuvastatin or atorvastatin

was associated with the improvement in brachial artery FMD in the absence of a reduction in plasma LDL-cholesterol level [115]. In hypertriglyceridemic T2D patients, atorvastatin or rosuvastatin significantly improved FMD and plasma levels of C-reactive protein (CRP), but associations were not reported [116].

However, a number of randomized, double-blind, placebo-controlled studies have shown no effect of statin therapy on ED in subjects with T2D [117, 118], despite improvements in dyslipidemia [119-121]. Forearm vascular reactivity in T2D subjects was improved with atorvastatin [122], but not with cerivastatin [123]. However, ACh-stimulated FABF increased with co-infusion of L-nitro-monomethyl arginine (L-NMMA), an inhibitor of NOS, suggesting an effect of cerivastatin on non-NO vasoactive mediators, such as EDHF [123].

Emerging LDL-cholesterol lowering therapies.

Emerging LDL-cholesterol lowering therapies merit investigation of their vascular effects in T2D patients. Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9), an important regulator of the LDL receptor, exerts beneficial effects on LDL and very low-density lipoprotein (VLDL) metabolism, but its role in humans is still to be elucidated [124]. Colesevelam, a more tolerable and potent bile acid sequestrant, is effective at lowering LDL-cholesterol either as monotherapy or in combination with a statin in patients with and without T2D [125, 126]. It has also been demonstrated to improve glycaemic control in T2D patients receiving concurrent antiglycemic therapy [125, 127, 128]. Colesevelam could potentially improve endothelial function by reducing lipotoxicity and glucotoxicity, but no studies reporting its effects on endothelial function are available. Mipomersen, a second-generation antisense oligonucleotide inhibitor of apolipoprotein B (apoB) synthesis, reduces serum apoB, total cholesterol, LDL-cholesterol and lipoprotein(a) (Lp(a)) in a dose dependent manner [129-133]. Studies have demonstrated mipomersen to be an effective lipid-lowering therapy in patients with familial hypercholesterolemia on maximally tolerated statin therapy and in healthy volunteers with mild to moderate hypercholesterolemia [130-133]. Studies in T2D patients are required.

Fibric acid derivatives. A meta-analysis has concluded that fibrates are effective in reducing CVD, primarily by prevention of coronary events [134]. Another recent meta-analysis also suggested that fibrates may be particularly useful in improving dyslipidemia and preventing CVD in people with

mild to moderate chronic kidney disease, including diabetics [135]. In addition to their lipid-regulating effects, fibrates may also reduce vascular inflammation and endothelial cell activation. In randomized controlled studies, fibrates appear to have a fairly consistent beneficial effect on endothelial function in subjects with and without T2D. Fenofibrate has been shown to improve brachial artery FMD in statin-naïve non-diabetic subjects with combined hyperlipidemia [136] or primary hypertriglyceridemia [137], and in T2D patients with dyslipidemia [138]. However, fenofibrate alone did not significantly improve forearm microcirculatory function in T2D patients [139]. Moreover, fenofibrate and coenzyme Q₁₀ (CoQ₁₀) independently and interactively lowered 24-h ambulatory blood pressure consistent with their beneficial effects on endothelial function in resistance arterioles [140]. Ciprofibrate and gemfibrozil have been shown to improve brachial artery FMD in type 2 diabetic subjects in fasting and postprandial states [141, 142]. However, fenofibrate therapy in T2D patients did not improve microvascular function when assessed by skin blood flow response to the iontophoresis of acetylcholine [143]. The effects of fenofibrate on markers of oxidative stress and insulin sensitivity are also inconsistent [138, 139, 141].

Although short-term fenofibrate therapy may improve endothelial function [136-138], a sub-study of the longer-term FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study was not associated with beneficial changes in carotid intima-media thickness, augmentation index, or biomarkers of endothelial function in T2D patients [144]. However, the FIELD study subjects were mostly low risk (as evidenced by the low CVD event rate), and were not selected for having ED at baseline.

Fenofibrate also has beneficial microvascular effects. In FIELD, monotherapy with fenofibrate, significantly reduced the need for laser therapy for diabetic retinopathy compared with placebo [145], and may delay albuminuria progression and impairment of renal function [146]. Recent reports from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid study show that both the addition of fenofibrate to simvastatin and intensive glycemic therapy reduced progression of diabetic retinopathy [147, 148]. In T2D patients with hypertriglyceridemia, adding a fibrate to statin therapy and weight reduction may be safe and effective treatment options for macrovascular and microvascular risk reduction compared with intensification of hypoglycemic and/or statin therapy.

