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10

Effects of Type 2 Diabetes on Arterial Endothelium

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1. Introduction

The endothelium, the innermost layer of blood vessels, has many important biological functions which are responsible for regulating vascular tone and structure. One of the major functions of a healthy endothelium is to ensure adequate blood supply to the different tissues. This particular process is regulated by the release and interaction of different vasoactive substances (i.e. vasodilators and vasoconstrictors), which are under tight balance. On the other hand, it is well known that the chronic exposure to certain stresses (e.g. inflammation, oxidative stress, and hyperglycemia) promotes changes in the endothelium leading to endothelial dysfunction.

Type 2 diabetes mellitus (T2DM) is among those chronic diseases that are associated with endothelial dysfunction which may contribute to limited glucose uptake in skeletal muscle. In fact, diabetes-related endothelial dysfunction has been reported to lead to morphologic and structural vascular changes present throughout the course of diabetes (Taylor and Poston, 1994). There are around 17 million people in the United States who have diabetes, of whom close to 95% have T2DM. Cardiovascular disease (CVD) is the major cause of morbidity and mortality in people with T2DM (Ness et al., 1999), and coronary heart disease is the most common cause of death among those individuals. For instance, people with T2DM are two to four times more likely to develop CVD compared with people without the condition (Stamler et al., 1993).

Interestingly, physical activity is an important therapeutic tool to maintain endothelial function. In fact, regular physical exercise has been reported to be effective in the prevention and delay of onset of T2DM (Bassuk and Manson, 2005; Sanz et al., 2010; Stewart, 2002). Thus the primary purpose of this chapter is to summarize the current available literature concerning the effects of T2DM on arterial endothelium. In addition, this chapter is intended to summarize evidence of the beneficial effects of physical activity on the untoward cardiovascular effects of T2DM and/or the apparent ability of physical activity to prevent progression of diabetes-induced CVD.

2. Vascular endothelial function

2.1 Role of the endothelium in vasoregulation

All blood vessels in the systemic and pulmonary circulations are lined by a continuous single cell layer of endothelium. This layer of endothelial cells continues throughout the

cardiac chambers as well. As a result of research over the past 30 years it is established that the endothelium constitutes a very important and exciting organ. The endothelium plays an important role in hemostasis, inflammation, lipid metabolism, vascular growth, cell migration, formation of (and interactions with) extracellular matrix molecules, as well as control of vascular permeability and vascular resistance (both vasodilator and vasoconstrictor responses) (Furchgott and Vanhoutte, 1989; Ganz and Vita, 2003). The endothelium can detect chemical substances within the blood and physical forces imparted to blood vessel walls (i.e. shear stress and distention) and initiate responses to these chemical and/or physical signals by releasing substances that modulate vascular tone and/or blood vessel structure (Adair et al., 1990; Furchgott and Vanhoutte, 1989). The vascular endothelium releases a variety of vasoactive substances, including vasodilator and vasoconstrictor substances such as endothelin, which contribute to vasomotor control in tissues throughout the body. As described below, the most common measure of the functional capacity of the endothelium is to measure endothelium-dependent dilation (EDD) primarily because of the potential to assess the health of the endothelium non-invasively. Usually, EDD is the result of release of endothelium-derived relaxing factors (EDRFs).

There appear to be at least three EDRF substances, two of which have been identified; prostacyclin (PGI_2) and nitric oxide (NO) (Furchgott and Vanhoutte, 1989; Palmer et al., 1988a; Palmer et al., 1987; Palmer et al., 1988b). The other EDRF, often referred to as endothelium-derived hyperpolarizing factor (EDHF) may not actually be a factor but perhaps represents electrical communication through the gap junctions between endothelial and vascular smooth muscle cells (Cohen and Vanhoutte, 1995; Feletou and Vanhoutte, 2004; Fichtlscherer et al., 2004; Triggle et al., 2003). The relative importance of endothelium-dependent control differs among the tissues of the body at least in part because the endothelial lining is not a homogeneous compartment. Rather the endothelium is characterized by significant structural and functional heterogeneity among tissues and within tissues (Aird, 2007a, b; Laughlin et al., 2008). Even within the vascular bed of a given skeletal muscle, the relative importance of endothelium-dependent vascular control mechanisms changes along the length of the arteriolar network (Laughlin et al., 2008; Laughlin et al., 2001; Laughlin et al., 2003; Laughlin et al., 2004).

NO is produced in endothelial cells by endothelial nitric oxide synthase (eNOS) from L-arginine and oxygen. In its role in vascular control, NO diffuses to the underlying smooth muscle cells, where it activates soluble guanylyl cyclase, resulting in production of cyclic guanosine monophosphate (cGMP) and activation of protein kinase G (PKG), which leads to vasodilation. eNOS is activated by phopshorylation stimulated by shear stress, chemical mediators, and/or by binding of calcium-calmodulin following increases in intracellular calcium signalled by mechanical forces (i.e. an increase in shear stress exerted by the blood flow on the endothelium, referred to as flow-induced dilation) and/or by a host of chemical factors (acetylcholine, bradykinin, substance P, noradrenaline)(Balligand et al., 2009; Barnes and Liu, 1995; Furchgott and Vanhoutte, 1989; Vanhoutte, 1989) acting on their respective receptors on the endothelium (Furchgott and Vanhoutte, 1989; Ganz and Vita, 2003). Flow-induced dilation has been demonstrated in conduit and resistance arteries in various vascular beds (Drexler et al., 1989; Miura et al., 1999; Miura et al., 2001; Sinoway et al., 1989). The weight of evidence suggests that an increase in wall shear stress, secondary to the increased flow, is the physical force that initiates dilation (Pohl et al., 1991). Selective removal or destruction of the endothelium typically abolishes the response (Hull et al., 1986;

Lie et al., 1970; Rubanyi et al., 1986) implicating the production and/or release of endogenous, transferable vascular smooth muscle relaxing factor(s) from endothelial cells (Kuo et al., 1991).

