

SECTION 12

Long term complications

A major goal in the management of diabetes is to **prevent** or **delay** the occurrence of long term complications.

Long term complications of diabetes present as either microvascular or macrovascular complications.

Macrovascular complications result from damage to major blood vessels and can include:

- coronary heart disease
- cerebrovascular disease (eg stroke)
- peripheral vascular disease.

Microvascular complications result from damage to smaller blood vessels and nerves and can include:

- nephropathy
- retinopathy
- neuropathy.

In both type 1 and type 2 diabetes the microvascular and macrovascular complications of diabetes substantially increase a persons morbidity and mortality. Two landmark studies the Diabetes Control and Complications Trial (DCCT)¹ and the United Kingdom Prospective Diabetes Study (UKPDS)² have demonstrated that a reduction in HbA1c can substantially lower the risk of long term complications.

In 1993 the DCCT showed unequivocally in type 1 diabetes that lowering blood glucose delayed the onset and slowed the progression of microvascular complications. These risk reductions varied from 35 to 75% amongst the microvascular complications. A reduction in macrovascular complications was seen but it did not reach significance (this may have been due to the small numbers of complications seen in the time frame). It was important to assess if these reductions would also be seen in type 2 diabetes and in 1998 the results from the largest and longest study on people with type 2 diabetes was published (UKPDS).² The UKPDS results demonstrated that retinopathy, nephropathy and possibly neuropathy are benefited by lowering blood glucose levels. The overall microvascular complication rate was decreased by 25%. As in the DCCT trial there was a reduction in cardiovascular complications but it did not reach significance. The study showed that lowering blood pressure significantly reduced strokes, diabetes-related deaths, heart failure, microvascular complications and visual loss.² The UKPDS was a landmark study which has resulted in a much more aggressive approach to the treatment of hyperglycaemia, hypertension and other associated risk factor reduction strategies.

Long term follow up of participants from the original DCCT and UKPDS groups have demonstrated a legacy effect associated with achieving glucose targets early in the course of diabetes even when this level of control is not maintained some years later.^{3,4}

It is important to be aware of the possible long term complications which may occur in a person with diabetes in order to:

- assist in educating the person about risk factors and indicators of long term complications
- assist in early detection and monitoring of existing problems
- assist in the management of complications which may already be present.

Note: Our aim in this manual is to alert health care providers to the types of problems which may occur. More extensive reading is required if you wish to study the pathophysiology relating to long term complications.

Prevalence

In 2005, diabetes was listed as an underlying or an associated cause of death in 11,900 deaths (9% of all deaths in that year).⁵

Prevalence of diabetes complications in type 2 diabetes in South Australia⁶

Complication	People with diabetes with complications (n=173)	
	%	95% confidence intervals
One or more microvascular condition	66.1	58.3 – 73.9
One or more macrovascular condition	52.7	44.5 – 60.9
IHD*	34.4	26.7 - 42.1
PVD*	31.9	24.3 - 39.5
IHD & PVD	13.7	8.1 - 19.3
Microalbuminuria	26.6	19.4 - 33.8
Macroalbuminuria	7.9	3.3 - 12.0
Neuropathy	47.9	39.9 - 55.9
Retinopathy (n=139)#	19.0	12.6 - 25.4

*IHD=ischaemic heart disease; PVD=peripheral vascular disease.

#n = 139 assessed for retinopathy

Macrovascular disease

Macrovascular disease accounts for 75% of diabetes related deaths.⁷ In macrovascular (large blood vessel) disease, damage to the vessel linings leads to thickened and blocked arteries. Macrovascular disease can result in heart attack, stroke, reduce blood flow to lower limbs causing slow healing of cuts and scratches on the feet, and high blood pressure.

Various forms of macrovascular disease tend to occur in the same individual. Thus people with diabetes undergoing operations for peripheral vascular disease are at special risk of peri-operative myocardial infarction or stroke. Assessment includes checking for risk factors and indicators of macrovascular disease.

Risk factors for macrovascular disease	
Fixed age >50 years family history of cardiovascular death under 60 years	Modifiable smoking hypertension hyperlipidaemia obesity (BMI >30) polycythaemia poor glycaemic control

Management of risk factors will reduce the risk of developing macrovascular disease.

