Evidence Summary

Long term complications

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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 arterial disease.

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

- nephropathy
- retinopathy
- neuropathy (peripheral or autonomic).

Morbidity from diabetes involves both macrovascular and microvascular disease. Interventions can limit end organ damage, and therefore it is important that patients with diabetes receive initial and ongoing evaluation for diabetes-related complications.

Contents

Background

In both type 1 and type 2 diabetes, the macrovascular and microvascular complications of diabetes substantially increase a person's morbidity and mortality.

In type 1 diabetes, the clinical evidence of macrovascular and microvascular complications is uncommon at diagnosis in childhood and adolescence. However, early functional and structural abnormalities may be present after a few years.

In type 2 diabetes, the onset is deceptive and diagnosis is often delayed. As a result, diabetic complications may be present at the time of diagnosis of diabetes, and their frequency increases over time.

The AIHW 2015 report states that in 2011-12, cardiovascular disease (CVD) and chronic kidney disease (CKD) were commonly present together among adults with diabetes.[1] It was estimated that:

- 68% of people who had diabetes also had at least one form of CVD and/or CKD
- 63% of people aged 45–64 with diabetes had CVD and/or CKD
- 81% of people aged 65 and over with diabetes had CVD and/or CKD.

Two landmark studies the Diabetes Control and Complications Trial (DCCT)[2] and the United Kingdom Prospective Diabetes Study (UKPDS)[3] 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).

In 1998, the UKPDS results demonstrated that retinopathy, nephropathy and possibly neuropathy are benefited by lowering blood glucose levels.[3] 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.[3] 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 the reduced risk is maintained. This demonstrates the importance of achieving target glucose from diagnosis.[4, 5]

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
- early detection and monitoring of existing problems
- 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 recommended.

Macrovascular disease

Macrovascular or cardiovascular diseases (CVD) are both terms that can be used to describe disease which affects the large blood vessels;

1. **Coronary artery disease** or ischaemic heart disease refers to disease of the coronary arteries (arteries that supply the heart), and can lead to angina and myocardial infarction (heart attacks). **Myocardial infarction (heart attack)** is caused by a ruptured cholesterol plaque occluding the coronary artery and can result in death to the affected area of the myocardium. One of the confounding factors in people with diabetes is that myocardial ischaemia may be silent (eg the person may not feel the usual warning symptoms of chest discomfort or tightness). Therefore, their condition may go undiagnosed for some time. Long term myocardial injury is likely to affect the way the heart is able to pump – a condition known as heart failure.
2. **Cerebrovascular disease** occurs due to narrowed blood vessels in the brain and can cause cerebrovascular accidents (CVA or strokes) and transient ischaemic attacks (TIA). People with diabetes who suffer a stroke will have a 3 fold increase in mortality.
3. **Peripheral arterial disease** is narrowing of the large blood vessels (usually the arteries) supplying the limbs, and it can lead to pain while walking (claudication), deficient healing of leg wounds and/or leg ulcers.

Morbidity and mortality from CVD are two to five times higher in patients with diabetes compared to those without diabetes. Women with diabetes have been shown to have a higher relative risk of death from CVD than men, although the absolute risk is lower. Among people with diabetes, CVD has an earlier onset, and is more resistant to treatment and therapies, compared to those without diabetes.[6]

For people with diabetes it is essential to treat all risk factors not just the glycaemia.

Type 1 diabetes

People with type 1 diabetes may not have the other metabolic risk factors often seen in type 2 diabetes eg hypertension, hyperlipidaemia and obesity. However, over time many people with type 1 diabetes will develop CVD with a mortality rate of approximately 40%. For people with type 1 diabetes there are two important issues for coronary heart disease (CHD).[7]

1. CHD events usually occur earlier in life in type 1 diabetes as compared with people who have type 2 or in the general community. This is due to the earlier onset of type 1 diabetes.
2. Diabetic nephropathy (eg albuminuria or proteinuria, or reduced GFR) are common and are the major factors that contribute to CHD events in type 1 diabetes.

Type 2 diabetes

The major complication risk for people with type 2 diabetes is macrovascular disease. People with type 2 diabetes frequently have coexisting metabolic risk factors such as hypertension, hyperlipidaemia and obesity. Furthermore, risk factors such as sleep apnoea may be present.