Nicotinic acid (niacin). Niacin may improve endothelial function through direct effects on the vasculature [149]. Compared with placebo, 12 weeks of no-flush niacin (1.5g/day) significantly improved brachial artery FMD in healthy men with low high-density lipoprotein (HDL)-cholesterol (<1.04mmol/l) [150]. However, no change was demonstrated in plasma lipids or chylomicron remnants suggesting a direct vascular effect by niacin [150]. In a placebo-controlled study in metabolic syndrome patients with low HDL-cholesterol (<1.00mmol/l), 52 weeks of extended release niacin (1000mg/day) significantly improved FMD, regressed CIMT, and decreased high sensitivity C-reactive protein (hsCRP). Plasma LDL-cholesterol, HDL-cholesterol and triglycerides were also significantly improved [151]. No studies have reported on patients with T2D. Collectively, these studies demonstrate that niacin is effective in improving endothelial function in subjects with low HDL-cholesterol. Further, improvements in both lipids and inflammatory markers suggest that both lipid-mediated and direct mechanisms are involved in the beneficial vascular effects of niacin.

Omega-3 fatty acids. Omega-3 fatty acids derived from marine fish oil predominantly lower triglycerides, but may also have beneficial effects on HDL subfractions and LDL-particle size, as well as direct actions on the vasculature to reduce inflammation and endothelial cell activation [152]. In randomized, double-blind, controlled trials in T2D patients, omega-3 fatty acid supplementation improved acetylcholine (ACh)-stimulated FABF [153], but not fasting brachial artery FMD [154, 155]. Compared with placebo, 6 weeks of purified eicosapentenoic acid (EPA)/docosahexaenoic acid (DHA) (2g/day) significantly reduced the postprandial decrease in FMD and improved postprandial microvascular function in T2D patients [156]. However, there was no effect on fasting vascular function [156]. In hypertriglyceridemic T2D subjects, inclusion of omega-3 fatty acids in a meal containing predominantly unsaturated fatty acids reduced postprandial lipemia and improved postprandial brachial artery FMD [157], possibly by attenuating the postprandial rise in lipoprotein subclass containing apolipoproteins B and C (LpB:C) [158]. Differential effects of the DHA and EPA components of fish oils were demonstrated in subjects with metabolic syndrome: DHA, but not EPA, enhanced vasodilator responses in the forearm [159].

Probucol. Experimental evidence suggests that probucol may limit oxidative LDL modification and reduce atherogenesis [160]. Probucol reduced coro-

nary restenosis rates following percutaneous transluminal coronary angioplasty [161] and CIMT in patients with hypercholesterolemia [162]. In T2D patients, administration of probucol or atorvastatin decreased urinary 8-hydroxy-2'-deoxyguanosine, a biomarker of overall systemic oxidative stress *in vivo*, probucol having a greater effect in patients with higher oxidative stress at baseline [163]. Whether probucol improves vascular function and decreases cardiovascular events in patients with T2D requires examination.

In summary, the lipid regulating agents discussed above all correct diabetic dyslipidemia, improving lipid and lipoprotein composition and concentrations to varying degrees and by different mechanisms. Collectively, these agents have been demonstrated to improve ED, but not all the findings are consistent. Endothelial dysfunction is a complex condition that may require a multifactorial strategy to achieve the best cardiovascular outcome.

4.3 Antiglycemic agents and insulin sensitizers

Hyperglycemia contributes to ED by multiple mechanisms, many of which result in increased oxidative stress. Insulin therapy has been shown to improve fasting and postprandial brachial artery FMD [164, 165] and FABF [166-168], possibly through reduced glycaemia and a direct increase in endothelial NO production through 1-phosphatidylinositol 3-kinase signaling [166, 169]. Studies investigating the effects of sulphonylureas on ED have demonstrated inconsistent results in T2D patients [170-172]. A double-blind, randomized, crossover trial suggested that gliclazide, but not glibenclamide, reduced FABF responses to reactive hyperemia, possibly due to differential binding of these agents to sulphonylurea receptors [173]. However, another study did not demonstrate any difference between these two agents on ACh-stimulated FABF in T2D patients [174]. Rapaglinide, a short acting insulin secretagogue, has been shown to improve brachial artery FMD in T2D patients [175] and to ameliorate ED in a glucose dependent manner in subjects with impaired glucose tolerance [176].