Indicators of macrovascular disease	
What can go wrong angina, myocardial infarct transient ischaemic attacks cerebrovascular accident (stroke) claudication lower limb	What are we looking for absent / reduced pulses or bruits abnormal fundal arterioles abnormal resting ECG

People with type 2 diabetes should be considered for prophylactic aspirin therapy unless contraindicated.⁷

Hypertension

Diabetes is a major risk factor for the development of hypertension.⁸ Untreated high blood pressure accelerates the blockage of arteries and increases the risk of heart attacks, stroke and peripheral vascular disease. The aim is to get values under 130 systolic and 80 diastolic, and <125/75 if proteinuria >1g/d present.⁷

Early detection, active treatment and frequent review are essential if morbidity is to be reduced. The treating medical officer / general practitioner should aim for lower blood pressure levels in the person with diabetes because their blood vessels (both macro and micro) are more susceptible to hypertension damage (eg $\leq 130/80$).⁹ Non-pharmacological treatment, especially maintenance of healthy weight, regular exercise and minimisation of salt and alcohol in the diet, should be emphasised.

There are various anti-hypertensive agents which can be used to control blood pressure, however there are some medications which may interfere with the control of diabetes. Agents such as the angiotensin converting enzyme (ACE) inhibitors are medications of choice in people with hypertension and diabetes.⁷ They do not affect glucose metabolism or lipid profiles and have beneficial effect on renal and cardiovascular function. Both lying and standing blood pressure must be assessed.

Angiotensin receptor antagonists (ARA's) have a role for people with micro or macro albuminuria when ACE inhibitors are not tolerated.⁹

Hyperlipidaemia

Hyperlipidaemia is frequently observed in diabetes and hypertension. Hyperlipidaemia is a common finding in people with diabetes. Dyslipidaemia is an independent risk factor for the macrovascular complications of diabetes. It is therefore important to identify and treat hyperlipidaemia. Often a poor lipid profile with persistent hyperglycaemia results in hypertriglyceridaemia. The triglyceride level will often drop to acceptable levels when adequate control of weight, diet and glycaemia is achieved. Cholesterol levels will often fall with weight reduction and metabolic control of diabetes.

The dietary management of dyslipidaemia is similar to that of diabetes. The diet should be low in saturated fat and total fat. If dietary measures fail pharmacological treatment should be instituted. The usual first line medication for isolated hypercholesterolaemia are statins.⁷ Adherence is good and they are extremely effective.

	Target Levels⁹
Total cholesterol	<4.0mmol/L
Triglycerides	<1.5mmol/L
HDL – C	>1.0mmol.L
LDL – C	<2.5mmol/L

Smoking

Smoking is by far the most powerful treatable risk factor for macrovascular disease for people with diabetes.^{10, 11} The added risk from smoking is compounded in comparison with people without diabetes.

There is evidence that minimal intervention in the general practice setting can improve cessation rates. The diagnosis of diabetes is often a crisis point for the person, and can be an opportunity to bring about cessation of smoking.

The health care provider can assist a person to quit by:

- recording the smoking status of the person
- determining the stage of readiness of the person (pre-contemplation / contemplation, etc)
- offering advice when the person is in the contemplative stage of quitting
- offering advice on the use of nicotine adjunctive therapy.

The national QUITLINE contact is 13 7848.

Cardiovascular risk profiles

As previously mentioned diabetes is a risk factor for cardiovascular disease (CVD). The National Heart Foundation has developed an Australian risk chart that can be used to estimate a 5 year risk level for CVD. These charts can be used by health professionals to demonstrate the level of risk for an individual. Using coloured squares the chart clearly demonstrates how risk can be decreased by addressing risk factors such as smoking, lipids and blood pressure. It can be used as a tool to explain to a person why certain risk factors are a priority. The tool can be accessed at http://www.heartfoundation.org.au/Professional_Information/Clinical_Practice/Pages/default.aspx.

Microvascular disease

Microvascular disease refers to disease of the small blood vessels associated with thickening of the basement membranes.

Consequences are: kidney damage – nephropathy
eye disease – retinopathy
nerve damage – neuropathy

Kidney damage – nephropathy

This is one of the microvascular complications and is closely related to hyperglycaemia and hypertension. In turn renal impairment aggravates hypertension and a vicious cycle develops. Early detection is important so that blood pressure and glycaemic control can be improved.

Microalbuminuria provides the easiest warning of renal damage, however once microalbuminuria is present, damage has already occurred. Proteinuria however is the hallmark of nephropathy and represents irreversible renal damage. The time of onset of proteinuria and the rate of increase is variable. Once clinical proteinuria occurs (dip stick positive, >500mg/day) progressive renal damage is likely. The rate of decline in renal function is accelerated by hypertension. Microalbuminuria should be checked annually as an early screening.