Estimates from the 2007-08 National Health Survey as per the AIHW Australia's health report 2010[8] show that the;

> prevalence rate of stroke among people with diabetes was 5 times the rate of those without diabetes

- prevalence of heart attack among people with diabetes was more than 10 times the rate among those without diabetes
- rate of angina was around 3 times as high.

Risk factors for CVD

In adults without known CVD a comprehensive assessment of cardiovascular risk includes;

Modifiable risk factors	Non-modifiable risk factors	Related conditions
> smoking status > blood pressure > serum lipids > (cholesterol, lipoproteins and triglycerides) > waist circumference and body mass index > nutrition > physical activity level > alcohol intake.	> age and sex > family history of premature CVD > social history including cultural identity, ethnicity, socioeconomic status and mental health.	> diabetes > chronic kidney disease (albuminuria ± urine protein, eGFR) > familial hypercholesterolaemia > evidence of atrial fibrillation (history, examination, electrocardiogram).

National Vascular Disease Prevention Alliance (2012) Guidelines for the assessment of absolute cardiovascular risk.[9]

- Some risk factors cannot be changed by pharmacological or lifestyle interventions, so greater attention to the ones that can be changed is necessary.
- The development of atherosclerosis is associated with increased age.
- Men are at greater risk than women although this tends to level out after the onset of menopause primarily due to decreasing levels of oestrogen.
- CVD in first degree relatives particularly if this occurred at a young age does increase the risk profile of an individual. This is often multifactorial but may be due to an inherited risk of developing hypertension and raised cholesterol.
- Lifestyle habits such as a poor diet and a tendency to smoke may worsen the overall risk of developing disease.
- It is often a good opportunity to ask questions about other family members lifestyle choices when screening a younger person with CVD, as this may raise some awareness among family members.

Calculating absolute risk

The assessment of absolute risk looks at the combined effect of multiple risk factors and is more accurate than using individual risk factors. This is because the cumulative effect of multiple risk factors may be additive or synergistic.[9]

Absolute risk refers to the numerical probability of a CVD event occurring within 5 years. It is expressed as a percentage eg if the person's risk is 15% then we would explain that 15 out of every 100 people are likely to have a CVD event in the next 5 years. This method of assessment provides a guide to clinicians when designing a risk management strategy, based on the individual's score. This can also be a very effective method of motivation for clients who struggle with making lifestyle change.

The National Heart Foundation has developed an Australian risk chart and an online calculator 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. To access the quick reference guide for health professionals go to the Heart Foundation website.

To access the online risk calculator go to the CVD Check website. To assist in educating clients about their risk score the National Vascular Disease Prevention Alliance has developed a factsheet titled 'Manage your heart and stroke risk' that provides a comprehensive overview of what the risk score means as well as a client centred action plan. To access this resource go to the Heart Foundation website.

Limitations of calculating absolute risk

It is important to realise that there are currently no risk factor engines for CHD events in type 1 diabetes. Current tools have only been validated in populations with type 2 and they have not been shown to perform well in individuals with type 1 diabetes.[8] People with type 1 diabetes often have their first CHD event at a younger age (eg 34-44 years) but the risk factor engines have not been designed for people in this younger age group. Furthermore the risk factor engines do not include renal as a parameter.[8]

Key Practice Points

- Calculating a person's absolute risk can assist the person with diabetes to understand what impact their lifestyle and medications can have on preventing CVD events.
- Although the Framingham Risk Equation might underestimate risk in the diabetic population, available evidence suggests that this approach will provide an estimate of minimum cardiovascular risk
- Adults with diabetes 60 years and older are identified as high risk of CVD
- Adults with diabetes with microalbuminuria (>20 mcg/min or urinary albumin:creatinine ratio >2.5 mg/mmol for males, >3.5 mg/mmol for females) are identified as high risk of CVD.

Cardiovascular risk should be assessed annually for adults with type 1 diabetes.

