Fundamentals in diabetes. Part 1: An introduction to vascular complications

Khalida Ann Lockman, Stuart Alexander Ritchie, Karen Ann Adamson

Macro- and microvascular complications can result in significant morbidity and mortality in people with diabetes. Hence the condition poses an enormous challenge to the healthcare system. The synergistic effect of hyperglycaemia and other risk factors have been directly linked with the development of these complications. These risk factors promote progressive damage to the vascular wall, specifically the endothelium, resulting in endothelial dysfunction (ED). ED precedes the clinical manifestation of atherosclerosis, and correlates with the severity of microvascular complications. Indeed, endothelial dysfunction underpins the pathophysiology of micro- and macrovascular complications in diabetes. In this article, the first in a series exploring the fundamental pathophysiology of diabetes-related complications, the authors examine the effects of hyperglycaemia and the underlying mechanisms that lead to ED in diabetes.

Article points

1. Hyperglycaemia has been directly linked with the development of micro- and macrovascular complications in diabetes.

2. An association between diabetes, both type 1 and type 2, with endothelial dysfunction is well established.

3. Tissues in the retina, renal and nervous system are particularly susceptible to the deleterious impact of hyperglycaemia owing to their inability to limit the influx of glucose inside the cells.

4. The coexistence of micro- and macrovascular complications further supports the need of an integrated approach with the aim of preventing the progression of endothelial dysfunction.

Key words

- Endothelial dysfunction
- Macrovascular
- Microvascular
- Oxidative stress

Authors' details can be found at the end of this article.

The prevalence of diabetes worldwide is rising at an alarming rate, currently affecting nearly 285 million people – approximately 5% of the adult population. In the UK alone, there are 2.6 million people with diabetes with a further 500 000 people suspected to have diabetes, but who remain undiagnosed (Holt et al, 2008; Diabetes UK, 2010). The prevalence is set to increase in tandem with the rise in the prevalence of obesity. It is estimated that diabetes will reach pandemic proportions, affecting 438 million people globally by 2030 (Diabetes UK, 2010).

Diabetes is the fifth leading cause of death in the developed world and this is largely attributed to its vascular complications (Roglic et al, 2005). Traditionally, diabetes-related vascular complications can be divided into microvascular and macrovascular complications. Macrovascular complications give rise to coronary artery, cerebrovascular and peripheral vascular disease (PVD). Microvascular complications are responsible for diabetes-related renal disease, retinopathy and neuropathy. Cardiovascular disease (CVD) accounts for 44% of deaths in people with type 1 diabetes (T1D) and 52% in people with type 2 diabetes

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1. Postprandially, insulin prevents hyperglycaemia. Insulin promotes glucose uptake in adipose tissue and skeletal muscles with concomitant suppression of gluconeogenesis (glucose formation) and glycogenolysis (glycogen breakdown) in the liver.

2. In the fasting state, the effects of insulin are suppressed and the hormone glucagon stimulates gluconeogenesis and glycogenolysis to prevent hypoglycaemia. Thus, insulin deficiency in diabetes is characterised by hyperglycaemia.

3. Hyperglycaemia has been directly linked with the development of micro- and macrovascular complications in diabetes. This is supported by the findings of several large clinical trials, which show that lowering blood glucose levels reduces the risk of microvascular complications in type 1 and type 2 diabetes.

(T2D) (Morrish et al, 2001). Microvascular complications also have a significant impact on mortality and morbidity. Furthermore, diabetes costs the NHS £5.2 billion per year, accounting for 9.2% of the annual budget in 1997 (Currie et al, 1997). Thus, the rising prevalence of diabetes and its attendant complications pose a serious challenge to the healthcare economy.

This article, the first in a series on the fundamental pathophysiology of diabetes complications, provides a broad overview of the role of hyperglycaemia and endothelial dysfunction (ED) in the development of vascular complications. Future articles will focus on the individual complications themselves, looking at each in more depth to give the reader a complete understanding of current thinking with regard to these conditions.