Goals for management of urinary albumin excretion:

- <20 µg/min timed overnight collection
- <20 mg/L spot collection
- <3.5 mg/mmol women, <2.5 mg/mmol men (albumin creatinine ratio)

Risk factors for diabetic nephropathy ¹²	
Fixed hereditary age duration of diabetes impaired renal function	Modifiable glycaemia dyslipidaemia cigarette smoking hypertension

The significance of proteinuria is as follows:⁹

- ten year survival is poor once persistent, significant proteinuria is present (ie 2+ or more)
- retinopathy often occurs simultaneously with nephropathy. The person should be reviewed for retinal problems and have treatment initiated (eg photocoagulation) if necessary.
- hypertension should be treated aggressively and blood pressure maintained at levels <130/80 (<125/75 if proteinuria >1g/d exists) in order to slow the progression of nephropathy
- urine should be screened regularly for infection, a common exacerbating factor in diabetic nephropathy.

If a kidney problem is suspected and the presentation is atypical think of less common problems related to diabetes – eg papillary necrosis and arterial disease.

Eye disease – retinopathy

Retinopathy occurs in one third of people with diabetes therefore regular review by an ophthalmologist or optometrist should occur at the time of diagnosis and then at least every 2 years. For children with the onset of diabetes pre-puberty, screening of eyes should occur at puberty.^{9, 13}

Retinopathy occurs as a result of microvascular disease of the retina. Loss of acuity not corrected with pinhole testing may be due to retinopathy.

Changes seen are:

- dot and blot haemorrhages
- soft and hard exudates
- proliferative blood vessel formation.

Damage affecting the retina responsible for control, colour and fine vision (maculopathy) is the most common cause of visual loss in people with diabetes.

Other eye problems like glaucoma and ischaemic neuropathy are also more common in people with diabetes.

Risk factors for diabetic eye disease	
Fixed age duration of diabetes family history (cataracts/retinopathy) other eye problems such as glaucoma, myopia other microvascular disease	Modifiable hypertension hyperlipidaemia polycythaemia poor glycaemic control smoking

Nerve damage – neuropathy

Foot problems cause a large proportion of all amputations and of hospital bed days. Many problems can be prevented by an organised program of education and supervision.^{14, 15}

Prevention is the most important aspect of management of the person's feet. Early and regular screening of feet to assess potential abnormal architecture and regular review of neuropathy, vascular disease or deformity is essential. Subsequent referral to podiatry services for those people with at risk feet is imperative.¹⁵

Features of peripheral neuropathy may be acute and / or chronic, sensory and / or motor, somatic and / or automatic. The commonest form is an insidious, unremitting sensory neuropathy.¹⁴

The aetiology of peripheral neuropathy is probably multi-factorial, ischaemic (microvascular) and metabolic (sorbitol accumulation and myoinositol depletion). Both components are affected by glycaemic control and may be related.

Risk factors for diabetic neuropathy	
Fixed long duration of diabetes age over 60 years other microvascular complications	Modifiable poor glycaemic control ethanol (alcohol) more than 4 drinks per day

Neuropathy can also be categorised as autonomic.

Autonomic neuropathy may result in:

- orthostatic hypotension
- impaired gastric emptying
- diarrhoea
- delayed / incomplete bladder emptying
- erectile impotence and retrograde ejaculation in males
- reduced vaginal lubrication with arousal in women
- loss of cardiac pain and 'silent' ischaemia or infarction
- sudden, unexpected cardio-respiratory arrest especially under an anaesthetic or treatment with respiratory depressant medications
- difficulty recognising hypoglycaemia.

Neuropathy associated with peripheral vascular disease is the major risk factor for foot problems. Ulcers and infections which lead to amputation can be asymptomatic in people who cannot feel their feet. Other risk factors for podiatric problems include:

- vascular disease alone
- abnormal foot structure
- lack of self care.

Ulcers

The most common site for ulceration is the plantar surface of the foot, directly under the metatarsal head. Abnormal shearing forces (such as movement within a shoe) can cause a bruise under the epidermis. Infection then intervenes; the overlying skin or callus becomes necrotic, sloughs and reveals an ulcer. Complications include cellulitis, thrombotic arterial occlusion and gangrene.

If the ulcer is deep, or if cellulitis is present, hospitalisation and bed rest are usually necessary. Subsequent antibiotic treatment and appropriate diabetes management will be required. Inappropriate management of an ulcer can lead to osteomyelitis and amputation. A podiatrist, endocrinologist and vascular surgeon should be involved in the care and management of the acute diabetic foot.⁹

If ulcer is not infected and is superficial, care can be ambulatory. Only health professionals who are experienced at managing diabetic foot ulcers or a podiatrist should remove excess callus from around the ulcer to facilitate drainage. The person should be encouraged to keep pressure off the lesion as much as possible to encourage wound healing. Continual pressure on the surface of an ulcer can cause delayed healing. Consult a podiatrist for advice about footwear modification to alleviate pressure.