National Vascular Disease Prevention Alliance have produced a number of resources that can be used to support discussions with clients about their absolute risk. All health professionals can play a role in helping clients understand their risks and their associated reduction strategies.[10]

Modifiable Risk Factors

Lifestyle changes in nutrition, physical activity and smoking status typically show excellent cost-effectiveness in lowering the burden of disease, especially with respect to obesity, future diabetes and heart disease.[11-14]

Smoking

Smoking is by far the most powerful treatable risk factor for macrovascular disease for people with diabetes.[15, 16] The added risk from smoking is compounded in comparison with people without diabetes.

For the purposes of CVD risk assessment, a non-smoker is defined as someone who has never smoked or has given up smoking and has not smoked for ≥12 months.

There is no safe level of smoking as both active and passive smoking increases the CVD risk by increasing the development of atherosclerotic plaque. Chemicals such as nicotine

and carbon monoxide contained in cigarettes, cigars and pipe tobacco will damage the cardiovascular system:

- nicotine affects blood pressure, heart rate, cardiac output and coronary blood flow
- carbon monoxide binds to haemoglobin thus reducing the amount of oxygen available to the body tissues
- smoking also increases the stickiness of platelets and blood vessels which allows cholesterol and other fatty substances to adhere.

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.[14]

Multiple therapies to assist clients to quit may be required, such as nicotine replacement therapy, drugs such as champix, and psychological support. It is common for people to need several attempts before they succeed.

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.

For further information visit the Quitline website.

Blood Pressure (BP)

High blood pressure (hypertension) causes blood vessels to stiffen and the pressure within artery walls increase. There is an increased workload required from the heart to pump blood around the body. Over time the myocardium thickens or hypertrophies, and becomes less efficient in circulating blood around the body.

There is a strong relationship between diabetes and the development of high blood pressure. Sustained high blood pressure can lead to organ damage such as cardiomegaly, kidney failure, brain or neurological damage, and examination of the eyes in hypertensive patients may reveal damage to the small blood vessels in the retina.

The development of hypertension is multifactorial and can include genetic factors, unhealthy lifestyle and some population groups are more susceptible to cardiovascular disease. For example, rates of death due to cardiovascular disease among the Aboriginal and Torres Strait Islander population are markedly higher as compared to other Australians.[11]

Key Practice Points

- For clinic BP measurement, the average of two seated BP measurements on both arms, over two separate occasions should be used to calculate risk.
- The most recently recorded pre-treatment value can be adopted for individuals taking antihypertensive medication.
- Ambulatory BP measurement is a better predictor of outcomes than clinic BP measurements and therefore should be used to monitor BP lowering therapy.
- Lowering BP reduces cardiovascular events and all-cause mortality in people with type 2 diabetes in the same manner as for the general population.

- The target levels for optimum BP is controversial, and have been based on little direct evidence. Meta-analyses demonstrate that more intensive BP control (SBP ≤130 mmHg) compared to usual (<140/90 mmHg) was associated with further reduction in stroke only, but there was a 40% increase in serious adverse events.

  This BP target is currently being reconsidered by a number of organisations worldwide and the systolic BP may be adjusted upwards. Until such deliberations are complete, the general international BP target for people with diabetes remains ≤130/80 mmHg.

- Absolute risk calculators have been developed using clinic BP measurements, therefore, if using ambulatory BP readings for risk assessment, clinicians should convert to the clinic equivalent using the appropriate tables.

For further information, visit the Heart Foundation website.

Antihypertensive therapy

The preferred initial agents for hypertension are angiotensin-converting enzyme (ACE) inhibitors (eg drugs whose name ends in 'pril' ie ramipril, perindopril) or angiotensin II receptor antagonists (eg candesartan, irbesartan)[11]

To achieve BP targets, combination therapy is often required.

Key Practice Points

- It is wise to start any of these medications at a lower dose, especially in the elderly until tolerability has been assessed.

- If optimal blood pressure readings are still not achieved, addition of either calcium channel blocker or thiazide diuretics as per the Heart Foundation Hypertension guidelines.[11] If not at target after second class of medication, specialist review is recommended.

- When a person commences any of these medications it is important that baseline renal function is assessed and recorded and that the levels are checked regularly.

Antiplatelet therapy

The role of aspirin in primary prevention remains uncertain.

For people with established CVD (eg in patients with known ischemic heart disease) there is clear evidence as to the benefits of aspirin in the absence of side effects or contraindications.