Insulin: Physiology, deficiency and resistance

Abnormalities in insulin physiology are the key to hormonal disturbance in all forms of diabetes. The abnormalities range from absolute insulin deficiency (T1D), resistance to the normal metabolic actions of insulin (T2D) and the monogenic forms of diabetes affecting individual transcription factors or enzymes, such as MODY (maturity-onset diabetes of the young).

Produced exclusively by beta-cells in the pancreas, insulin is the principal hormone in glucose homeostasis. Maintaining blood glucose concentrations involves a complex interplay of several metabolic pathways fine-tuned to the energy demand of the body. Postprandially, insulin prevents hyperglycaemia. Insulin promotes glucose uptake in adipose tissue and skeletal muscles with concomitant suppression of gluconeogenesis (glucose formation) and glycogenolysis (glycogen breakdown) in the liver. In the fasting state, the effects of insulin are suppressed and the hormone glucagon stimulates gluconeogenesis and glycogenolysis to prevent hypoglycemia. Thus, insulin deficiency in diabetes is characterised by hyperglycaemia (*Figure 1*).

Absolute insulin deficiency in T1D is the result of autoimmune pancreatic beta-cell destruction and accounts for approximately

10% of diabetes (Diabetes UK, 2010). The incidence of T1D continues to increase worldwide (Fourlanos et al, 2008).

T2D represents 90% of diabetes (Diabetes UK, 2010) and is characterised by insulin resistance and progressive beta-cell dysfunction. Altered insulin signaling has been shown to occur in insulin resistance although the precise molecular mechanisms that lead to the defect in signaling transduction remain to be elucidated (DeFronzo, 1992; Lin and Sun, 2010). Initially, insulin resistance is compensated for by hyperinsulinaemia; however, the inevitable loss of beta-cell function with the progression of T2D eventually culminates in hyperglycaemia (Donath et al, 2005) (*Figure 2*).

The role of hyperglycaemia in the development of vascular complications

Hyperglycaemia has been directly linked with the development of micro- and macrovascular complications in diabetes. This is supported by the findings of several large clinical trials, which show that lowering blood glucose levels reduces the risk of microvascular complications in T1D (Diabetes Control and Complications Trial [DCCT] Research Group, 1993; Epidemiology of Diabetes Interventions and Complications [EDIC] Research Group, 1999) and T2D (Stratton et al, 2000).

The benefit of blood glucose lowering on macrovascular complications, however, is less clear-cut (Stratton et al, 2000). Other risk factors, such as hypertension, smoking, hypercholesterolaemia, dyslipidaemia and obesity, are often present thus magnifying the physiological insults incurred by hyperglycaemia. The synergistic effect of these risk factors and hyperglycaemia is particularly relevant to the development of atherosclerosis in macrovascular complications. Indeed, the term "metabolic syndrome" has been coined to denote the cluster of hypertension, dyslipidaemia, obesity and insulin resistance (Alberti et al, 2005). The presence of metabolic syndrome heralds the risk of CVD even in those without diabetes (Butler et al, 2006; DECODE Study Group, 2007). Irrespective of vessel diameter, the combination of these factors

and hyperglycaemia promotes progressive damage to the vascular wall characterised by the presence of ED (Vanhoutte et al, 2009).

Endothelium: Function and dysfunction

Once considered as a simple monolayer lining the blood vessels, the endothelium has emerged as a dynamic organ that plays a crucial role in maintaining the balance between vasodilation and vasoconstriction. Such balance is mediated by various vasomotor factors synthesised and released by the endothelial cells.

