DIABETES MELLITUS: CHRONIC COMPLICATIONS

Many of the chronic complications of diabetes can be prevented with correct management of the disease.

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Long-term diabetes mellitus leads to clinically recognisable complications in both type 1 and type 2 diabetes. Type 1 diabetes accounts for 5 - 10% of all diabetes cases, and around 90% of diabetics in the world have type 2 diabetes. Diabetes affects about 170 million people worldwide with an expected further projected increased incidence of 50% by the year 2010. It is anticipated that most of the increase will occur in developing countries. Complications associated with diabetes result in socioeconomic and disease burdens that put an enormous strain on the health care systems of many countries in the world, including those of South Africa.

Insulin resistance, partly related to obesity and pancreatic beta cell function decline, is an early manifestation of type 2 diabetes. In type 1 diabetes there is destruction of the pancreatic beta cells which leads to absolute insulin deficiency. Both diseases have a strong genetic component.

The chronic complications associated with long-term diabetes mellitus are serious, devastating to the sufferers, and lead to premature and increased morbidity and mortality. Adults with diabetes have an annual mortality that is double that of non-diabetic adults. While many of the complications may be prevented or delayed by good management, once present they are largely irreversible.

Various risk factors interact with diabetes to affect the disease and its complications. These are:
- hypertension
- smoking
- hyperlipidaemia (specifically low-density lipoprotein (LDL) hypercholesterolaemia).

Attention to risk factors, together with tight control of blood glucose, anticoagulation and a sustained increase in physical activity, will lessen the incidence and retard the onset of most diabetic complications. Generally, diabetes leads to accelerated atherogenesis and atherosclerosis, which in turn leads to microvascular and macrovascular disease.

MICROVASCULAR COMPLICATIONS

The incidence and progression of microvascular complications are strongly related to glycaemic control. In the UK Prospective Diabetes Study (UKPDS) of patients with type 2 diabetes, intensive control of glucose levels that lowered glycated haemoglobin (HbA_{1c}) by an average of 0.9% compared with conventional treatment, resulted in a 25% reduction in the overall microvascular complications. It was also estimated that for every 1% reduction in HbA_{1c} concentration there is a 35% reduction in microvascular disease. In the Diabetes Control and Complications Trial (DCCT) that involved patients with type 1 diabetes mellitus, microvascular complications were reduced by 34 - 74% in patients on intensive insulin therapy.

Diabetic retinopathy

The cause of diabetic retinopathy has been hypothesised as endothelial dysfunction that leads to capillary occlusion, leakage and regression, causing ischaemia. This ischaemia results in neovascularisation with subsequent proliferative retinopathy. However, vision-threatening retinopathy is usually due to neovascularisation in type 1 diabetes and to maculopathy in type 2 diabetes. One-fifth of patients with newly diagnosed type 2 diabetes have retinopathy. Vision-threatening retinopathy almost never occurs in the first 5

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years after diagnosis or before puberty in type 1 diabetes. Almost all patients with type 1 diabetes and two-thirds of those with type 2 diabetes have non-proliferative retinopathy (previously called background retinopathy) after 15 years. Retinopathy is the leading cause of blindness in people aged between 30 and 69 years in the developed world.

The following are recognisable stages in the progress of retinopathy:

- **Early non-proliferative stage** (previously called background retinopathy). At this stage there are microaneurysms, hard exudates and small blot haemorrhages. This appears in almost all individuals with type 1 diabetes who have had the disease for about 20 years. Maculopathy can be present at this stage and it is the predominant lesion in type 2 diabetic retinopathy. It may be ischaemic, exudative or oedematous. This will cause central visual loss, e.g. reading difficulty.
- **Pre-proliferative retinopathy** is the next stage. In this stage there are cotton-wool spots, venous abnormalities, large blot haemorrhages and microvascular abnormalities.
- **Proliferative retinopathy** is characterised by new vessel formation on the disc and elsewhere on the retina. There is extensive fibrovascular proliferation. There is a risk of retinal detachment, vitreous haemorrhage and thrombotic glaucoma.

