Life Sciences 102 (2014) 1–9

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Minireview

# The diabetic vasculature: Physiological mechanisms of dysfunction and influence of aerobic exercise training in animal models

Maria A. Delbin [a,*], Aaron J. Trask [b,c,d]

[a] Department of Structural and Functional Biology, Institute of Biology, University of Campinas (UNICAMP), Campinas, SP, Brazil
[b] Center for Cardiovascular and Pulmonary Research, The Research Institute at Nationwide Children's Hospital, Columbus, OH, USA
[c] The Heart Center, The Research Institute at Nationwide Children's Hospital, Columbus, OH, USA
[d] Department of Pediatrics, The Ohio State University College of Medicine, Columbus, OH, USA

ARTICLE INFO

*Article history:*
Received 29 October 2013
Accepted 15 February 2014
Available online 28 February 2014

*Keywords:*
Diabetes mellitus
Vascular responsiveness
Vascular remodeling
Aerobic exercise training

ABSTRACT

Diabetes mellitus (DM) is associated with a number of complications of which chronic vascular complications are undoubtedly the most complex and significant consequence. With a significant impact on health care, 50–80% of people with diabetes die of cardiovascular disease (including coronary artery disease, stroke, peripheral vascular disease and other vascular disease), making it the major cause of morbidity and mortality in diabetic patients. A healthy lifestyle is essential in the management of DM, especially the inclusion of aerobic exercise, which has been shown effective in reducing the deleterious effects in vasculature. Interest in exercise studies has increased significantly with promising results that demonstrate a future for investigation. Considering the importance of this emerging field, the aim of this mini-review is to summarize and integrate animal studies investigating physiological mechanisms of vascular dysfunction and remodeling in type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) and how these are influenced by chronic aerobic exercise training.


**Contents**



## Introduction

Diabetes mellitus (DM) is a chronic disease characterized by hyperglycemia and it has become a public health problem of considerable magnitude affecting children, adolescents and adults. It is estimated that 347 million people worldwide have diabetes and epidemiological studies indicate that the global prevalence of diabetes will continue to increase to a predicted doubling by 2030. Recent evidence has shown that high blood glucose is the third leading risk factor for global mortality, with 5.8% of deaths globally (World Health Organization-WHO, 2009; Danaei et al., 2011). There are two major forms of diabetes – type 1 and type 2 however, diabetes may also occur as a consequence of pregnancy, genetic disorders in beta-cell function, genetic disorders in insulin action, pancreatic exocrine disease, drug and chemical toxicity and infection (American Diabetes Association-ADA, 2005).

Type 1 diabetes mellitus (T1DM), accounts for 5–10% of all diabetic cases and is a well-characterized disease associated with impaired insulin production caused by pancreatic beta-cell destruction. This occurs as

* Corresponding author at: Rua Monteiro Lobato, 255, Campinas, SP, Brazil. Tel.: +55 19 35216188.
*E-mail address:* nadelbin@hotmail.com (M.A. Delbin).

http://dx.doi.org/10.1016/j.lfs.2014.02.021
0024-3205/

a result of a complex process where genetic and environmental factors lead to an autoimmune response; however, the exact cause of T1DM is not known and remains to be fully elucidated. T1DM can occur at any age, although it is more commonly diagnosed in children and young adults, and it is not preventable with current knowledge. Daily insulin administration is required for treatment (ADA, 1997). Animal models of T1DM usually employ the use of beta cell toxins such as streptozotocin and alloxan, although there are a few spontaneous rodent models (e.g. Non-Obese Diabetic mouse and Long-Evans Tokushima Lean rat) and one large animal model (Celebes black ape) (Rees and Alcolado, 2005).

In contrast, Type 2 diabetes mellitus (T2DM) presents as peripheral insulin resistance mostly caused by reduced insulin sensitivity in skeletal muscle, adipose tissue, and liver, resulting in a compensatory hypersecretion of insulin. This chronic imbalance may precede the reduction in beta-cell secretory function, termed beta cell exhaustion. There is consensus that this relative reduction in insulin secretion is the final event leading to hyperglycemia, although residual insulin secretion can persist for prolonged periods despite considerable disease progression (Forbes and Cooper, 2013). T2DM compromises approximately 90–95% of all diabetic cases and is typically considered adult-onset diabetes. However, T2DM can no longer be considered just an adult disease as more adolescents are being diagnosed (Molnár, 2004; Celik et al., 2010). Treatment regimens include anti-hyperglycemic agents such as insulin sensitizers or insulin secretion stimulators. Prevention of T2DM is possible and manageable, requiring lifestyle modifications such as diet restriction and increased physical activity (ADA, 2005; WHO, 2004). There are several animal models of T2DM, including, but not limited to , *ob*/*ob* and *db*/*db* mice, the Zucher fatty and Otsuka Long-Evans Tokushima Fatty rats, the diet-induced obesity C57Bl/6J mouse, and the Ossabaw swine with metabolic syndrome (Surwit et al., 1988; Rees and Alcolado, 2005; Dyson et al., 2006).

A healthy lifestyle is essential in the management of diabetes, especially the inclusion of chronic aerobic exercise, which has been shown effective in reducing the deleterious effects in vasculature. Several lines of evidence have shown that regular physical exercise promotes cardiovascular benefit and physically-active patients have increased longevity associated with reductions in morbidity and mortality (Fiuza-Luces et al., 2013). However, elucidating the underlying mechanisms of the extent of cardiovascular benefit of exercise relies heavily on the use of animal models. Animal models are important tools in basic science and many studies have utilized them in studying vascular complications in diabetes. In fact, studies have begun to investigate the effects of exercise in both micro- and macrovascular diabetic complications. Considering the importance of this emerging field, the aim of this mini-review is to summarize and integrate animal studies on the physiological mechanisms of vascular dysfunction and remodeling in T1DM and T2DM and how these are influenced by chronic aerobic exercise training.