The National Vascular Disease Prevention Alliance guidelines (2012) states, that aspirin should not be routinely recommended in primary prevention. Whilst awaiting the results of clinical trials the decision to use aspirin in primary prevention should be individualised.[10]

Serum Lipids (Cholesterol, Lipoproteins and Triglycerides)

Cholesterol plaque is a major factor in the development of atherosclerosis, a chronic inflammatory response and the principle cause of disease within the large blood vessels.[6]

Atherosclerosis results in macrophages and low density lipoproteins invading the endothelial layer of the artery wall and restricting blood flow. Partial blockage of a coronary artery may result in angina, shortness of breath, fatigue, and reduced exercise tolerance. Myocardial infarction or heart attack often occurs suddenly in response to a complete blockage of a coronary artery, resulting in death to that part of the myocardium.

Hyperlipidaemia is a common risk for macrovascular disease in people with diabetes. and reducing cholesterol has a positive impact on the progression, morbidity and mortality associated with coronary artery disease, particularly in people at higher risk.[12]

According to the 2004 National Health and Medical Research Council report[13], lipid abnormalities in the people with diabetes can be grouped into two categories;

1. Elevated total cholesterol and low density lipoproteins which is similar to the non-diabetic population.
2. Elevated triglycerides and reduced high density lipoprotein specifically related to diabetes.

Both forms of hyperlipidaemia may require separate pharmacological approaches.

Insulin resistance and central obesity are two commonly found features in type 2 diabetes and has an impact on the type of lipid abnormality often associated with diabetes. Insulin resistance causes release of free fatty acids from increased amounts of abdominal adipose tissue resulting in an increase in secretion of triglycerides and small particles of low density lipoproteins. Insulin resistance is also responsible for the reduction in clearance of these particles.[13]

Lipid Fractions

- High density lipoproteins (HDL). Described as “good cholesterol”, the main function is to scavenge the “bad” cholesterol ie LDL and triglycerides. Levels of HDL are decreased in type 2 diabetes.
- Low density lipoproteins (LDL). Although levels of LDL are similar in both the diabetes and non-diabetes population, the particles are denser and smaller in type 2 diabetes.
- Total cholesterol (TC) levels are similar in both the diabetes and non-diabetes population.
- Triglycerides (TG) are small particles and are increased in type 2 diabetes.
- It is important that people with diabetes undergo an annual lipid assessment which assesses all lipid fractions rather than just measuring total cholesterol.

Lipid Fractions	**Target Levels**[17]
Total cholesterol	<4.0mmol/L
Triglycerides	<2.0mmol/L
HDL	>1.0mmol.L
LDL	<2.0mmol/L

Key Practice Points

- Annual screening and management of lipid disorders is essential.
- Triglycerides are usually higher.
- LDL particles more atherogenic eg promotes the formation of fatty deposits in the arteries.
- Fasting lipid profile (TC, LDL, HDL ratio and TG) should be taken.
- Lipid levels are measured after 10-12 hour fast.
- When a fasting sample is not possible, a non-fasting TC:HDL ratio may be used for an initial screening assessment of CVD risk, however treatment decisions should be made on the basis of fasting lipid levels.

- Increased body weight, poor glycaemic control and chronic kidney disease will aggravate lipid abnormalities in people with diabetes.

Cholesterol lowering therapy

- Lipid-lowering drug therapy (eg Rosuvastatin 20mg, Simvastatin 40 mg or Atorvastatin 10 mg) is recommended for primary prevention in patients with type 2 diabetes aged >40 years regardless of baseline cholesterol.
- Lipid-lowering drug therapy with simvastatin 40 mg should be considered for primary prevention in patients with type 1 diabetes aged >40 years.
- Bile acid binding resin or low dose nicotinic acid can be added in the case of hypercholesterolaemia.
- Fibrates may be used as first line therapy in people with diabetes who have high triglycerides and low HDL.
- Fish oil may have additional benefit.

Waist Circumference and Body Mass Index (BMI)

Waist circumference, as a measure of central obesity, is a better predictor of CVD risk than BMI. A waist circumference of >94 cm in men (>90 cm in Asian men) and >80 cm in women (≥80 cm in Asian women) is suggestive of central obesity.