Prostanoid EDRFs are metabolites of arachidonic acid produced by the cyclooxygenase pathway. Arachidonic acid itself can produce vasoconstriction or vasodilation in some vascular beds such as the pulmonary vascular bed, depending on concentration and tone at the time of administration (Barnes and Liu, 1995; Furchgott and Vanhoutte, 1989; Vanhoutte, 1989). These effects of arachidonic acid on the vasculature are largely due to formation of prostanoids and/or thromboxane A_2 (Barnes and Liu, 1995; Furchgott and Vanhoutte, 1989; Palmer et al., 1988a; Palmer et al., 1987; Selig et al., 1986; Vanhoutte, 1989). There is evidence that the chemical identity of EDHF may vary across vascular beds (Laurindo et al., 1994; Miura et al., 2003; Sorop et al., 2003). The five leading candidates for the identity of EDHF include extracellular potassium (Edwards et al., 1998), hydrogen peroxide and/or superoxide anion, epoxygenase/cytochrome P450 metabolites, and electrical conduction of hyperpolarization through myoendothelial gap junctions (Feletou and Vanhoutte, 2004; Fichtlscherer et al., 2004; Fisslthaler et al., 1999; Triggle et al., 2003).

Endothelins are vasoactive peptides produced by vascular endothelial cells (Korth et al., 1999). Three different isoforms of endothelins (ET) have been identified, namely, ET-1, ET-2 and ET-3 (Haynes and Webb, 1998; Masaki, 2004). ET-1 is the most abundant isoform expressed and secreted in endothelial cells and it is one of the most potent vasoconstrictor agents described to date (Haynes and Webb, 1998). ET-1 is constitutively released by endothelial cells with the majority (~80%) released luminally towards vascular smooth muscle (Wagner et al., 1992). Thus ET-1 appears to act primarily in a local paracrine, rather than circulating endocrine, manner. ET receptors are expressed on endothelial and vascular smooth muscle cells of both arteries and veins throughout the pulmonary and systemic vascular trees (Loesch, 2005; Rubanyi and Polokoff, 1994). Binding of ET to the Gq-protein coupled endothelin type A (ET_A) and to endothelin type B (ET_B) receptors on vascular smooth muscle leads to vasoconstriction whereas activation of ET_B receptors on the endothelium leads to production of NO and prostacyclin, which induce vasodilation (Rubanyi and Polokoff, 1994; Schiffrin and Touyz, 1998; Webb and Haynes, 1995). Although the role of ET-1 in determination of regional blood flow remains unclear, it appears that ET-1 contributes to the control of blood flow to the heart, lungs, kidneys, visceral organs and skeletal muscle but likely not to the brain under normal conditions (Koedel et al., 1998; Maeda et al., 2002; Merkus et al., 2003). Also, there is evidence that alterations in the ET-1 system contribute to vascular dysfunction in T2DM (Lam, 2001; Schneider et al., 2007).

2.2 Endothelial function assessment

2.2.1 Non-invasive techniques

These techniques are mainly used to evaluate the vasomotor response to physical and/or pharmacological stimuli of the endothelium. For instance, flow-mediated vasodilation (FMD), using ultrasonography, is the classic technique used to detect changes in superficial arteries (e.g. brachial, radial or femoral), allowing the measurement of blood flow, blood flow velocity and vascular diameter changes (Corretti et al., 1995). The vasodilatory response, after a period of transient ischemia (~ 5 min), is dependent upon a series of neurologic, myogenic and chemical intermediates, which includes the release of NO. There is a good correlation between this post-ischemic vasodilation observed in the forearm (i.e.

FMD) and the coronary vasodilation caused by acetylcholine (Anderson et al., 1995). Thus FMD is used as a surrogate of endothelial health. In addition, strain gauge plethysmography is also used to determine blood flow.

2.2.2 Invasive *in vivo* techniques

These techniques are used to evaluate endothelial function of arteries and to determine the probable changes in their diameter, by ultrasonograhpy, or blood flow, by plethysmography, after cardiac catheterization to access the coronary circulation. These methods allow also the intra-arterial infusion of different drugs and/or neurohumoral factors to study the endothelial-dependent or independent properties. Finally, it is worth noting that the use of *in vitro* direct methods. For instance, cell culture allows the evaluation of the different vasoactive substances that can be secreted by the endothelium in response to changes in blood flow and/or shear stress (Malek et al., 1999). Isolated arteries, from different vascular beds, can be used to determine the specific responses to diverse endothelial-dependent dilators and/or inhibitors (Luscher and Noll, 1996).

