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In this article...

- Long-term effects of hypoglycaemia on different parts of the human body
- Macrovascular, microvascular and non-vascular complications of diabetes
- Advice on how complications of diabetes can be delayed, reduced or avoided

Diabetes management 2: long-term complications due to poor control

Key points

1 Good control of blood sugar is essential to reduce the risk of complications in diabetes

2 Most complications of diabetes arise from damage to blood vessels due to hyperglycaemia

3 Cardiovascular disease is the leading cause of death in patients with poorly controlled diabetes

4 Peripheral vascular disease and peripheral neuropathies are common in diabetes and often result in infections, particularly in the feet

5 Diabetic nephropathy and retinopathy are leading causes of renal failure and sight loss

Authors John Knight is senior lecturer in biomedical science; Yamni Nigam is associate professor in biomedical science; Maria Andrade is senior lecturer in interprofessional studies; all at the College of Human Health and Science, Swansea University.

Abstract Diabetes is a long-term systemic disease that can damage all regions of the body. Poor glycaemic control can lead to a variety of pathologies, some of which can be life threatening. The second article in this three-part series explores the cumulative effects of poorly controlled blood glucose and describes the complications of diabetes, which can be delayed, reduced or even avoided through appropriate monitoring, drug management and lifestyle changes.

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Glucose is the preferred energy source for most human cell types and, in health, is maintained in the blood at relatively stable concentrations. In poorly controlled diabetes, a consistently high blood glucose concentration (hyperglycaemia) can damage all the major organs and organ systems, leading to characteristic complications of diabetes (McCance and Huether, 2014) (Table 1). Most arise from damage to blood vessels (vascular complications), but there are also non-vascular complications.

Vascular complications Atherosclerosis

The innermost layer of a blood vessel (endothelium) is only as thick as a single cell and it is in continuous contact with circulating blood. In poorly controlled diabetes, hyperglycaemic blood can irritate and damage this delicate layer through a variety of mechanisms (Chait and Bornfeldt, 2009). Injury to the endothelium can trigger a series of events that lead to atherosclerosis, a build-up of fatty deposits, reducing the diameter of blood vessels and restricting

blood flow; this is the most common form of blood vessel disease in diabetes.

Anything that can damage the endothelium or increase blood lipids (fats) can increase the rate of atherosclerosis. George and Johnson (2010) cite the following risk factors:

- Hypertension: in patients with high blood pressure, the force exerted on the internal lining of the vessel can mechanically damage the endothelial cells;
- Smoking: many of the chemicals in cigarette smoke cross from the lungs into the blood; some are highly damaging to endothelial cells;
- A diet high in saturated fat: this raises the level of circulating triglycerides and low-density lipoprotein (LDL) cholesterol, which in turn increases the amount of fat available for the formation of fatty deposits, leading to atherosclerotic occlusion.

In people with poorly controlled diabetes, the rate of atherosclerosis is much faster than in those with normal blood glucose control (Pasterkamp, 2013). It is therefore essential that people with diabetes pay

particular attention to maintaining their glucose levels within the normal range and avoid other factors that can accelerate blood vessel disease. Unfortunately, many patients with type 2 diabetes also have features of metabolic syndrome: they may be overweight or obese and have high blood pressure, both of which can contribute to blood vessel narrowing.

Peripheral vascular disease

Peripheral vascular disease (PVD) is an atherosclerotic narrowing of blood vessels that results in poor blood flow to the periphery, particularly to the hands and feet; it is particularly common and problematic in patients with poorly controlled diabetes.

Patients often get an early warning when their calf muscles start to ache and become sore when walking. This phenomenon is referred to as claudication and is caused by poor blood flow through diseased and narrowed blood vessels in the leg (Scott and Stansby, 2009). A lack of oxygen progressively leads to a painful build-up of lactic acid in the calf muscles. The poorer the blood flow, the more severe the PVD and the shorter the distance the person can walk before experiencing pain (often described as cramp). Patients often need to rest and rub their calf muscles until the pain dissipates before they can resume walking.

Peripheral neuropathy

A common feature of diabetes is progressive damage to nerves, particularly in the extremities. This peripheral (or sensory) neuropathy is often described as having a 'glove and stocking' distribution, reflecting the gradual loss of sensation in the hands and feet. There are two main reasons for this nerve damage:

- Poor blood flow: PVD diminishes blood flow to the nerves, which begin to shrink when deprived of oxygen and nutrients; some nerve fibres may eventually die;
- Build-up of sorbitol: hyperglycaemia causes glucose to flood into nerve fibres and the excess is converted into the sugar alcohol sorbitol, which can quickly build up, interfering with metabolism and causing osmotic stress; affected nerve cells start to atrophy and become less efficient in conducting impulses (Obrosova, 2009).