Body Mass Index (BMI) uses weight and height to determine if an adult is within the healthy weight range, underweight, overweight or obese. BMI provides an estimate of total body fat and your risk of developing weight-related diseases.

BMI is calculated by dividing weight by the square of height as follows:

BMI = Weight (kg)/Height (m)2

using this calculation:

BMI<25 kg/m2 is desirable

BMI >25 kg/m2 is overweight

BMI >30 kg/m2 are obese and at increased risk CHD and stroke

A BMI Calculator is available on the Heart Foundation website.

There is evidence to support the promotion of weight loss interventions in people who are overweight or obese. Such interventions can favourably influence CVD risk factors such as BP and blood lipid levels.[14]

Nutrition

Whilst the Australian Dietary Guidelines for Adults (2013) have been developed for general health measures and not specifically for CVD prevention, the recommendations are consistent with the aim of CVD prevention.

Dietary recommendations (eg to decrease consumption of fat, saturated fatty acids, cholesterol, salt and/or increase consumption of fruit, vegetables, polyunsaturated fatty acids, monounsaturated fatty acids, fish, fibre and potassium) in reducing total blood pressure and cholesterol.[18]

Referral for nutritional review and dietary counselling should be considered, depending on need.

For further information, refer to the Evidence Summary - '*Nutrition and Diabetes'.*

Physical activity

Physical inactivity, including sitting time and leisure activity, is a growing public health problem and is associated with an increased risk of ill health and death, particularly relating to CVD.[10]

All forms of physical activity appear to be effective, with a positive influence on CVD risk factors: lowering LDL and triglycerides, increasing HDL and insulin sensitivity, reducing body fat and lowering blood pressure.[14, 19]

The Australian Physical Activity and Sedentary Behaviour Guidelines (2014) address the relationship between physical activity and health outcome indicators, including the risk of chronic disease and obesity; and the relationship between sedentary behaviour/sitting time and health outcome indicators, including the risk of chronic disease and obesity.[20]

For further information, refer to the Evidence Summary - *'Physical Activity'*.

Alcohol

Alcohol is known to have both beneficial and harmful effects on the risk of cardiovascular events and the psychological consequences of diabetes.

Different study designs and beverage types demonstrated consistent findings. Recent studies provide indirect pathophysiological support for a protective effect of moderate alcohol use on CHD. However, it is important to note that these studies focus on the link between alcohol intake and CVD only and do not consider other known detrimental effects of high alcohol consumption, including the risk of alcohol abuse.[21]

The National Health and Medical Research Council (NHMRC) alcohol guidelines include recommendations that healthy men and women should drink no more than two standard drinks per day, For people with diabetes, hypertension, chronic heart failure, CVD, CHD and/or liver disease, the Heart Foundation recommends less than the above recommended limits.

Related conditions

Microalbuminuria is an important clinical marker of renal disease, and is an independent risk factor for the development of CVD. Microalbuminuria is defined as urinary albumin:creatinine ratio (UACR) >35 mg/mmol in females and >25 mg/mmol in males. Persistent microalbuminuria is defined as two positive measurements, three months apart.

Key Practice Points

- The preferred method for assessment of microalbuminuria in patients with diabetes is UACR in a first void spot specimen.
- Where a first void specimen is not possible or practical, a random spot urine specimen for UACR is acceptable.
- A positive UACR test should be repeated to confirm persistence of albuminuria.

Renal function should be estimated from GFR. An eGFR <60 ml/min/1.73m2 is indicative of stage 3 CKD. CKD is present if two out of three tests (including the initial test) are positive. If the first positive UACR is a random spot (as it may be for opportunistic testing), then repeat test results should ideally be first morning void specimens.

The presence of microalbuminuria predicts early mortality and morbidity in people with hypertension and diabetes.

Hyperglycaemia

High blood glucose levels (hyperglycaemia) contributes to the damage of blood vessels, and are associated with increased risk of CVD morbidity and mortality.

Glycated haemoglobin (HbA1c) goals in patients with diabetes should be tailored to the individual, balancing the improvement in microvascular complications with the risk of hypoglycaemia.