3. Link between endothelial dysfunction and T2DM: Pathophysiology

3.1 Vascular inflammation

Endothelial dysfunction is characterized by a chronic, systemic pro-inflammatory state, reduced vasodilation (reduction in relaxing factors and an increase in contracting factors), and a pro-thrombotic state. T2DM is among the multiple diseases and conditions that are initiated or associated with endothelial dysfunction (Beckman et al., 2003; Laight et al., 1999; Schofield et al., 2002). In fact, it has been suggested that endothelial dysfunction is an important factor in the pathogenesis of vascular disease observed in patients with diabetes (De Caterina, 2000; Schalkwijk and Stehouwer, 2005). There is evidence that inflammatory states are associated with T2DM, obesity, and insulin resistance (Hotamisligil et al., 1993; Lehrke and Lazar, 2004).

The plasma concentrations of C-reactive protein (CRP), fibrinogen, interleukin-6, interleukin-1, and tumor necrosis factor alpha (TNFα) are increased in diabetes (Grau et al., 1996; Shurtz-Swirski et al., 2001). Hotamisligil et al. (Hotamisligil et al., 1993) reported that the expression of TNFα, a pro-inflammatory cytokine, was markedly increased in obese mice; and when TNFα was counterbalanced insulin resistance improved. Interestingly, the increased levels of CRP would mediate opposite actions on the vasculature. It promotes the increase of adhesion molecules (intracellular adhesion molecule; ICAM-1, vascular cell adhesion molecule; VCAM-1), E-selectin, monocyte chemotactic protein-1 (MCP-1), and ET-1. On the other hand it decreases eNOS expression, NO and prostacyclin bioavailability, and elevates the expression of angiotensin receptor type 1 in the vessel wall (Pasceri et al., 2000; Schalkwijk and Stehouwer, 2005; Venugopal et al., 2002). Insulin exerts anti-inflammatory effects at the cellular and molecular levels in vitro and in vivo. It has been shown that low-dose infusion of insulin reduces reactive oxygen species generation, and suppresses NADPH oxidase expression and plasma ICAM-1 and MCP-1 concentrations. Conversely, long-term insulin infusion (~ 4 hours) in healthy subjects was associated with an induction of endothelial dysfunction (Hartge et al., 2006).

Clearly, the increased levels of these inflammatory cytokines resulted in increased vascular permeability, change in the vasoregulatory responses, and increase in the adhesion of leucokytes to the endothelium. The diabetes-associated alterations on the endothelium that

lead to endothelial dysfunction can be summarized as follows; a) impairment of NO production and/or bioavailability, b) reduced NO responsiveness, c) elevated expression and plasma levels of different vasoconstrictors, d) increased adhesion molecule expression, and e) associated enhanced adhesion of vascular cells (e.g. platelets and monocytes) to the endothelium.

3.2 The metabolic syndrome: Obesity and cardiovascular disease

The metabolic syndrome is a collection of risk factors for CVD, typically characterized by endothelial dysfunction. Metabolic syndrome is diagnosed if there are three of the five following components; a) increased abdominal adiposity, b) atherogenic dyslipidemia, c) elevated blood pressure, d) insulin resistance and/or glucose intolerance (i.e. T2DM), and e) a proinflammatory and prothrombotic state (Grundy et al., 2005; Kahn et al., 2005). Incidence of metabolic syndrome has been on the rise over the last decade both in the United States (Ford et al., 2002; Park et al., 2003) and world-wide (Gupta et al., 2004; Magi et al., 2005). Individuals with identified metabolic syndrome are at increased risk for CVD (Malik et al., 2004; Mottillo et al., ; Wilson et al., 2005), an observation independent of age (Ferreira et al., 2007; Lakka et al., 2002; McNeill et al., 2006). The key findings of these studies were that metabolic syndrome leads to a 2-fold increase in CVD and a 1.5-fold increase in all-cause mortality (Mottillo et al.), that increased risk for CVD is not gender specific (Wilson et al., 2005), and that children with metabolic syndrome possess high levels of multiple risk factors (e.g. hypertension, dyslipidemia, and glucose intolerance) for CVD (Ferreira et al., 2007; Taha et al., 2009).

Obesity and/or adipose tissue disorders are also recognized as a potential primary etiological origin for metabolic syndrome. However, independent of the metabolic syndrome, obesity has been increasing in incidence in both adults and children (Klein et al., 2004; Poirier et al., 2006), and is a risk factor for CVD (Hubert et al., 1983; Larsson et al., 1984). It is also well established that metabolic syndrome and obesity linked with metabolic syndrome promote endothelial dysfunction in adults and children (Aggoun, 2007; Singhal, 2005). More current studies over obesity have elucidated that adipose tissue is not just a simple reservoir for energy storage and thermoregulation but rather a complex, indispensable, active metabolic and endocrine organ (Rosito et al., 2008; Sacks and Fain, 2007). Recent studies have demonstrated that adipose tissue possesses the potential to undergo a phenotypic switch in inflammatory and obese-like environments leading it to secrete "adipokines" that increase risk for CVD (Chatterjee et al., 2009; Payne et al., 2010; Sacks and Fain, 2007) and negatively impact endothelial function (Bunker and Laughlin, 2010; Ketonen et al., 2010; Ma et al., 2010; Payne et al., 2009).