In type 1 diabetes, screening for diabetic retinopathy should begin 5 years after diagnosis in individuals of 15 years of age or older. The presence of diabetic retinopathy requires laser therapy. It also requires special attention to blood pressure, lipid and glycaemic control. Treatment of proliferative retinopathy and maculopathy with laser therapy prevents further visual loss and will not restore diminished visual acuity.

Other ocular manifestations of diabetes may be apparent during the examination of the eye and these are: optic nerve neuropathy, third and fourth cranial nerve neuropathy and cataracts.

Diabetic neuropathy

The mechanism of hyperglycaemia in causing neuropathy involves a complex interaction between neurotoxic products that are produced by abnormal metabolic pathways (e.g. peroxynitrite), oxidative damage and ischaemia. Diabetic neuropathy may be focal or generalised. Focal neuropathy involves isolated peripheral or cranial nerves. The commonest form of generalised neuropathy is sensorimotor polyneuropathy. This usually presents as a diffuse peripheral polyneuropathy affecting mainly the feet. Because of the diffuse nature of this condition autonomic nerve function will also be affected. This will cause cardiac dysfunction as evidenced by orthostatic hypotension, tachycardia or bradycardia. Erectile dysfunction, troublesome diarrhoea, constipation and gastroparesis are other characteristic autonomic neuropathy features. Alleviation of neuropathic pain can present a serious challenge to any clinician. Non-steroidal anti-inflammatory drugs, anticonvulsants, tricyclic antidepressants and second-generation antidepressants such as SSRIs have been used with some success.

The loss of protective sensation coupled with poor peripheral circulation can lead to the development of ulcers of the lower limb. Because of peripheral vascular disease, these ulcers do not heal easily and can rapidly lead to gangrene, resulting in a need for amputation. Good foot care is essential to minimise ulceration.

Glycaemic control is important to reduce neuropathic complications. There was a 36% reduction in the risk of neuropathy in patients with type1 diabetes practising intensive versus conventional glycaemic control who were followed up for 8 years after completing the DCCT. Screening for neuropathy should be done at regular intervals. Loss of sensation in the feet should be tested with a 10 g monofilament.

Diabetic nephropathy

Diabetic nephropathy is characterised by proteinuria, increased blood pressure and progressive renal function decline.

The disease progresses through a series of recognisable steps. The first stage is the subclinical disease stage. This is followed by the earliest detectable phase of microalbuminuria, defined as a urinary albumin excretion rate of > 20 µg and < 200 µg per day. The next stage is overt nephropathy (macroalbuminuria with renal dysfunction), which is defined as an albumin excretion rate of > 200 µg per day. This is end-stage renal disease.

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course of the disease. Positive tests must be further confirmed by urine spot check for the albumin-creatinine ratio. Persistent positive results are a compelling indication for starting renal protective measures. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor-blocking (ARB) agents are the drugs of choice to slow the progression of renal disease in these patients. These agents have renoprotective effects above those that can be attributed to blood pressure-lowering properties. They are beneficial even in normotensive patients and can ameliorate other complications.

In hypertensive diabetics, such as in type 2 diabetes patients, ACE inhibitors are still preferred as the first line of treatment. However, achieving blood pressure control is more important than the choice of the agent.

MACROVASCULAR COMPLICATIONS

Atherosclerosis is the cause of large-vessel disease. Smoking, high blood pressure, hyperlipidaemia and proteinuria are particularly important risk factors for atheromatous large-vessel disease in diabetics. Seventy per cent of all deaths in people with type 2 diabetes are attributable to cardiovascular disease. In type 1 diabetes the relative risk of cardiovascular disease is around 10 times greater than that in the general population.

The risk factors for cardiovascular disease in type 1 diabetics include the presence of diabetic nephropathy, autonomic neuropathy, dyslipidaemia and hypertension. Predictors of cardiovascular mortality in type 1 and type 2 diabetes are listed in Table I.

Risk reduction for cardiovascular disease requires attention to weight control, physical activity, optimum glycaemic and blood pressure control and smoking avoidance. In type 2 patients the lipid profile is atherogenic with a high concentration of LDL cholesterol. Hypertension affects about half of all diabetic patients, probably as a consequence of hyperinsulinaemia (type 2 diabetes), endothelial dysfunction and nephropathy. In the UKPDS it was shown that tight blood pressure control significantly reduces the risk of stroke, heart failure and diabetes-related deaths.