Nitric oxide (NO) is a key vasodilator released by the endothelium. NO regulates vascular tone, inhibits cell adhesion, platelet aggregation and smooth muscle proliferation, giving an overall antithrombogenic effect (Radomski et al, 1987; Wheatcroft et al, 2003). In addition to NO, endothelium-dependent relaxation is also mediated by prostacyclin and endothelium-derived hyperpolarising factor (Félétou and Vanhoutte, 2006). In contrast, endothelin and angiotensin II mediate endothelium-dependent vasoconstriction. Furthermore, endothelin and angiotensin II promote smooth muscle cell proliferation and, therefore, could potentially contribute to the formation of atherosclerotic plaque (Kinlay et al, 2001; Sowers, 2002). The balance between vasoconstriction and vasodilation is tightly regulated and the involvement of each pathway differs depending on the levels of vascular tree. In addition, the endothelium also releases factors that modulate inflammatory and coagulation processes (Rubanyi, 1993).
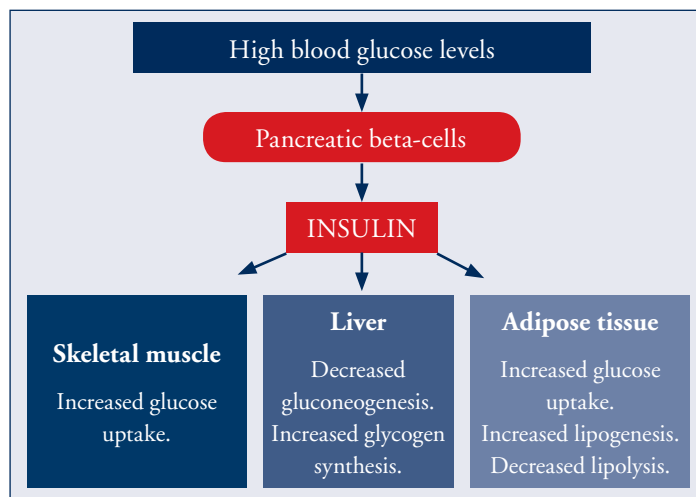

Figure 1. The role of insulin in glucose homeostasis. Insulin is secreted by beta-cells in the pancreas in response to raised blood glucose concentrations. Insulin increases glucose uptake in skeletal muscle and adipose tissue. The action of insulin in the liver is particularly important in glucose homeostasis. Gluconeogenesis (glucose formation) and glycogen breakdown is suppressed in favour of glycogen synthesis. Similarly, in adipose tissue, lipolysis (lipid breakdown) is diminished by insulin and lipid metabolism is geared towards lipid storage (lipogenesis).

ED occurs when the disruption to the endothelium alters vascular homeostasis, impairing endothelial-dependent vasodilation, accompanied by low-grade inflammation favouring the formation of thrombus. ED is the earliest sign of atherosclerosis preceding any overt clinical manifestation of CVD; evidence of endothelial dysfunction has been shown in normotensive, normoglycaemic first-degree relatives of individuals with T2D (Balletshofer et al, 2000). Similarly, the presence of ED has been documented in people with metabolic syndrome in the absence of clinically apparent CVD (Engler et al, 2003).

Diabetes and endothelial function

An association between diabetes, both T1D and T2D, with ED is well established (de Jager et al, 2006), and the pathophysiology involved is complex. ED in the normoglycaemic, normotensive, first-degree relatives of individuals with T2D suggests potential genetic components. More importantly, insulin plays a significant role in the physiology of the endothelium. Insulin increases NO availability,

thus stimulating vasodilation, and is proposed to act in an antiatherogenic manner (Muniyappa and Quon, 2007). The insulin receptor is widely expressed on the endothelial cell surface and has a high affinity for insulin. Insulin-stimulated endothelial-dependent vasodilation is impaired in diabetes (Cleland et al, 2000; Wheatcroft et al, 2003). Such impairment can occur even at an early stage of diabetes and is associated with structural changes akin to atherosclerosis (Jarvisalo et al, 2004). Similarly, ED correlates with the severity of microvascular complications in T2D, independent of the presence of macrovascular disease and other traditional risk factors such as hypertension and hyperlipidaemia (Targher et al, 2005).

Tissues in the retina, renal and nervous system are particularly susceptible to the deleterious impact of hyperglycaemia owing to their inability to limit the influx of glucose inside the cells. Consequently, hyperglycaemia remains constant inside the cells allowing a significant concentration of glucose to enter the oxidative pathways.