3.3 Insulin resistance

In addition to possessing metabolic actions, it is also established that insulin exerts influence over vascular function via; a) stimulation NO production from endothelium, leading to vasodilation; b) increased skeletal muscle blood flow; and c) augmentation of glucose disposal in skeletal muscle (Baron and Clark, 1997). Insulin resistance is typically defined as decreased responsiveness to insulin's actions that stimulate glucose uptake in the tissues (Lebovitz, 2001). Endothelial dysfunction and insulin resistance often co-exist, however at present it remains unclear as to which one leads to/causes the other. A key characteristic of T2DM, insulin resistance is also an independent risk factor for endothelial dysfunction

associated with various forms of CVD (Arcaro et al., 2002; Campia et al., 2004; Williams et al., 1996). Cross-sectional studies indicate endothelial dysfunction can independently predict incidence of insulin resistance/diabetes in humans (Meigs et al., 2004; Meigs et al., 2006; Thorand et al., 2006). Additionally, studies examining rodent models of endothelial dysfunction have demonstrated that even partial defects in endothelial function are sufficient to cause insulin resistance (Cook et al., 2004; Duplain et al., 2001). Taken together current evidence supports a causal role for endothelial dysfunction in the development of insulin resistance.

On the other hand a very recent study, the Women's Health Initiative Observational Study (WHIOS), was conducted calling into question the utility of using endothelial dysfunction biomarkers for insulin resistance and T2DM prediction (Chao et al., 2010). The WHIOS involved 1,584 incident T2DM cases and 2,198 matched controls to evaluate the utility of plasma markers of inflammation and endothelial dysfunction for T2DM risk prediction. Results indicated that none of the inflammatory and endothelial dysfunction markers improved T2DM prediction in a multiethnic cohort of postmenopausal women. Other recent studies have also shown that in humans with insulin resistance, a subsequent impairment occurs in insulin's ability to induce endothelium dependent vasodilation that is dramatically improved with insulin therapy (Franklin et al., 2008; Rask-Madsen et al., 2001; Vehkavaara et al., 2000). It was also demonstrated recently in rat model of T2DM that insulin resistance manifested prior to a dramatic (20-35%) progressive decline in endothelial function concurrent with T2DM disease development (Bunker et al., 2010). Collectively these studies suggest a potential causal role of insulin resistance in the development of endothelial dysfunction.

Whichever pathology manifests first, endothelial dysfunction or insulin resistance, it is demonstrably clear that development of either pathology rarely occurs without the subsequent development of the other pathology.

3.4 Hyperglycemia

Generally speaking, hyperglycemia can be divided into two broad categories; a) impaired fasting glucose, and b) impaired glucose tolerance. The latter is commonly characterized by 2-hour post-prandial hyperglycemic spikes of 140mg/dl to ≥200mg/dl (Node and Inoue, 2009). These post-prandial spikes in plasma glucose are known to contribute to endothelial dysfunction and CVD in humans, independent of the metabolic syndrome (Ceriello et al., 2002; Su et al., 2008; Title et al., 2000). Indeed, hyperglycemia is the major causal factor in the development of endothelial dysfunction in diabetes. Results from these studies and many others suggest that endothelial dysfunction is mediated through mechanisms that primarily involve generation of oxidative stress that subsequently lowers NO bioavailability.

Impaired fasting glucose is defined by an elevated fasting plasma glucose concentration of ≥100mg/dl and <126 mg/dl (Genuth et al., 2003), which is also an indication of chronically elevated plasma glucose levels. Evidence from recent human studies suggests that fasting hyperglycemia, independent of diabetes and the metabolic syndrome, contributes to endothelial dysfunction and CVD (Rodriguez et al., 2005; Su et al., 2008). However, evidence is slowly mounting from human and animal studies that suggest oscillating glucose levels seen with impaired glucose tolerance can have more deleterious effects than the constant high glucose levels seen with impaired fasting glucose on endothelial function and oxidative stress (Ceriello et al., 2008; Horvath et al., 2009; Monnier et al., 2006).

3.5 Oxidative stress

Elevated production of reactive oxide species (ROS) has been implicated in the development of T2DM (Avogaro et al., 2006; Irani, 2000; Liu et al., 2005; Tesfamariam and Cohen, 1992; Yang et al., 2010). The molecular basis for excessive mitochondrial ROS in diabetes has been extensively reviewed elsewhere (Irani, 2000; Yang et al., 2010; Avogaro et al., 2006). These free radicals also play a critical role in the pathogenesis of diabetes-associated vascular complications (macro-and microangiopathy) (Giugliano et al., 1996; Spitaler and Graier, 2002). In T2DM, the endothelium, due to glucose oxidation, promotes the increase of free radicals (e.g. superoxide and hydrogen peroxide) leading to enhanced intracellular production of hydroxyl radical which has been linked to diabetes-induced endothelial dysfunction (Giugliano et al., 1996; Pieper et al., 1997; Shi and Vanhoutte, 2009; Spitaler and Graier, 2002; Tesfamariam and Cohen, 1992). In that regard, animal models of diabetes have been associated not only with reduced NO bioavailability but also with impaired EDD (Durante et al., 1988; Rosen et al., 1995; Tesfamariam, 1994) as the result of the hyperproduction of superoxide and hydrogen peroxide. In addition, there is evidence that indicates that increased ROS plays an important role in the development of diabetic complications. Maejima et al. (Maejima et al., 2001) reported that the decrease EDD observed in patients with T2DM is linked to NO inactivation resulting from increased oxidative stress, and that abnormal NO metabolism is related to advanced diabetic microvascular complications. Furthermore, endothelial cells in patients with T2DM are not able to produce sufficient amount of NO and therefore fail to vasodilate in response to vasodilators (e.g. acetylcholine, bradykinin, shear stress) (Avogaro et al., 2006).