Inconsistent vascular effects with metformin treatment have been demonstrated. In a placebo-controlled trial, metformin compared with placebo treatment increased ACh-stimulated FABF and insulin sensitivity in diet-treated T2D patients [177]. In a randomized cross-over study, metformin, but not glimepiride, improved carotid artery diameter and total and systolic blood flow in

uncontrolled T2D patients [178]. However, metformin did not improve insulin sensitivity nor ACh-stimulated FABF, despite improved glycemic control, in a randomized, double-blind, placebo-controlled trial in T2D patients [179].

Thiazolidinediones modulate peroxisome proliferator-activated receptor (PPAR) activity and may have direct anti-inflammatory and anti-atherogenic effects on the vasculature through the presence of PPAR-gamma receptors in the endothelium, vascular smooth muscle cells and macrophages [180]. Both troglitazone and pioglitazone increased brachial artery FMD in T2D patients without macrovascular disease [181-183]. However, troglitazone did not improve FMD in T2D patients with more long-standing disease or macrovascular complications [181]. In double-blind, crossover trials, rosiglitazone was shown to increase ACh-stimulated FABF in T2D patients [179, 184].

Acarbose, an alpha-glucosidase inhibitor that targets postprandial hyperglycemia, has been shown to attenuate postprandial impairment of hyperemic FABF response when administered as a single dose in diet-treated T2D patients [185].

Glucagon-like peptide (GLP)-1 is an incretin that decreases glycaemia by stimulating insulin secretion, suppressing glucagon secretion and slowing gastrointestinal motility. GLP-1 may also have a direct modulatory effect on several cardiovascular pathways involved in atherogenesis [186]. Gliptins inhibit dipeptidyl peptidase-4 (DPP4), thereby increasing incretin levels [187]. Infusion of recombinant GLP-1 increased brachial artery FMD in T2D subjects, without any change in insulin resistance [188]. Following a single subcutaneous injection of exenatide (a DPP4 inhibitor) in T2D patients, improved postprandial endothelial function was associated with decreased triglyceride but not glucose concentrations [187]. In a randomized cross-over trial, vildagliptin compared with acarbose improved ACh-stimulated FABF in T2D patients [189].

Pramlintide, a synthetic amylin agonist, lowers postprandial glucose and glucagons, and delays gastric emptying [190]. It is associated with modest improvements in HbA1c levels and weight loss in insulin-requiring T2D patients [190, 191]. Pramlintide also improves cardiovascular risk factors in T2D patients. Modest reductions in triglyceride levels have been reported, and a dose response relationship is suggested [190, 192]. Improvements in markers of inflammation and oxidation have been reported, but there was no significant effect on blood pressure [190, 192].

Future longer-term cardiovascular outcome studies and postprandial arterial function studies, investigating the effects of incretins, gliptins, alpha-glucosidase inhibitors and amylin agonists in statin-treated T2D patients are warranted to establish if their effects translate to improved cardiovascular outcomes.

4.4 Other emerging therapies for T2D

Type 2 sodium-glucose cotransporter inhibitors (SGLT2) have been shown to normalize glycaemia by promoting renal glucose excretion in animal models [193]. Clinical trials in patients with T2D have shown SGLT2 inhibitors to be efficacious in lowering HbA1c, promoting weight loss, having a low incidence of hypoglycemia and complementing other antiglycemic agents [194]. However, correct patient selection and close monitoring after commencement of treatment is advised due to side effects, such as repeated urinary tract infections, genital infections, increased hematocrit and decreased blood pressure [194]. Evidence suggests that succinobucol, a probucol analogue, has protective effects in diabetes via antiatherosclerotic, anti-inflammatory, antioxidant and potential antidiabetic activities [195].

Endothelin 1 (ET-1), a potent vasoconstrictor chronically elevated in T2D, stimulates the production of reactive oxygen species. An experimental model in non-obese moderately diabetic rats showed that the ET-1 system contributes to increased oxidative stress [196]. ET_A receptor blockade, but not ET_B receptor blockade, abrogated this effect in a dose dependent manner [196]. Coronary microvascular endothelial function improved following 6 months treatment with Atrasentan, a potent and highly selective ET_A receptor antagonist, in patients with coronary microvascular endothelial dysfunction on coronary angiography [197].