Glucose oxidation is essential to generate energy. This occurs in the mitochondria of the cells and is tightly regulated by energy demand. In hyperglycaemic conditions, the surge in glucose oxidation overburdens the mitochondria, leading to the release of reactive oxygen species (ROS) molecules. Excessive ROS formation overwhelms the antioxidant capacity thus promoting a state of oxidative stress. ROS also activate pathways known to have important roles in the pathogenesis of vascular complications; first, polyol pathways; second, the formation of advanced glycosylation end (AGE) products; third, diacylglycerol (DAG) and protein kinase C (PKC) pathways; and finally, hexosamine biosynthetic pathways (Brownlee, 2001; Muniyappa and Quon, 2007). These pathways culminate in ED through a variety of mechanisms including decreased NO availability.

Oxidative stress also has an important role in initiating macrovascular complications. Insulin resistance in T2D is associated with increased free fatty acids in the circulation. The flux of free fatty acids
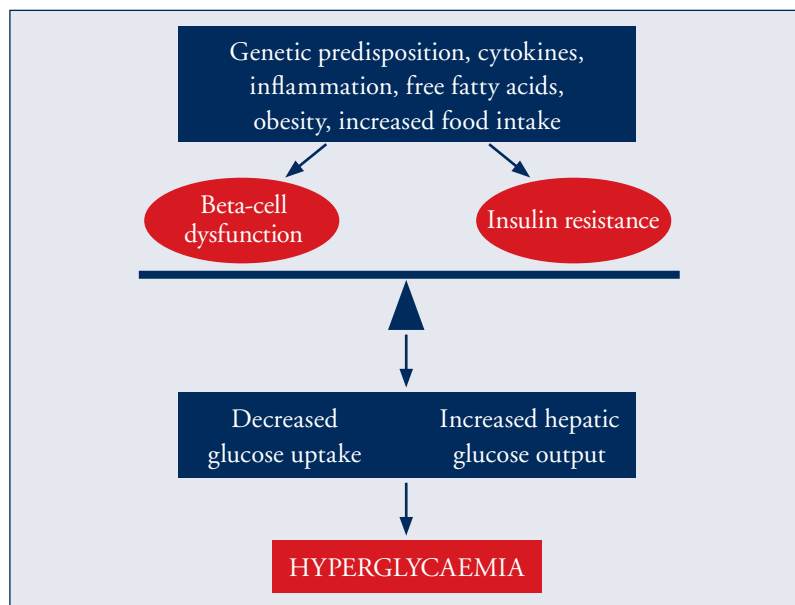

Figure 2. The pathogenesis of type 2 diabetes. Several factors are involved in the development of type 2 diabetes resulting in the development of insulin resistance and beta-cell dysfunction. Insulin resistance promotes decreased glucose uptake and increased glucose formation from the liver. The combination of reduced insulin production and impaired insulin sensitivity culminate in hyperglycaemia.

into the endothelial cells is increased in macrovascular, but not microvascular, endothelium. Free fatty acids enter oxidative pathways. Similar to hyperglycaemia, fatty acid oxidation overwhelms the mitochondria generating ROS, thus promoting oxidative stress. ROS, in turn, activate various pathways that affect NO production in the endothelial cells, similar to that observed with hyperglycaemia (Brownlee, 2001).

There is a significant overlap between the risk factors for micro- and macrovascular complications. In addition to glycaemic control, the duration of diabetes and hypertension exert a considerable influence on the development of microvascular disease (Alleyn et al, 2010). Hypertension, dyslipidaemia and cigarette smoking are the strongest risk factors for macrovascular disease (Shah et al, 2009). For nephropathy in particular, a strong but unknown genetic influence exists (Schelling et al, 2008).

Micro- and macrovascular complications
A shared pathophysiology

Given the shared pathophysiology underpinning the development of both macro- and microvascular complications, it is not surprising that macrovascular complications often coexist with microvascular disease. For example, the presence of diabetic nephropathy is associated with CVD morbidity and mortality, even at the stage of microalbuminuria (urinary albumin 30–300 mg/day) (Yudkin et al, 1988). The cardiovascular mortality in people with T2D with microalbuminuria is two times higher than those with normoalbuminuria (Drury et al, 2011).