Ischaemic heart disease

The incidence and severity of ischaemic disease is increased in diabetic patients. They suffer a worse immediate and long-term prognosis following presentation with a myocardial infarct or unstable angina. These patients are at a substantially higher risk of developing heart failure after an infarct than those without diabetes.

The following are other features of ischaemic heart disease among diabetic patients:

- The protective effect of the female sex is lost among these patients.
- There is a higher incidence of diffuse multivessel disease.
- Plaque rupture leading to unstable angina is more common.
- Complications following myocardial infarct are more common.
- Mortality is reduced by insulin glucose infusion if given immediately after the event.

Two major secondary prevention studies (the 4S: Scandinavian Simvastatin Survival Study, and the CARE trial: Cholesterol and recurrent events trial) of cholesterol reduction show that statins are beneficial in the diabetes subgroups. Recommendations on prevention of coronary heart disease in clinical practice are given in Table II.

Peripheral vascular disease

Atherosclerotic disease in the blood vessels of the legs affects mostly the distal vessels, producing diffuse lesions that are less amenable to bypass surgery or dilation angioplasty. The earliest clinical sign of peripheral vascular disease (PVD) is intermittent claudication in the legs when the patient takes a walk. Claudication can be relieved after a period of rest. Because gravitational pull may aid lower limb perfusion when the patient is upright during the day, claudication may return to trouble the patient at night. Patients with PVD have a high 10-year mortality. Signs of ischaemia include cool to cold extremities, absent pulses, dependent rubor, delayed venous filling, blanching on elevation, shiny atrophic skin and loss of hair on the legs. Ultimately this leads to subcutaneous tissue atrophy and eventually to gangrene.

Medical management includes a walking programme, risk factor modification such as cessation of smoking, and antiplatelet medication. The aim of revascularisation is

Table I. **Predictors of cardiovascular mortality** (Adapted from *BMJ* 2000; **320:** 1062 - 1066)

Type 1 diabetes	Type 2 diabetes
Overt nephropathy	Presence of coronary heart disease
Hypertension	Overt proteinuria
Smoking	Glycated haemoglobin
Microalbuminuria	Hypertension
Age	

Table II. **Recommendations on prevention of coronary heart disease in clinical practice** (Adapted from *BMJ* 2000; **320**: 1062 – 1066)

	Glycaemic control	Blood pressure control	Lipid control
Target	Glycated haemoglobin < 7.0% Fasting blood glucose 4 - 7 mmol/l	< 140/80 mmHg without macrovascular disease < 130/80 mmHg with macrovascular disease	Serum cholesterol < 5.0 mmol/l in patients with established coronary heart disease Primary prevention in those with > 305 points on risk of coronary heart disease over 10 years
Treatment (in addition to lifestyle and dietary advice)	Metformin (first line if BMI > 25) Sulphonylurea Glitazones Insulin Combination therapy	ACE inhibitors: renoprotective, caution in renal artery stenosis Diuretics β blockers α blockers Long-acting calcium antagonists 50% of patients will require > 3 drugs for optimum control	Statins

for the relief of lifestyle-limiting claudication and limb preservation. Revascularisation will not reverse neuropathy and some of the indications for this procedure are pain at rest, ulcer and non-healing wounds.

The diabetic foot

Foot ulceration, sepsis and amputation are among the most feared complications of diabetes. Foot care techniques tend to minimise the incidence of these events. Ischaemia and neuropathy are the principal disorders underlying diabetic foot problems. Ulceration and sepsis of the ischaemic foot carries a higher risk of amputation. Therefore foot ulcers may be neuropathic, ischaemic or neuro-ischaemic. Any diabetic patient with an ulcer or even just a skin break below the knee that has not healed for 2 weeks with proper care should be referred for specialised treatment. Primary care practitioners will not have the resources and facilities to take care of foot ulcers. These should be referred to hospital or specialised care (if available).

The neuropathic foot

The neuropathic foot has diminished sensation with reduced perception of touch, deep pressure, temperature and joint position. Ulcers develop on the tips of the toes and pressure areas of the plantar aspect of the metatarsal heads. They are often preceded by callus formation. They become infected with different species of bacteria, leading to cellulitis, abscess formation and osteomyelitis. The foot is usually warm with intact bounding pulses.

