



What are the complications of diabetes?

One of the main considerations with hyperglycaemia (raised blood sugar level) is the impact of chronic exposure to high blood sugar levels on the organs in the body and specifically the blood vessels. Long-term, hyperglycaemia can cause persistent damage to the blood vessels which can result in further organ damage and highlights one of the main reasons why it is imperative to ensure blood sugar levels are at the appropriate range. Traditionally complications of diabetes are classified according to the size of the blood vessels affected and are termed microvascular and macrovascular. More recently, there has been acknowledgement that there are certain 'extravascular' complications that are equally as important such as psychological/mental health impact of diabetes.

Microvascular complications

This is the term given to complications that arise as a result of the damage in the smaller blood vessels of the body due to chronic hyperglycaemia. The main 3 complications are retinopathy, nephropathy and neuropathy. Chronic hyperglycaemia leads to extravasation of fluid from the small blood vessels in the body, inflammation and damage.

The UKPDS and DDCT trials showed that reduction in HbA1c by 1% resulted in 37% reduction in development of microvascular complications. This highlights that any reduction in HbA1c would have positive impact on complications and forms the mainstay of why glucose lowering is so important.

- Retinopathy:
 - Chronic hyperglycaemia to the blood vessels that supply the retina can lead to inflammation, vessel blockage and damage. It also results in formation of new, weaker blood vessels resulting in leakage of fluid and further damage to the retina. This can then lead to a reduction in vision and ultimately blindness. Diabetic retinopathy is the leading cause of blindness in the working age population in the UK.
 - There are three main stages of retinopathy:
 - R1 or background retinopathy
 - R2 or pre-proliferative retinopathy
 - R3 or proliferative retinopathy
 - If the macula, which is a specific part of the retina, is affected then this is called maculopathy (M1).
 - People with diabetes, regardless of the type, are enrolled on to a regular retinal screening programme and invited to attend for their eye screens. This may initially be 1-2 yearly with frequency increased depending on stage of retinopathy and if treatment is required. They may not notice this damage to the retinas until later stages when their vision is affected, hence the need for screening.
 - The mainstay of treatment for retinopathy is prevention and early detection through optimisation of blood sugars and reducing the time spent with hyperglycaemia/sugars above target range and attendance at the screening invitations to ensure any early changes are picked up.
 - Where retinopathy is established and neovascularisation (new blood vessels) has occurred, then there may be specific treatment options such as intravitreal injections or laser treatment.

- Nephropathy:
 - The small blood vessels that supply the kidney and specifically the nephrons (which carry out the filtration processes) are affected by chronic hyperglycaemia.
 - This results in inflammation and changes in the nephron that cause further damage and impact the filtering ability of the kidneys initially for small protein molecules (specifically albumin) then, as damage continues, with larger protein molecules passing through.
 - These can be picked up in the urine and classified based on albumin amounts compared to creatinine levels (i.e. the urinary albumin: creatinine ratio (uACR)). This forms the basis of annual diabetes reviews with urine testing.
 - Microalbuminuria is defined as uACR 3-30mg/mmol from a urine sample.
 - Macroalbuminuria is defined as uACR >30mg/mmol from a urine sample.
 - Generally development of nephropathy is associated with presence of retinopathy.
 - Patients may not notice this until very late when they have advanced kidney failure though some may notice frothy urine as a result of excess protein leakage.
 - If left untreated damage to kidneys can progress and lead to end stage dialysis, renal failure and increase risk of mortality.
 - Improving HbA1c is the mainstay of treatment as well as reducing further impact on kidneys with blood pressure reduction. There are also medications (sodium glucose co-transporter 2 inhibitors - SGLT2 inhibitors) that, irrespective of glucose lowering, have been shown to reduce progression of kidney disease.
- Neuropathy:
 - Damage to the small blood vessels that supply the peripheral nerves in the body causes damage and loss of sensation resulting in diabetic peripheral neuropathy with the hands and feet affected first (a so called 'glove and stocking' distribution).
 - Patients may complain of pins and needle, pain or loss of sensation in their extremities. In advanced cases they may not realise they are damaging their feet due to loss of sensation and develop wounds and ulcers which are worsened by poor blood supply and reduced healing.
 - Neuropathy is assessed at the annual review by checking sensation in the hands and feet.
 - Whilst there is no specific treatment for neuropathy, improving glucose control as with other complications is beneficial and medications are possible to treat the associated pain.

Macrovascular complications

This is the term given to complications that arise as a result of the damage in the larger blood vessels in the body. The main complications are cardiovascular disease, cerebrovascular disease and peripheral arterial disease. People with diabetes are at higher risk of blockages to the larger blood vessels via process called atherosclerosis. This results in reduced blood flow to the main organs supplied by these vessels - namely the heart, brain and lower limbs. This can increase the risk of angina and myocardial infarctions (heart attacks), strokes and ischaemic limbs.

Whilst improving glucose control is of benefit, it does not directly reduce the progression of macrovascular complications but is part of multiple risk factor management such as avoiding smoking, cholesterol reduction and blood pressure lowering. Recently, medications such as certain SGLT2 inhibitors and GLP-1 receptor agonists have been shown to reduce the risk of some of these complications.

Summary

Effective management involves not only tight control of blood glucose but also addressing co-morbid factors such as hypertension, dyslipidemia, and lifestyle. Regular monitoring and early intervention can help reduce the burden of complications and improve the quality of life for people with diabetes.

References

- Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000 Aug 12;321(7258):405-12
- Diabetes Control and Complications Trial (DCCT): results of feasibility study. The DCCT Research Group. *Diabetes Care*. 1987 Jan-Feb;10(1):1-19
- King P, Peacock I, Donnelly R. The UK prospective diabetes study (UKPDS): clinical and therapeutic implications for type 2 diabetes. *Br J Clin Pharmacol*. 1999 Nov;48(5):643-8
- Beckman JA, Creager MA. Vascular Complications of Diabetes. *Circ Res*. 2016 May 27;118(11):1771-85.
- Under the lens: diabetic retinopathy. *The Lancet Diabetes & Endocrinology*, Volume 8, Issue 11, 869