The increased glucose levels ("hyperglycemia") also promote mitochondrial formation of ROS. It has been reported that in aortic endothelial cells hyperglycemia induced increased superoxide production which prevents eNOS activity and expression (Srinivasan et al., 2004). The formation of peroxynitrite (superoxide and NO interaction) promotes blunted NO-mediated vasodilatory response and further induces cellular damage through depletion of tetrahydrobiopterin (BH4), an important co-factor for eNOS activity (Pannirselvam et al., 2002). In addition, there are reports indicating that glucose variability ("intermittent low and high glucose levels") is associated with an excessive production of ROS (Monnier et al., 2006; Piconi et al., 2004) which promotes even more detrimental effects to the endothelium (Ceriello et al., 2008; Piconi et al., 2004). Shi et al. (Shi et al., 2007; Shi and Vanhoutte, 2009) reported that elevated levels of ROS not only reduce NO bioavailability, but also facilitate the production and/or action of EDCFs in the course of T2DM. Finally, the augmented production of ROS in T2DM can also promote the inactivation of antioxidant proteins and therefore reduce the antioxidant defense mechanisms (Laight et al., 1999; Shi et al., 2007).

3.6 Dyslipidemia

T2DM promotes elevated total cholesterol, high levels of oxidized lipoproteins, especially low density lipoptotein (LDL), high triglycerides levels, and decreased high-density lipoprotein (HDL) (Watkins, 2003). It has been suggested that abnormal lipids and lipoproteins play a role in endothelial dysfunction in T2DM (McVeigh et al., 1992). For instance, endothelium-dependent vasodilation was negatively and significantly correlated with elevated triglyceride, LDL and low HDL cholesterol concentrations (Watts et al., 1996). In the same manner, it has been shown that only LDL size was inversely correlated with the

acetylcholine-induced brachial EDD (Makimattila et al., 1999). Clearly, we can infer from the above studies that LDL is one of the chief factors involved in endothelial dysfunction.
LDL and other lipoproteins are able to cross the endothelial cells layer by vascular transport, and later they are oxidatively modified at the sub-endothelial space into reactive oxygen species generated by macrophages, endothelial cells and smooth muscles (Steinberg, 1997). The accumulation of oxidized-LDL is toxic to endothelial cells, which in turn alters the function and structure of the endothelium (McVeigh et al., 1992; Tribe and Poston, 1996). Oxidized-LDL decreases NO production by reduction of NOS (Tribe and Poston, 1996) or by stimulating the synthesis of caveolin-I (Bist et al., 1997), consequently contributing to defective vasodilatation. In addition, there are indications that oxidized-LDL could also enhance the release of ET-1, a main endothelial constrictor peptide (Boulanger et al., 1992).

3.7 Mechanisms of endothelial dysfunction in T2DM

Over 170 million people in the world were affected by diabetes in 2000 and this is expected to increase to over 360 million by the year 2030 (Bakker et al., 2009; Ostergard et al., 2007). Type 1 diabetes is characterized by an absence of insulin while T2DM is characterized by insulin resistance followed in time with decreased plasma insulin. Vascular disease is the major cause of death in individuals with T2DM. The vascular complications of T2DM take two major forms; a) atherosclerosis in conduit arteries and b) microvascular dysfunction in skeletal muscle vascular beds. The vasodilatory effects of insulin account for up to 40% of insulin-mediated glucose disposal in skeletal muscle following a meal. In obesity and T2DM, the vasodilatory action of insulin is impaired. Insulin-stimulated NO production via the insulin-receptor substrate-1 (IRS-1) pathway is diminished, while vasoconstriction through the mitogen-activated protein kinase (MAPK) pathway, endothelin-converting enzyme (ECE) and subsequent secretion of the vasoconstrictor ET-1 may be augmented. As a result, microvascular blood flow and delivery of glucose to muscle tissue are diminished, contributing to reduced skeletal muscle glucose uptake and peripheral insulin resistance. Insulin resistance in T2DM appears to be the result of abnormal insulin-induced glucose uptake by skeletal muscle and microvascular dysfunction in skeletal muscle (blunted insulin-induced vasodilation).
Control of blood flow to skeletal muscle is abnormal in diabetes as muscle blood flow is less than normal during exercise in forearms of obese women (Hodnett and Hester, 2007), obese children (Ribeiro et al., 2005), in legs of diabetes subjects during cycle exercise (Hodnett and Hester, 2007; Kingwell et al., 2003), and in obese Zucker rats (Frisbee, 2003; Frisbee et al., 2006; Xiang et al., 2005). The abnormal control of vascular resistance in diabetes is associated with decreased arterial compliance, decreased microvascular density, altered smooth muscle dependent vascular reactivity and endothelial dysfunction (Frisbee et al., 2006; Hodnett and Hester, 2007). Local metabolic control of blood flow is abnormal and myogenic control of vascular smooth muscle tone is affected in diabetes as well. For instance, arterioles isolated from obese Zucker rat skeletal muscle exhibit increased spontaneous tone due to changes in vascular smooth muscle and to changes in an endothelium-derived factor (Frisbee et al., 2006). The endothelium of both conduit arteries and resistance arteries is dysfunctional in diabetes (Hodnett and Hester, 2007). Endothelial dysfunction in conduit arteries appears to be associated with decreased bio-availability of NO with sustained (or normal) eNOS content, decreased phospho-eNOS, deceased BH4 and cytochrome P450 expression as well as increased thromboxane (TXA_2) content. In the conduit arteries, endothelial dysfunction is