Experimental inhibition of PKC has been shown to ameliorate functional endothelial resistance and smooth muscle cell hypersensitivity in diabetic hypertensive rats [198]. However, ACh-stimulated endothelial-dependent vasodilation was not restored [198]. Inconsistent effects of PKC beta inhibition have been demonstrated in patients with T2D. Compared with placebo, 6 weeks of treatment with ruboxistaurin, a PKC beta-specific inhibitor, significantly improved brachial artery FMD in patients with T2D [199]. In a placebo-controlled, cross-over design study, 14 days of ruboxistaurin did not change methacholine stimulated (endothelium-dependent) FABF in either T2D patients or healthy control subjects [200].

Future longer-term cardiovascular outcome studies and arterial function studies investigating the effects of these emerging therapies in statin-treated T2D patients are warranted.

4.5 Combination therapies

In large prospective clinical outcome trials, the residual risk of CVD events remains high in T2D patients, despite achievement of optimal or near optimal LDL-cholesterol levels with statin therapy [102, 201-203]. The evidence from studies examining the effects of statins on ED in T2D has been inconsistent and contradictory (**Table 3**) [109-123]. It is possible that in T2D, treatment with a single therapeutic agent may not adequately improve ED and that combination therapy is required. Several complementary treatment options are possible and reviewed below.

Statins and fibrates. Combination statin and fibrate therapy can significantly benefit dyslipidemia and cardiovascular risk status in T2D patients with combined hyperlipidemia [204-207]. However, evidence for the effects of combined statin/fibrate therapy on ED in T2D patients is limited. In a randomized, double-blind, crossover study, fenofibrate significantly improved endothelial function in the brachial artery and forearm resistance arterioles in statin-treated T2D patients with LDL-Cholesterol <2.6mmol/l and ED [208]. Improvement in brachial artery FMD was inversely associated with on-treatment LDL-cholesterol and apoB concentrations, suggesting that the improvement in endothelial function may in part relate to enhanced reduction in LDL-cholesterol and apoB concentrations [208]. In contrast, microvascular endothelial function was not improved in T2D subjects treated with combination cerivastatin and fenofibrate therapy [143]. Both statin and fibrate therapies have been shown to improve biomarkers of inflammation in subjects with T2D. In 300 subjects with diabetic dyslipidemia, simvastatin or fenofibrate alone or in combination, lowered levels of plasma high sensitivity CRP (hsCRP) and lipoprotein-associated phospholipase A₂ (Lp-PLA₂). However, there was no additive effect from the combination therapy [209].

Statins and niacin. Nicotinic acid effectively raises HDL-cholesterol, lowers triglycerides and increases LDL particle size [210]. In patients with hyperlipidemia or dyslipidemia, combination niacin extended release/simvastatin therapy resulted in greater favorable changes in size and number of HDL particle subclasses and distribution of HDL particle size compared with atorvastatin alone

[211]. In diabetic subjects combination niacin and atorvastatin therapy improves the atherogenic lipid profile more effectively than monotherapy [212].

Combined statin and niacin therapy has been shown to reduce the progression of coronary and carotid atherosclerosis [213-216]. In patients with CAD, the addition of niacin significantly improved endothelial function in patients with low HDL-cholesterol levels [217, 218]. In statin-treated patients with low HDL-cholesterol and CVD (65% T2D with CAD), 12 months of niacin treatment, when compared with placebo, significantly reduced carotid atherosclerosis, but did not alter either aortic distensibility or brachial artery FMD [219]. Statin-treated T2D with LDL-cholesterol <2.5mmol/L and ED were randomized to niacin (nicotinic acid prolonged release) or no additional therapy [220]. Niacin significantly improved small artery vasodilatory function and compliance and reduced serum triglycerides by 47%. An inverse association between maximal forearm post-ischemic blood flow and change in serum triglycerides, suggests that a reduction in triglycerides may in part explain the improvement in endothelial function [220].