## Vascular dysfunction in diabetes

Normal blood vessels have a well-established structure consisting of three layers: tunica intima (endothelial cells), tunica media (smooth muscle cells) and tunica adventitia (extracellular matrix). Specifically, endothelial cells are responsible for the synthesis, metabolism and release of a large variety of mediators that regulate vascular tone, vascular permeability, the metabolism of endogenous and exogenous substances, and platelet and leukocyte activity. Therefore, integrity of the endothelial cells is of fundamental importance in the maintenance and control of the cardiovascular system.

It is now established that endothelium-dependent responses occur in most blood vessels of all species. Vasoconstrictors include endothelin-1 (ET-1), prostaglandins, angiotensin II, thromboxane $A_2$ ($TXA_2$) and reactive oxygen species (ROS), and vasodilators include: nitric oxide (NO), prostacyclin ($PGI_2$) and endothelium-derived hyperpolarizing factor (EDHF) (Vanhoutte and Mombouli, 1996). NO requires special attention, as its production and bioavailability are essential in regulatory functions such as control of hemostasis, fibrinolysis, platelet and leukocyte interactions with the arterial wall, regulation of vascular tone, proliferation of vascular smooth muscle cells (VSMCs), and homeostasis of blood pressure (Napoli and Ignarro, 2009). In this context, endothelial dysfunction as observed in diabetes is characterized by an imbalance between endothelium-derived relaxing and contracting factors, and is mostly associated with lower production and/or bioavailability of NO by endothelial cells.

Diabetes is associated with both micro- (small vessels, including small arteries and veins, arterioles, capillaries and venules) and macrovascular (large vessels, including arteries and veins) complications, affecting nearly all organs (Cade, 2008). Although micro- and macrovascular complications in diabetes have distinct mechanisms, they also share similar etiologic characteristics such as smooth muscle (Mokelke et al., 2003; Bruno and Ghiadoni, 2013) and endothelial dysfunction (Avogaro et al., 2008). The mechanisms underlying this phenomenon are complex and multifactorial. Below, we will first discuss the mechanisms of endothelial dysfunction in diabetes, followed by vascular smooth muscle dysfunction.

Impaired endothelial function, mainly verified by acetylcholine concentration-response curves, has been consistently demonstrated in animal model of T1DM (Hattori et al., 1991; Pieper et al., 1997; Palmer et al., 1998; Chakraphan et al., 2005; Shi and Vanhoutte, 2008; Leo et al., 2010; Claudino et al., 2011; Mayhan et al., 2011; Delbin et al., 2012; Zguira et al., 2013) and T2DM (Sakamoto et al., 1998; Minami et al., 2002; Pannirselvam et al., 2003; Khazaei et al., 2008; Su et al., 2008; Bunker et al., 2010; Lee et al., 2011; Park et al., 2011; Martin et al., 2012).

Increasing studies have shown that decreased bioavailability of NO by increased production of superoxide anions ($O_2^-$) is the hallmark for vascular dysfunction in the diabetic state (De Vriese et al., 2000). Endothelial cells are capable of producing ROS such as $O_2^-$ and its reaction with endothelial-derived NO reduces its bioavailability and leads to a highly unstable molecule, peroxynitrite ($ONOO^-$). The damage in cells and tissues by ROS has been linked to the development of endothelial dysfunction, and consequently with cardio-metabolic diseases (Bianchi and Antunes, 1999). All cellular components are susceptible to ROS, but the membrane is one of the most affected as a result of lipid peroxidation (Stoppa et al., 2006; Baluchnejadmojarad and Roghani, 2008; Rupérez et al., 2008; Arozal et al., 2009; Kamper et al., 2010).

On the other hand, maintenance of the normal intracellular redox status relies upon endogenous antioxidant enzyme defenses. Antioxidant enzymes are capable of intercepting generated ROS, avoiding the deleterious effects of these agents and therefore cellular damage (Maron and Michel, 2012). Among the enzymes, superoxide dismutase (SOD) scavenges $O_2^-$ and requires metal cofactors such as copper (Cu), zinc (Zn), or manganese (Mn) for proper activation. There are three known isoforms with different cellular locations: SOD-1 (or Cu/Zn-SOD) is localized in the cytosol and the nucleus, SOD-2 (or Mn-SOD) is localized in mitochondria and SOD-3 (EC-SOD) is located in extracellular matrix (ECM). SODs convert $O_2^-$ in to hydrogen peroxide ($H_2O_2$). Catalase (CAT) and glutathione peroxidase (GPx, present in all cells and localized in cytosolic, mitochondrial and peroxisome cellular ultrastructure) then convert $H_2O_2$ to water (Kwon et al., 2012). The imbalance between oxidant and antioxidant molecules resulting in increased and/or accumulation of ROS is known as oxidative stress.

In fact, it has been reported that hyperglycemia alters the intracellular reduction-oxidation state of the cell in several ways: by increasing pro-oxidant enzyme activity, or by forming advanced glycation end products (AGEs) that can promote ROS production (Srinivasan et al., 2004; Delbin et al., 2012). In endothelial cells, the interaction of AGEs with their receptor (RAGE) can activate complex signaling pathways