Loss of pain, together with the rarefaction of the bones of the neuropathic foot, can result in the neuropathic joint (Charcot's joint). The patients usually present with a hot swollen foot, sometimes painful and often mistaken for an infection. This may be preceded by a minor, often unnoticed, injury. Unilateral warmth and swelling in a patient with neuropathic feet should alert the clinician to the development of a Charcot's joint. Correct and early diagnosis is essential for this condition to be managed appropriately for a better outcome. The management of this condition consists of bed rest and the use of crutches to eliminate weight bearing (on the joint) until the swelling and warmth have subsided. Some authorities advocate the use of plaster cast immobilisation until the bone repair is complete after initial bed rest. The plaster cast is left in place for 12 weeks.

Neuropathic oedema is an uncommon condition that consists of severe peripheral neuropathy together with swelling of the feet and the lower legs. It is thought that vasomotor dysfunction together with arteriovenous changes may be a cause. Clinical features of the neuropathic foot are listed in Table III.

The ischaemic foot

This is characterised by the absence of foot pulses. The lesions are found on the margins of the foot without callus formation. In dark-skinned individuals the colour of the foot will be darker (instead of pink). The foot will be painful, pulseless and cold. The pain may be extreme and persistent day and night. Doppler ultrasound studies to measure the ankle-brachial pressure index may give a guide to the presence or absence of ischaemia. The ankle-brachial pressure index is the ratio of systolic blood pressure at the ankle and brachial artery. Arterial (angiography, arteriography) imaging may be done with a view to bypass or angioplasty. These surgical operations are now well established and are important for limb salvage.
Clinical features of the diabetic foot are summarised in Table III.

Table III. **Clinical features of the neuropathic and ischaemic foot** (Adapted from *BMJ* 2003; **326**: 977- 979)

Neuropathic	Ischaemic
• Warm with intact pulses	• Pulseless, not warm
• Diminished sensation; callus	• Usually diminished sensation
• Ulceration (usually on tips of toes and plantar surfaces under metatarsal heads)	• Ulceration (often on margins of foot, tips of toes, heels)
• Sepsis	• Sepsis
• Local necrosis	• Necrosis or gangrene
• Oedema	• Critical ischaemia (urgent attention) foot pink, painful, pulseless, and often cold
• Charcot's joints	

Stroke

The risk of strokes is 2 - 3 times higher in diabetic patients and these are mostly ischaemic owing to atherothrombosis. The disease does not appear to increase the risk of intracerebral or subarachnoid haemorrhage. In the Rochester Epidemiology Project the distribution of stroke types in diabetic patients was as follows:

- ischaemic 88%
- intracerebral and subarachnoid haemorrhage 8%
- other (not determined) 4%.

Hyperglycaemia on admission to hospital after a stroke is one of the most predictive factors of deterioration following cerebral infarction. Diabetes increases the risk of stroke and worsens the outcome independently of other risk factors. Diabetic patients have higher death rates after strokes. Survivors have poor neurological outcome and more severe disability than those without diabetes. Long-term survival is reduced because of a high rate of recurrence. Anticoagulation prophylactic therapy is recommended as it has been shown to reduce the incidence of stroke among diabetic patients. The recommended drug is low-dose aspirin (75 – 150 mg). Clopidogrel can be prescribed to those who cannot tolerate aspirin.

Erectile dysfunction

At least 50% of diabetic men over the age of 50 years will report erectile problems compared with 20% of non-diabetic men of the same age. Erectile dysfunction may be the first presenting complaint, signifying undiagnosed long-standing glucose intolerance and undiagnosed diabetes mellitus. It may also give an idea of the extent of neurovascular disease in diabetic patients.

The negative effect of this condition on partner and family relationships can be devastating and should not be underestimated. Clinicians should always enquire about sexual history in all diabetic and non-diabetic patients as patients may be too shy to bring up the subject.