Peripheral neuropathy (PN) is often experienced as a loss of sensation in the affected region. This means patients might not realise they have injured themselves by

Table 1. Complications of diabetes

Macrovascular complications (involving larger blood vessels)	<ul style="list-style-type: none"> ● Peripheral vascular disease: often manifests early as claudication and may lead to diabetic foot ulcers, infection and amputation ● Coronary artery disease: often results in angina, or silent angina if sensory neuropathy is present ● Myocardial infarction: the leading cause of mortality in diabetes ● Cerebrovascular disease; often results in strokes and transient ischaemic attacks (mini-strokes) ● Sexual dysfunction: poor blood flow can lead to erectile dysfunction in men and loss of libido, vaginal dryness and pain during sex in women
Microvascular complications (involving smaller blood vessels)	<ul style="list-style-type: none"> ● Peripheral neuropathy: results in lack of sensation in the hands and feet, increasing the risk of injury ● Autonomic neuropathy: may cause reduced sweating, leading to the skin drying and cracking ● Diabetic nephropathy: the leading cause of end-stage renal failure ● Diabetic retinopathy: gradually leads to loss of vision
Non-vascular complications	<ul style="list-style-type: none"> ● Cataract: gradually reduces visual acuity and can lead to sight loss ● Poor wound healing: diabetes is often associated with poor immune function and slower tissue regeneration ● Opportunistic infections: hyperglycaemia increases the risk of infection (fungal, bacterial and viral), which is compounded by diabetic foot ulcers

stepping on something sharp or wearing shoes that are too tight. Such injuries, particularly on the soles of the feet, provide routes of entry for the infections commonly seen in diabetic feet (covered in part 3 of this series).

In some patients, PN can result in numbness, pins and needles or occasionally itchiness (paraesthesia); it can also result in the nerve endings becoming supersensitive to stimuli (hyperaesthesia) (Volmer-Thole and Lobmann, 2016). Hyperaesthesia can lead to extreme pain when the feet come into contact with hot or cold materials; for example, patients may find it impossible to have a warm bath or slip into cold bed linen.

Autonomic neuropathy

As well as the sensory nerves and nerve endings, the nerves of the autonomic nervous system may sustain damage from prolonged hyperglycaemia. One common manifestation of autonomic neuropathy is reduced sweat production in the feet.

The skin of the hands and feet is the thickest skin in the human body. To prevent it drying out, sweat production in hands and feet is generally greater than in other areas. Each sweat (eccrine) gland is controlled by an autonomic nerve fibre. If these fibres are damaged, sweat production is not stimulated and the skin, particularly on the feet, may dry and crack

(Volmer-Thole and Lobmann, 2016). This creates a potential entry route for pathogens and may lead to gangrene (see part 3).

Another common manifestation of autonomic neuropathy is gastroparesis. After a meal, food remains in the stomach for 2-4 hours while the autonomic nervous system initiates churning movements in the gastric wall to mix food with enzymes and hydrochloric acid produced by the stomach. Periodically, it opens the small ring of muscle (pyloric sphincter) at the bottom of the stomach, releasing small portions of partially digested material into the duodenum.

Damage to the autonomic nerves can lead to reduced churning and reduced (or no) opening of the pyloric sphincter. The result is gastroparesis – literally a 'paralysed stomach' – where partially digested food remains in the stomach for long periods, fermenting and producing large amounts of gas, causing bloating and nausea (Camilleri et al, 2011). Gastroparesis can reduce appetite and lead to significant weight loss, as well as hinder the ability to control blood glucose levels through diet.

Coronary artery disease

Patients with poorly controlled diabetes are prone to increased atherosclerosis of the coronary blood vessels, which supply blood to the heart. This narrowing of the

coronary arteries often leads to chest pain, particularly on exertion, after a heavy meal or when suddenly entering a cold environment: this is referred to as angina pectoris. Angina occurs because poor blood flow to the continuously active myocardium leads to a build-up of lactic acid in the cardiac muscle fibres (McCance and Huether, 2014).

Patients with sensory neuropathy may not experience the pain normally associated with angina; this is referred to as silent angina (Tabibiazar and Edelman, 2003). They are therefore at increased risk of silent angina and require more routine cardiovascular screening tests, such as stress electrocardiogram testing using treadmills, which can reveal underlying coronary artery disease.

The endothelial layer of blood vessels produces a simple molecule, nitric oxide (NO), which helps dilate blood vessels, keeping the rate of blood flow high. In people with diabetes, endothelial damage results in reduced production of NO, leading to less blood vessel dilation and poorer blood flow (Tessari et al, 2010). This can exacerbate angina by further depriving the myocardium of blood. The standard treatment for angina is glyceryl trinitrate administered sublingually, either in tablet or spray form; this increases the amount of NO in the blood, dilating blood vessels and quickly relieving symptoms.