However, caution is indicated with the addition of niacin to statins in individuals with low HDL-cholesterol given the recent negative reports from the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL-cholesterol/High Triglyceride and Impact on Global Health Outcomes) study and HPS2-THRIVE (Heart Protection Study-2 and the Treatment of HDL to Reduce the Incidence of Vascular Events). AIM-HIGH was discontinued after 36 months of follow-up due to lack of clinical benefit from the addition of extended release (ER) Niacin to statin ($\pm$ ezetimibe) therapy, despite significant improvements in HDL-cholesterol and triglycerides [221]. A further consideration in discontinuing AIM-HIGH was an increased stroke risk, but overall this was less than 1% and previous studies have not demonstrated an increased stroke risk with niacin. HPS2-THRIVE compared Tredaptive (ER niacin 2 g plus laropiprant (an anti-flushing agent) 40 mg daily) with placebo in 25,673 patients treated with simvastatin plus ezetimibe if required. Following 3.9 years of follow-up, no significant benefit was demonstrated on the primary endpoint of major cardiovascular events and a four-fold greater rate of myopathy was also reported with Tredaptive across all subgroups [222, 223]. Importantly, the safety data showed an excess of new onset diabetes, diabetic complica-

tions, infections, bleeding (gastrointestinal and intracranial) and gastrointestinal symptoms with treading. A caveat is that the volunteers were mainly Chinese and had very well controlled LDL-cholesterol (1.6 mmol/l at baseline), so that use of this agent, which has now been withdrawn from the market by Merck, should not be used in people with low HDL cholesterol/high triglyceride and LDL-cholesterol at target. A recent review suggests that the cardiovascular benefits of niacin alone may be independent of effects on HDL-cholesterol [224]. Whether any such benefits from niacin-ER in HPS2-THRIVE were nullified by laropiprant, a prostaglandin D2 inhibitor, remains open to question.

Statins and antihypertensive agents. Statins and antihypertensive agents have differing mechanisms of action on the arterial wall. Therefore, it is possible that in combination they will have an additive and synergistic effect on vascular function [109, 225-227]. Compared to monotherapy, ramipril combined with simvastatin significantly improved FMD and reduced malondialdehyde (MDA) and hs-CRP levels in hypercholesterolemic T2D patients [225]. Adiponectin levels and insulin sensitivity were improved with ramipril alone and combination therapy, but no additive effect was demonstrated with combination therapy [225]. In T2D, postprandial hyperglycemia and hypertriglyceridemia independently and cumulatively decreased FMD and increased biomarkers of inflammation [109]. These detrimental effects were counterbalanced by short-term (1 week) administration of atorvastatin and irbesartan, either alone or in combination; combination therapy being more effective than either monotherapy [109]. Longer-term studies utilizing combined statin and angiotensin receptor blockers in T2D are required. In patients with hypercholesterolemia and hypertension, evidence supports the anti-atherosclerotic effects of combined statin and calcium channel blocker therapy, particularly the combination of amlodipine and atorvastatin [226, 228-230].

Combination therapy with antioxidants. Together with dyslipoproteinemia, increased oxidative stress is a major factor involved in the pathogenesis of ED in T2D. Therefore, supplementation with antioxidants has the potential to improve ED in T2D:

- Statins and antioxidants. In patients with ischemic cardiomyopathy (40% with diabetes), atorvastatin (10mg/day) significantly improved post-ischemic FABF, but this ef-

fect was blunted by the co-administration of vitamin E (400 IU/day) [231]. Given the potential for statins to inhibit the cellular synthesis of plasma CoQ₁₀, a by-product of isoprenoid metabolism, their full benefit on improving endothelial function may be blunted [232, 233]. In a randomized, double-blind, crossover study, CoQ₁₀ supplementation significantly improved brachial artery FMD in statin-treated T2D patients with LDL-cholesterol <2.5mmol/l and ED [234]. In patients with CAD (20% with diabetes and 80% statin-treated), CoQ₁₀ supplementation improved ecSOD levels and brachial artery FMD, indicating that the beneficial effects of CoQ₁₀ on endothelial function are in part related to improvements in local vascular oxidative stress [235].

- Fibrates and antioxidants. In dyslipidemic T2D patients with ED, combination fenofibrate and CoQ₁₀ normalized forearm microcirculatory dysfunction [139]. Moreover, fenofibrate and CoQ₁₀ independently and interactively lowered 24-hour ambulatory blood pressure [140], consistent with their beneficial effects on endothelial function in resistance arterioles. This synergistic effect of fenofibrate and CoQ₁₀ may involve co-activation of peroxisome proliferator-activated receptor alpha (PPAR- α) in endothelial and smooth muscle cells, improving the production and action of NO and decreasing the synthesis of endothelin-1.