Foot care

Preventative foot care is an important aspect of management. Early foot risk assessment and self care education is essential. Refer to *Footcare* – Section 6 for more in-depth information.

Neuropathic joint damage

A painful, swollen, reddened and / or hot foot is not always due to infection. It is important to differentiate between infection and Charcot's arthropathy as the treatment is very different. This damage can occur as a result of minor trauma. Initial X-ray can be normal but serial X-rays will show fracture, new bone formation and joint disorganisation. The metatarsal joints are most commonly affected but the ankle and metatarso-tarsal joints can also be affected. An early bone scan will confirm the diagnosis. Differentiation from osteomyelitis or septic arthritis can usually be made by a normal white cell count and absence of fever.

Treatment is with non-weight bearing crutches, appliances fitted by a podiatrist to reduce further damage and possibly a below knee cast until inflammation has subsided.

Sexual function

It is important to inquire about this in the annual screening because the prevalence in men over 40 years old with diabetes may be as high as 50%.⁹

It is important to differentiate psychogenic from organic erectile impotence. Usually inquiring about spontaneous erections while asleep or in non-sexual situations will help. Psychogenic impotence requires counselling and behavioural therapy. People with organic impotence should be counselled supportively.

The help of a sympathetic specialist urologist should be sought for those considering penile injection with vasoactive agents (preparations now commercially available) or surgical treatment.

Women with diabetes do not seem to suffer from as much sexual dysfunction as men. Some women with diabetes complain of impairment in vaginal lubrication with arousal, presumably due to pelvic autonomic neuropathy. Explanation and use of lubricants may be useful.

Other problems

Diabetes, its complications and hyperglycaemia may cause other problems.

Thrush

Poor glycaemic control predisposes to refractory moniliasis (thrush). Other predisposing factors include the oral contraceptive pill and antibiotic therapy.

Urine infections

Urinary tract infections are more common and more refractory, especially in women with diabetes. Incomplete bladder emptying may contribute and may require drug or surgical therapy. Urinary tract infections may be asymptomatic and should be looked for especially in women (eg by a dipstick testing for blood, pyuria and bacteriuria).

Skin infections

High blood glucose levels and glycosuria encourage the growth of monilia (thrush) and a number of bacteria (especially staphylococci). Often these infections persist until blood glucose levels are controlled.

Refractive changes

Can occur because of high blood glucose levels.

Cataracts

Can occur because of long term osmotic effect on the lens.

Dental and periodontal problems

Dental and periodontal problems are more common in people who have diabetes. Regular dental review and good oral hygiene is important.

What to discuss with your doctor

Your eyes

- Early detection means early treatment.
- If you have type 2 diabetes, have your eyes checked at diagnosis and every 1-2 years depending on risk factors.
- If you have type 1 diabetes, have your eyes checked within 5 years from diagnosis, then 1-2 yearly depending on risk factors.

Your blood pressure

- Have your blood pressure checked at each visit. Treatment of high blood pressure can prevent or minimise further diabetes complications.

Your feet

- Have your feet checked every six months. The health professional should check the skin, pulses and sensation in your feet. Remember to wear shoes and socks that are easy to take off.
- Know if your feet are at risk and have a footcare action plan.

Your weight and height

- Keeping your weight stable (or losing weight if overweight) will help manage blood glucose levels.
- Check your weight regularly.

Your insulin injection sites (if applicable to you)

- Your doctor needs to examine your injection sites because problems at these sites can make your diabetes control worse.

Your teeth

- Visit your dentist regularly to ensure any existing problems are treated immediately.
- Learn how to take care of your mouth, gums and teeth.
- Tell your dentist you have diabetes.

Your exercise plan

- It is important to see your doctor before starting a new exercise program.
- Your doctor can make sure your exercise program is safe for you.

Pathology tests

Become interested in the tests ordered by your doctor, and know your numbers.

Common ones are:

- **Glycosylated haemoglobin**
This test is usually done 3-4 times a year and shows your overall blood glucose control over the past three months. Target is less than 7%.
- **Cholesterol**
Have this measured every year. High cholesterol is a risk for heart attacks (coronary artery disease) and circulation problems. Total cholesterol target is less than 4.
- **Microalbuminuria**
First morning urine collected and done each year.

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