The pathogenesis of erectile dysfunction in diabetic patients is multifactorial. Vascular insufficiency due to atherosclerosis and resultant endothelial dysfunction reduces blood supply to the penis. Autonomic neuropathy as part of diffuse polyneuropathy affects the arteriovenous blood flow that plays an important role in initiation and sustaining an erection. Failure to achieve an erection at a critical moment results in psychological problems that feed a vicious cycle to ensure that erection is never achieved. The introduction of the 5-phosphodiesterase inhibitors such as sildenafil, has been an important advance in the treatment of this condition among diabetics. The reported success rate of this treatment is around 50 - 70% among diabetic patients.

Other rare and unusual manifestations and complications of diabetes will not be discussed in detail in this article. A few are: claw toes, diabetic dermopathy (shin spots), acanthosis nigricans and the diabetic hand syndrome.

SURVEILLANCE OF CHRONIC COMPLICATIONS AND MONITORING OF TREATMENT

The Society of Endocrine and Metabolic Disorders of South Africa (SEMDSA) has put together a protocol to guide primary health care practitioners in monitoring diabetic patients (Table IV).

Early detection of diabetes is essential because half of type 2 diabetics have vascular complications at the time of diagnosis. Routine screening should be done for high-risk individuals such as those with a family history of diabetes, the obese and those who have a history of gestational diabetes.

Eye screening for retinopathy requires fundoscopic skills and practitioners should practise fundoscopic examinations routinely so as to develop and maintain their skills.

Cardiovascular risk prediction charts are easily available and these should be used to identify patients at the highest risk of developing cardiovascular events.

All patients with diabetes should be offered a comprehensive annual clinical assessment with emphasis on detection, management and prevention of complications. The following are some important elements of an annual complications assessment:

Table IV. **Adapted from revised SEMDSA guidelines for diagnosis and management of type 2 diabetes mellitus for primary care (2002)**

Test/exam*	Frequency
Glycated haemoglobin	Quarterly if treatment changes or not meeting goals; at least 2 times/year if stable
Dilated eye exam	Yearly
Comprehensive foot exam	At least yearly (more often in patients with high-risk foot conditions)
Lipid profile	Yearly (less frequently if normal)
Serum creatinine level	Yearly
Microalbumin measurement	Yearly
Blood pressure	Each regular diabetes visit
BMI (body mass index) and waist circumference	Initially and weigh at each regular diabetes visit
ECG	Yearly if possible

*All key tests/exams to be done initially.

Physical examination

Body mass index calculation; blood pressure measurement; palpation of foot pulses; measurement of foot sensation using 10 g monofilament, vibration of 128 Hz tuning fork over the medial malleolus and ankle jerk reflex assessment with a hammer; inspection of feet for nail care, callosities, fissures, fungal infection, blisters, ulcers, claw toes, prominent metatarsal heads and Charcot's arthropathy; visual acuity in corrected state using the standard 6 m or 3 m Snellen chart (pin-hole use is advised if corrected acuity is > 6/9) and retinal examination.

Biochemical analysis

Dipstick urine examination for proteinuria; urine testing for microalbuminuria in type 1 diabetes; blood testing of glycated haemoglobin, serum creatinine, serum total cholesterol and HDL lipoprotein cholesterol.

Advice and education

History and advice against smoking; education and reinforcement of advice on diet, aerobic exercise and lifestyle; review of treatment with attention to side-effects and compliance; assessment of diabetes knowledge, self-management skills and warning signs of complications, e.g. intermittent claudication, angina pectoris and foot problems; review of footwear; assess need for contact with dietician, chiropodist, orthotics and diabetes specialist nurse support; assess and advice on erectile dysfunction in men; pre-pregnancy counselling, if desirable; ischaemic heart disease risk calculation and modification of risk factors.

Further reading

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IN A NUTSHELL

Diabetes patients are prone to irreversible complications.

Diabetes complications can be largely grouped into microvascular and macrovascular complications.

There are modifiable risk factors associated with the development of chronic complications.

Retinopathy, nephropathy and neuropathy are caused by microvascular complications.

Ischaemic heart disease, peripheral vascular disease, stroke, diabetic foot and erectile dysfunction are the result of macrovascular complications.

Screening for diabetes among high-risk individuals is valuable in detecting the disease early.

Screening for complications and instituting appropriate treatment will decrease morbidity.

Appropriate guidelines should be used in the diagnosis and the management of diabetes.

All patients should be offered an annual clinical assessment where possible.

Team approach to diabetes care is recommended.