Conversely, the presence of features of metabolic syndrome and macrovascular disease in people with T2D has been shown to predict the mortality in individuals with diabetic nephropathy (Thorn et al, 2009). The progression of microalbuminuria to overt albuminuria (urinary albumin >300 mg/day) is

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accompanied by significant risk of atherosclerosis and mortality (Bruno et al, 2007).

A similar association has also been observed with retinopathy, the most common microvascular complication of diabetes. Data from the Framingham Heart Study and the Framingham Eye Study have demonstrated an association between diabetic retinopathy and macrovascular disease (coronary heart disease, intermittent claudication, congestive heart failure and stroke) (Hiller et al, 1988). This relationship exists for both T1D and T2D. Individuals with T2D and proliferative retinopathy had a higher risk of cardiovascular events (Kramer et al, 2011), while a similar relationship has been demonstrated for people with T1D in the European Diabetes (EURODIAB) study (van Hecke et al, 2005).

Another example is the association between PVD and the diabetic foot. The occlusions of microcirculation supplying the peripheral nerves – the vasa nervorum – have been proposed to contribute to diabetic nephropathy. In a study by Karvestedt et al (2009), the prevalence of PVD was three times higher in individuals with diabetic peripheral sensory neuropathy than those without. Furthermore, the prevalence of neuropathy correlates with the severity of retinopathy and nephropathy, thus highlighting generalised ED in diabetes. It is plausible that abnormal autonomic regulation also plays an important role in the pathogenesis of CVD (Gerritsen et al, 2001).

Multifactorial intervention

The importance of good glycaemic control in the prevention of micro- and macrovascular complications cannot be overstated. Large clinical studies such as the UKPDS (UK Prosepective Diabetes Study) and the DCCT have provided compelling evidence for the benefit of long-term glycaemic control in preventing micro- and macrovascular complications in people with T1D (DCCT Research Group, 1993) and T2D (Holman et al, 2008).

It is increasingly recognised, however, that optimal glycaemic control should be combined with long-term intensified intervention aimed at multiple risk factors, including lifestyle modifications such as exercise, weight reduction and smoking. Indeed, the Steno-2 study demonstrated that such efforts reduce the risk of cardiovascular and microvascular events by about 50% in people with T2D (Gaede et al, 2008).

There is strong evidence to suggest that lipid-lowering with statins prevents cardiovascular events in people with T2D (Colhoun et al, 2004). Similarly, good blood pressure management has been shown to reduce the risk of micro- and macrovascular complications (UKPDS Group, 1998). Moreover, the protective effect of antihypertensive angiotensin-converting enzyme (ACE) inhibitors on renal function has been proposed to be independent of the reduction in blood pressure (Hershon, 2011). The beneficial effects of these interventions emphasise the need to screen for both micro- and macrovascular complications in people with diabetes.

Conclusion

Vascular complications dictate the magnitude of the challenges faced by healthcare professionals caring for people with diabetes. Preventing the onset of these complications is paramount. The approach has to be multifactorial, encompassing all the risk factors involved in endothelial dysfunction. The coexistence of micro- and macrovascular complications further supports the need of an integrated approach with the aim of preventing the progression of ED.

Understanding the molecular events surrounding ED, insulin resistance and ROS formation is the key to optimising future therapy aimed at reducing the onset and the progression of micro- and microvascular disease. ∎

Authors

Khalida Ann Lockman is a Specialist Registrar in Diabetes and Endocrinology, St Johns Hospital, Livingston; Stuart Alexander Ritchie is a Specialist Registrar in Diabetes and Endocrinology, Western General Hospital, Edinburgh; Karen Ann Adamson is Consultant Physician, Department of Diabetes, St Johns Hospital, Livingston, Scotland.

"Understanding the molecular events surrounding endothelial dysfunction, insulin resistance and reactive oxygen species formation is the key to optimising future therapy aimed at reducing the onset and the progression of micro- and microvascular disease."

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