believed to contribute to development of atherosclerosis while in the resistance arteries endothelial dysfunction leads to disruptions in the control of blood flow as well as blunted angiogenesis and structural vascular remodeling (rarefaction)(Frisbee et al., 2006). In normal skeletal muscle insulin-mediated EDD-induced increases in blood flow are responsible for 25-50 % of the increase in glucose clearance stimulated by insulin administration (Kim et al., 2006). Thus, it appears that endothelial dysfunction of resistance arteries in muscle tissue includes blunted insulin-stimulated vasodilation (Mikus et al., 2010).

Endothelial dysfunction in T2DM is associated with glucotoxicity, lipotoxicity, and inflammation which impair insulin signaling (i.e. endothelial cell insulin resistance). These effects may be the result of cytokine signaling and/or increased ROS in the arteries. There are at least two sources of ROS believed to cause endothelial dysfunction in diabetes; a) hyperglycemia, and b) vascular inflammation (Kim et al., 2006; Luscher and Steffel, 2008). Kim et al (Kim et al., 2007) concluded that nutrient excess (excess glucose/lipid) stimulates cellular inflammatory responses that produce insulin resistance leading to decreased Akt and eNOS phosphorylation and increased NF-kB expression leading to expression of inflammatory cytokines in endothelial cells. For instance, Romero et al. (Romero et al., 2008) concluded that hyperglycemia plays a key role in increasing ROS in diabetes through stimulation of arginase activity/expresson in vascular cells. Insulin binding to its receptor signals through two distinct pathways in endothelial cells; a) activation of the IRS-1/phosphatidylinositol 3-kinase (PI3-kinase)/phosphor- Akt/phosphor-eNOS causing release of NO and EDD; b) increased release of ET-1through the mitogen-activated protein kinase (MAPK) pathway. Evidence indicates that T2DM produces an imbalance in the production of NO and ET-1 in response to insulin so that ET-1 release is up-regulated (Kim et al., 2006). It appears that when endothelium is insulin resistant, due to blunted signaling through the IRS-1/Akt/p-eNOS signaling pathway, ET-1 induced constriction leads to decreased muscle blood flow during insulin stimulation (Eringa et al., 2007).

4. Physical activity and type 2 diabetes: Focus on the endothelium

4.1 Benefits of physical activity

Physical activity may be beneficial in slowing the initiation and progression of T2DM and its cardiovascular sequelae through favorable effects on body weight, insulin sensitivity, glycemic control, blood pressure, lipid profile, fibrinolysis, inflammatory defense systems, and endothelial function. More comprehensive reviews regarding the beneficial effects and/or recommendations of physical activity in patients with T2DM have been previously published (Bassuk and Manson, 2005; Sanz et al., 2010; Stewart, 2002; Colberg, 2010). The following section is intended to present the available evidence of the beneficial effects of physical activity focusing on endothelial function. For instance, in clinical trials of patients with diabetes, physical activity (e.g. aerobic exercise) has been shown to increase vasodilator bioavailability (e.g. NO and prostacyclin) and to improve EDD (Moyna and Thompson, 2004; Roberts et al., 2002).

4.2 Acute effects of exercise

4.2.1 Aerobic exercise

Studies examining the acute effects of aerobic exercise training on endothelial function in T2DM are somewhat limited. A series of experiments examining the effects of a single bout of maximal (Colberg et al., 2003) and moderate (Colberg et al., 2006b) aerobic cycling

exercise training found that baseline skin blood flow following local heating significantly increased following the exercise in subjects with T2DM (Colberg et al., 2003; Colberg et al., 2006b) and that this effect was independent of interstitial subcutaneous NO levels (Colberg et al., 2006b).

A study by Kingwell et al. (Kingwell et al., 2003) demonstrated that leg blood flow during aerobic cycling exercise and in response to acetylcholine infusion was significantly impaired in T2DM. Infusions of sodium nitroprusside were not different between diabetic subjects and weight-matched controls, suggesting that the impaired leg blood flow during aerobic exercise in T2DM was a result of endothelial dysfunction.

4.2.2 Resistance exercise

Even more limited are studies examining the acute effects of resistance exercise training on endothelial function in T2DM. Currently only one study has examined the acute effects of resistance exercise training on endothelial function in subjects with T2DM. Indeed, Colberg et al. (Colberg et al., 2006a) investigated whether 8-weeks of cycle-ergometery resistance exercise would affect cutaneous perfusion following local heating in T2DM subjects. Their results indicated that resistance exercise training does not significantly affect cutaneous perfusion, either at baseline or following local heating. This finding was independent of unchanged interstitial NO levels. More studies are needed in this area for a better understanding of how resistance exercise training affects the endothelium in T2DM.

4.3 Chronic effects of exercise training

4.3.1 Aerobic exercise

Very few studies exist examining the effects of chronic aerobic exercise training alone on endothelial function in T2DM. A positive association between aerobic status, skin blood flow, and endothelial function has been demonstrated in patients with T2DM (Colberg et al., 2002); however further studies from this same group revealed that 10 weeks of aerobic exercise training intervention does not improve impaired cutaneous perfusion (i.e. endothelial function) in patients with T2DM (Colberg et al., 2005).