Myocardial infarction

Myocardial infarction (heart attack) is the leading cause of death in people with diabetes (Kapur and De Palma, 2007). Coronary arteries that are severely narrowed by atherosclerosis can lead to a turbulent blood flow, which increases the risk of thrombosis (clot development) and plaque rupture (when fatty deposits are dislodged from the vessel wall). Clots or ruptured plaque can completely block a coronary artery, leading to the death of part of the heart muscle. If the infarction is large enough, the heart can no longer function and patients enter a state of cardiogenic shock, from which many will not recover.

Cerebrovascular accident

Diabetes, particularly with poor glycaemic control, significantly increases the risk of cerebrovascular accident (stroke) (Bit.ly/StrokeAssociationDiabetes). The brain receives most of its blood through the two internal carotid arteries in the neck. In patients with poorly controlled diabetes, these vessels are at increased risk of narrowing from atherosclerosis.

As described for coronary arteries, blood flow through these narrowed vessels can become turbulent, which can trigger plaque rupture or clot formation. Small clots or tiny fragments of dislodged plaque can travel into the cerebral circulation, blocking small blood vessels and causing a mini-stroke (transient ischaemic attack); this is a short-lasting event with symptoms that usually resolve within 24 hours. If larger clots or pieces of plaque (emboli) travel into the cerebral circulation, this will cause a more significant stroke, with permanent and sometimes life-threatening damage.

Sexual dysfunction

Damage to both sensory nerve endings and blood vessels can lead to poor blood flow to the penis during sexual arousal, leading to erectile problems and impotence. Erectile dysfunction is estimated to affect up to 50% of men with diabetes and its frequency increases with age. Women may experience a loss of libido and vaginal dryness, often resulting in pain during sexual intercourse (Bit.ly/DiabetesUKSex).

Diabetic nephropathy

Diabetes is the leading cause of end-stage renal failure (Wylie and Satchell, 2012). The elevated blood glucose levels seen in poorly controlled diabetes damage the delicate filtration membranes of the nephrons, the urine-producing units of the kidneys.

Intact filtration membranes prevent large molecules, such as proteins, from crossing from the blood into the nephrons, but glucose-damaged filtration membranes are more porous and therefore let larger molecules across (Fig 1). The beginning of diabetic nephropathy usually

corresponds to the gradual appearance of protein in the urine (microalbuminuria). Proteins in the urine are detectable using standard urinalysis strips.

Diabetic retinopathy

One of the most devastating consequences of poorly controlled diabetes is the gradual loss of vision seen in many patients. The retina (photosensitive region of the eye) receives a rich supply of blood through small blood vessels. In diabetes, the weakening of the walls of these vessels can lead to leakage of plasma and, if they rupture, blood onto the retina.

Retinal cells (rods and cones) that are exposed to blood quickly die off, leaving patches of retina that are no longer sensitive to light. These regions are perceived as 'black spots' which, as the disease progresses, expand and join up, reducing the field of view and eventually leading to complete loss of sight. The damaged blood vessels at the back of the eye release growth factors that promote the growth of new blood vessels (angiogenesis), but these often grow in abnormal tangles, further obscuring the visual field.

Diabetic retinopathy is a leading cause of blindness and affects up to 80% of patients who have had diabetes for 10 years or more (bit.ly/MoorfieldDiabRetinopathy). Early changes, before vision is affected, are often detected during a standard eye test; this is often patients' first indication that they may have diabetes.

Non-vascular complications

Cataract

Vision may also be compromised by cataract formation. The eyeball consists of two chambers: the anterior chamber, which is filled with a watery fluid called aqueous humour, and the posterior chamber, which is filled with a jelly-like material called vitreous humour. Sitting between the two chambers is the lens, which focuses light in the eye.

In patients with diabetes, both the aqueous and vitreous humours contain high levels of glucose, which enters the lens and is metabolised into sorbitol. This accumulates in the lens and, together with glucose, attracts water by osmosis. The lens begins to swell, damaging its internal structure, and takes on the opaque appearance indicative of cataract (Pollreis and Schmidt-Erfurth, 2010).