Other combinations therapies. Other therapies with complementary but differing mechanisms of action have the potential to benefit endothelial function. In T2D patients, aggressive LDL-cholesterol lowering with statins alone or statins plus ezetimibe achieved a similar regression of CIMT in patients who had equivalent LDL-cholesterol reductions [236], but comparative therapeutic effects on endothelial function were not studied. Omega-3 fatty acid supplementation has been shown to improve endothelial function in T2D [153, 156-159], including postprandial endothelial function [156-158]. However, the ORIGIN trial found a lack of cardiovascular benefit with daily supplementation of 1gm of n-3 fatty acids (Omacor) in patients with or at risk for T2D (50% treated with a statin) [237]. The benefit of adding higher dose EPA to statins in hypertriglyceridemic subjects at high CVD risk is currently being tested in the REDUCE-IT trial (A Study of AMR101 to

Evaluate Its Ability to Reduce Cardiovascular Events in High Risk Patients with Hypertriglyceridemia and on Statin) [238].

Patients with coronary heart disease (CHD) or CHD risk equivalent, below average HDL-cholesterol and treated with a statin and/or other cholesterol lowering agents to a LDL-cholesterol <2.6mmol/l were randomized in a double-blinded, placebo-controlled study (Dal-VESSEL study) to Dalcetrapib, a cholesterylester transfer protein (CETP) inhibitor, for 36 weeks [239]. Dalcetrapib reduced CETP activity by almost 50% and HDL-cholesterol by 30%, but brachial artery FMD, ambulatory blood pressure and biomarkers of inflammation, oxidative stress and coagulation did not alter with either dalcetrapib or placebo [240]. However, the Dal-PLAQUE study suggested a small trend to improvement in plaque volume [241]; diabetics were not specifically studied and the effect on clinical endpoints must await publication of the Dal-OUTCOMES study. The effect of CETP inhibitors on endothelial function in diabetes warrants investigation.

5. Conclusions

Type 2 diabetic patients are at markedly increased risk of CVD events. Endothelial dysfunction is the earliest manifestation of vascular involvement in diabetes and heralds the increased risk of CVD. Endothelial function may be measured by invasive and non-invasive methods in the coronary and peripheral circulations. In the peripheral circulation ED can be examined indirectly by several non-invasive methods. Studies of ED serve two useful purposes in cardiovascular research. First, they have the potential to identify therapeutic agents that could be tested as monotherapy or combination therapy in clinical endpoint trials. Second, they can help elucidate the mechanisms for the cardiovascular benefits of these treatments. Clinical trials examining the effects of interventions on ED may be limited by sub-

ject selection bias, statistical under-powering and technical imprecision in measurements. These factors may account for variation in findings among some of the studies reviewed. As methodologies are refined, measurement of endothelial function could in time provide a practical clinical tool for risk stratifying patients and guiding the intensity of treatments to reverse or prevent progression of cardiovascular disease in diabetes.

Several large clinical trials have demonstrated that statins decrease cardiovascular events in T2D. However, the residual risk of CVD remains high in statin-treated T2D patients. This residual risk may relate to persistent abnormalities in Triglyceride-rich lipoproteins and HDLs which are not fully corrected by statins. Combined therapies have complementary but differing mechanisms of action with the potential to improve atherogenic dyslipidemia and endothelial function. However, not all studies demonstrated a consistently beneficial effect on ED. In our opinion, on the basis of a recent clinical trial, niacin should not be added to a statin in individuals with low high-density lipoprotein cholesterol and very well controlled LDL-cholesterol. Other interventions, such as incretins and amylin agonists, have been shown to reduce triglycerides and improve ED in diabetes, but there is no evidence that they reduce cardiovascular events. These and other new and emerging therapies, such as the LDL-cholesterol lowering agents colesevelam and mipomersen, require investigation in longer term clinical outcome studies. Well-designed studies of endothelial function in appropriately selected volunteers afford a good opportunity to test new therapeutic interventions and their eventual utilization in the care of the diabetic patient.

Disclosures: GFW has received honoraria for Advisory Boards and lectures from the following industry-related companies: Pfizer, Merck Sharpe and Dohme, Solvay, AstraZeneca, GalaxoSmithKline, Sanofi-Aventis.

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