Several human studies exist examining the combined effects of chronic aerobic and resistance exercise training on endothelial function in T2DM, but yield conflicting results. For instance, Mairoana et al. (Maiorana et al., 2001) found that 8 weeks of combined aerobic and resistance exercise training exerted a significant positive effect on conduit (i.e. brachial artery FMD) and resistance artery (i.e. forearm plethysmography) endothelial function in patients with diagnosed T2DM. Okada et al. (Okada et al., 2010) also found very recently that 3 months of combined chronic aerobic and resistance exercise training improved brachial FMD in patients with T2DM.

However, the study by Miche et al. (Miche et al., 2006) found that 4 weeks of combined aerobic and resistance exercise training had no effect on brachial artery endothelial function in patients with severe T2DM. Lastly Middlebrooke et al. (Middlebrooke et al., 2006) demonstrated in elderly patients with T2DM (60+ years of age) that 6 months of regular aerobic exercise training does not improve microvascular function (i.e. skin blood flow) or aerobic fitness. It should be noted that the patients in the Colberg et al. (Colberg et al., 2005), Miche et al. (Miche et al., 2006), and Middlebrooke et al. (Middlebrooke et al., 2006) studies had numerous other co-morbidities in addition to T2DM, thereby underscoring the importance of starting exercise training programs before the disease manifests into a

complex, multidimensional condition that is difficult to treat. Further studies in humans are needed at this time to know whether chronic aerobic exercise training alone exerts beneficial effects on endothelial function during T2DM.

Current studies using the Otsuka Long-Evans Tokushima Fatty (OLETF) rat model of T2DM and obesity have revealed that chronic aerobic exercise training alone maintains endothelial function in conduit (i.e. aortic EDD) (Bunker et al., 2010) and resistance arteries (i.e. skeletal muscle arterioles) (Mikus et al., 2010) during the progression of T2DM. Other OLETF studies demonstrated the positive effect of chronic aerobic exercise training alone as a preventative measure for endothelial function (thoracic aorta and mesentery artery EDD) at single time-points during T2DM progression (Minami et al., 2002; Sakamoto et al., 1998). It is worth noting that the experimental design of the OLETF studies was such that aerobic exercise training served as a preventative measure for endothelial dysfunction associated with T2DM, whereas in the human studies discussed above it served as an interventional measure for endothelial dysfunction associated with T2DM. The findings thus far from long-term studies of aerobic exercise training alone collectively suggest that alterations in vascular NO bioavailability, due to direct or indirect changes in eNOS activity/expression, are contributing in part to endothelial dysfunction associated with T2DM.

4.3.2 Resistance exercise

The effects of chronic resistance exercise training on endothelial function are equally unclear at present. Chronic resistance exercise training alone has been shown to have little to no effect on skin blood flow and endothelial function in patients with T2DM (Colberg et al., 2006a). This study observed in ten individuals with T2DM and nine similar non-diabetic controls that 8 weeks of moderate-intensity resistance training did not enhance baseline skin blood perfusion or interstitial NO levels. Results from this study are in agreement with the studies by Miche et al. (Miche et al., 2006) and Middlebrooke et al. (Middlebrooke et al., 2006), discussed in the previous section (i.e. aerobic exercise), which showed that combined aerobic and resistance exercise training had no effect on endothelial function in T2DM.

However they conflict with a recent study conducted by Cohen et al. (Cohen et al., 2008) where 14-months of resistance exercise training alone significantly improved endothelial function in the skin of men and women with diagnosed T2DM. They also conflict with the Mairoana et al. (Maiorana et al., 2001) and Okada et al. (Okada et al., 2010) studies, discussed in the previous section, where combined aerobic and resistance exercise training was found to positively influence endothelial function in T2DM. At present it remains very unclear as to the effect of chronic resistance exercise training alone on endothelial function in T2DM and more studies are warranted in this area.

4.4 Physical activity: Mechanisms for its vascular benefits

The mechanisms responsible for the beneficial effects of physical activity on endothelium in T2DM are under intense investigation at this time. As for other forms of CVD, it is possible that exercise has beneficial effects on endothelial function directly due to the effects of shear stress or other hemodynamic effects of each exercise bout on the vascular wall or through effects of physical activity on systemic risk factors. For instance, exercise bouts influence circulating cytokines released by skeletal muscle and adipose tissues and can alter circulating lipid profiles. However, most in the field seem to consider that physical activity positively impacts the vascular wall directly via episodic increases in shear stress and

indirectly via reduction of comorbidities often associated with insulin resistance (i.e., hyperglycemia, hypercholesterolemia) (Joyner and Green, 2009).
It is known that endurance and interval sprint training enhance vascular function of the gastrocnemius, but not soleus, vasculature of healthy animals (Laughlin et al., 2004; McAllister, 2005) and that daily wheel running is sufficient to prevent the declines/changes in endothelial function associated with insulin resistance in feed arteries of skeletal muscles but effects in the aorta are less clear (Bunker et al, 2010). Physical activity also sustains insulin induced EDD (Mikus et al, 2010). Beneficial effects could also be the result of exercise-induced improvements in antioxidant systems in the vascular cells of the arteries, either endothelium or smooth muscle. It is important for research to establish the exact mechanisms so that exercise protocols can be designed to maximize these benefits.