Poor wound healing

Consistently elevated blood sugar may interfere with immune function and

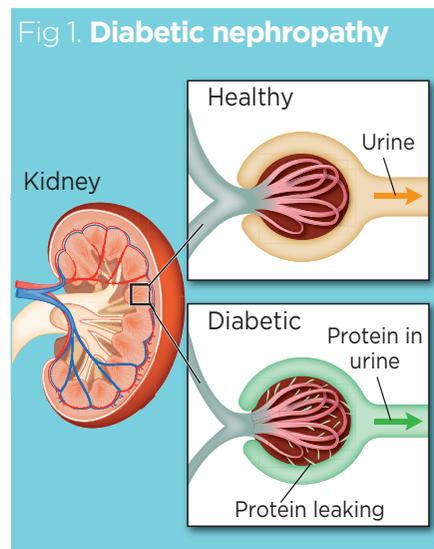


Fig 1. Diabetic nephropathy

wound healing mechanisms. Blood vessel disease with resultant poor blood flow will contribute to slower wound healing (see part 3 of this series).

Opportunistic infections

Hyperglycaemia can encourage a wide variety of microbial growth in different regions of the body. Glucose is an attractive energy source for many species of bacteria and fungi, including *Candida albicans*, which causes the common fungal infection known as thrush. It exists in two main forms (Mayer et al, 2013):

- **Yeast form:** unless growth is excessive, this oval form is generally less pathogenic; indeed most individuals harbour populations of candida on their skin, in their mouths and reproductive tracts;
- **Hyphal form:** when *C. albicans* is able to grow rapidly, it often changes its shape to elongated filaments called hyphae. This form is far more invasive and can attach to tissues such as the mucosa of the mouth and reproductive tract; this leads to the itching, irritation and soreness characteristic of thrush.

Increased availability of glucose allows *C. albicans* to grow rapidly and switch to its invasive hyphal form. Oral and vaginal thrush is a common problem in patients with diabetes, who may occasionally develop a widespread candida infection (systemic candidiasis).

In addition to fungal infections, the abundance of glucose in the blood and other bodily fluids provides a perfect energy source for many common bacteria. The enhanced growth of staphylococcal, streptococcal and clostridium species is particularly problematic in the diabetic foot, where ulcers and cracked skin provide a route of entry for pathogens (see part 3).

Patients with diabetes also appear to be more susceptible to many viral infections and may experience more severe symptoms. During influenza epidemics, patients with diabetes are up to six times more likely than the general population to need hospitalisation (Peleg et al, 2007); mainly because their respiratory secretions are rich in glucose, which may encourage secondary infection. Hyperglycaemia can also impair immune function, making

Box 1. Key guidance to reduce complications of diabetes

- **Blood glucose monitoring:** monitoring glycated haemoglobin (HbA1c) levels gives a good indication of glycaemic control over the last three months in type 2 diabetes. Readings of 7% (53mmol/mol) or below indicate good glycaemic control; 7.5% and above (58mmol/mol) means more aggressive interventions are required
- **Blood pressure monitoring:** in patients with type 2 diabetes who have no history of hypertension, blood pressure should be measured at least annually; in those with high blood pressure, antihypertensive medication should be introduced if lifestyle advice does not reduce blood pressure to below 140/80mmHg (or below 130/80mmHg if there is kidney, eye or cerebrovascular damage)
- **Fatty foods intake:** patients with diabetes should carefully control their intake of foods containing saturated and trans fatty acids, aiming to keep their total cholesterol level below 4mmol and their low-density lipoprotein cholesterol level below 2mmol (Bit.ly/DiabetesUKHealthGuidelines)

Source: National Institute for Health and Care Excellence (2016)

viral infections and the reactivation of dormant viruses more likely.

Keeping complications at bay

Many of the complications of diabetes are life changing or life threatening. However, patients who strictly control their blood glucose levels can delay, reduce the severity of, or even avoid these complications, most of which occur as a result of blood vessel disease. Box 1 highlights key current guidance on monitoring blood glucose, blood pressure and fatty foods intake.

Two types of medication can be helpful:

- **Antihypertensives:** although exercise will lower blood pressure in most people, medication may be needed to bring blood pressure within the normal range;
- **Statins:** many patients with diabetes are prescribed these cholesterol-reducing drugs to help normalise their blood lipid profile.

Key lifestyle changes are also effective in reducing the progression of atherosclerosis and its associated pathologies (NICE, 2016; Diabetes Research Institute 2009):

- **Moderate amounts of exercise:** even light exercise such as walking for 30 minutes a day has been shown to improve the lipid profile, reducing the levels of triglycerides and LDL cholesterol while raising the level of high-density lipoprotein cholesterol, which protects blood vessels;
- **Dietary measures:** increasing intake of oatmeal, oily fish and certain seeds and nuts has a beneficial effect on the lipid profile; reducing the level of saturated animal fat is also recommended;
- **Stopping smoking:** this will reduce additional endothelial damage caused by the toxins from cigarette smoke. **NT**

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Diabetes management series Date

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| Part 1: types, symptoms and diagnosis | April |
| Part 2: long-term complications | April |
| Part 3: the diabetic foot | May |

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- The role of diet and exercise in type 2 diabetes management
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