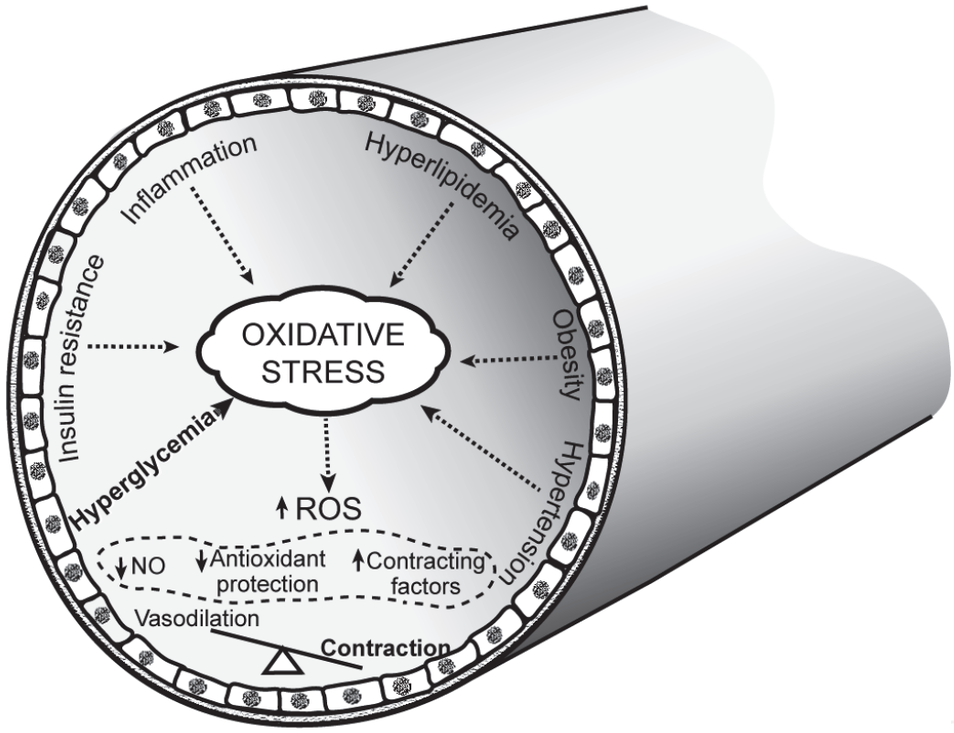


Fig. 1. Factors that participated in the pathogenesis of endothelial dysfunction in T2DM. NO; nitric oxide, ROS; reactive oxygen species.

5. Conclusion

Clearly, the information presented in this chapter emphasizes the major role of endothelial dysfunction in the development and/or progression of T2DM. However, the relationship of endothelial dysfunction and the many independent factors associated with T2DM (e.g. hyperglycemia, inflammation, hyperlipidemia, oxidative stress, insulin resistance, hypertension, obesity), presented in figure 1, is not completely understood. Furthermore, the precise mechanisms responsible for the beneficial effects of physical activity on the endothelium of individuals with T2DM are still under intense investigation. Obviously, more research is needed in this area, but we could speculate that the beneficial effects of

exercise on endothelial function are due to the effects of shear stress and/or other hemodynamic effects acting directly on the vascular wall or through effects of physical activity on systemic risk factors.

6. Acknowledgment

This work was supported by National Institutes of Health Grant HL-35088.

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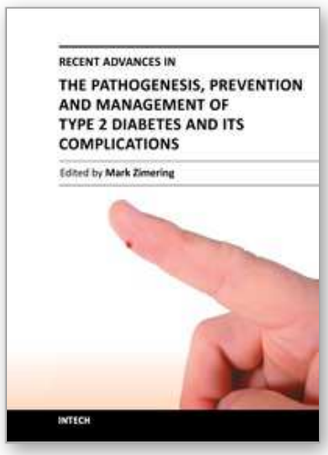
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Recent Advances in the Pathogenesis, Prevention and Management of Type 2 Diabetes and its Complications
Edited by Prof. Mark Zimering

ISBN 978-953-307-597-6
Hard cover, 442 pages
Publisher InTech
Published online 29, August, 2011
Published in print edition August, 2011

Type 2 diabetes â€œmellitusâ€ affects nearly 120 million persons worldwide- and according to the World Health Organization this number is expected to double by the year 2030. Owing to a rapidly increasing disease prevalence, the medical, social and economic burdens associated with the microvascular and macrovascular complications of type 2 diabetes are likely to increase dramatically in the coming decades. In this volume, leading contributors to the field review the pathogenesis, treatment and management of type 2 diabetes and its complications. They provide invaluable insight and share their discoveries about potentially important new techniques for the diagnosis, treatment and prevention of diabetic complications.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Arturo A. Arce-Esquivel, Aaron K. Bunker and M. Harold Laughlin (2011). Effects of Type 2 Diabetes on Arterial Endothelium, Recent Advances in the Pathogenesis, Prevention and Management of Type 2 Diabetes and its Complications, Prof. Mark Zimering (Ed.), ISBN: 978-953-307-597-6, InTech, Available from: http://www.intechopen.com/books/recent-advances-in-the-pathogenesis-prevention-and-management-of-type-2-diabetes-and-its-complications/effects-of-type-2-diabetes-on-arterial-endothelium

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