Key Practice Points

- Generally the goal of therapy is a HbA1c value of <7.0% (53mmol/moL) for most patients.
- Glycaemic targets are generally set somewhat higher (eg, HbA1c <8% or 64mmol/moL) for older patients and those with comorbidities or a limited life expectancy and little likelihood of benefit from intensive therapy.
- More stringent control (HbA1c <6% or 42mmol/moL) may be indicated for individual patients with type 1 diabetes and during pregnancy.

Each 1% (11 mmol/mol) lower HbA1c was associated with a 21% (95% CI 15 to 27%) lower risk of diabetes-related death and specifically a 14% lower risk of myocardial infarction (MI) over ten years.

For further information, refer to the Evidence Summary - *'Monitoring blood glucose and ketones'.*

Microvascular disease

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

Given that most people with type 1 diabetes acquire the disease early in life we expect that many people with type 1 diabetes will develop some microvascular end-organ complications in their lifetime. Of these some will develop clinically significant and more severe progression of complications eg vision threatening retinopathy, diabetic nephropathy or painful neuropathy. On a positive note the frequency of severe complications are lower now than previously reported especially when the disease is treated intensively.[7]

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

Many people with type 2 diabetes will have their condition go undiagnosed for many years. Consequently, it is not uncommon for people with type 2 diabetes to have some evidence of microvascular complications at diagnosis. It is for this reason that the person with newly diagnosed type 2 diabetes undergoes screening for all complications at the time of diagnosis.

Diabetic nephropathy

Chronic kidney disease (CKD) occurs when there is kidney damage and/or reduced kidney function lasting more than 3 months.[8] Diabetic nephropathy is one of the main causes of CKD (32% of all new patients). Amongst Aboriginal and Torres Strait Islander peoples 80% of new patients presenting for dialysis have diabetes.[23]

Other causes of CKD include glomerulonephritis (24%), hypertension (14%) and reflux nephropathy (3%). Regardless of the cause the treatment is the same.

People with diabetes and CKD have worse outcomes from cardiovascular events and worse survival rates on dialysis and post transplantation than those who do not have diabetes.[24] The recent Two of a KinD report states 'the relationship between diabetes and

the kidney is truly a sinister one'[24] Despite this, much can be done to prevent and slow down kidney damage if it is identified early in its disease course.

For more information on the guidelines, go to the Caring for Australian with Renal Impairment (CARI) website.

Definition of CKD:[23]

Kidney function is measured by the glomerular filtration rate (GFR), which is the amount of blood cleared of waste products by the kidneys in one minute. As GFR cannot be measured directly, current practice is to estimate GFR (eGFR) using age, gender and creatinine levels in the blood.

CKD is defined as:

- an estimated or measured glomerular filtration rate (GFR) <60 mL/min/1.73m2 that is present for >3 months with or without evidence of kidney damage

or

- evidence of kidney damage with or without decreased GFR that is present for >3 months as evidenced by as evidenced by albuminuria, haematuria (after exclusion of urological causes), structural abnormalities (eg on kidney imaging tests) or pathological abnormalities (eg renal biopsy).

Why is early detection important?

Both eGFR and significant albuminuria are independent risk factors for CVD.[23] For example individuals with CKD have a 2 to 3 fold greater risk of cardiac death than those without CKD. For people with CKD, the risk of dying from a CVD event is up to 20 times greater than requiring dialysis or transplantation. However if it is detected early and managed appropriately the deterioration of kidney function can be reduced by up to 50% and may even be reversible. This will have a positive effect on quality of life.[23]

Clinical presentation

CKD is generally asymptomatic whereby the person may lose up to 90% of their kidney function before they notice symptoms. The first signs of CKD may include but are not limited to:

- hypertension
- pruritus
- nocturia
- restless legs
- haematuria
- dyspnoea
- lethargy
- nausea/vomiting
- malaise
- anorexia.

Annual kidney checks are therefore crucial if early intervention is to occur.

Screening for CKD

Screening for CKD for people with diabetes should occur annually and include:

- urine ACR for albuminuria
- blood test for serum creatinine to estimate glomerular filtration rate.

Tests used to investigate CKD

Urine albumin creatinine ratio (ACR)

Excessive amounts of proteins in the urine are a key marker of kidney damage and of increased renal and CVD risk.

Microalbuminuria provides the earliest warning of renal damage, however once microalbuminuria is present, damage has already occurred. Once clinical proteinuria occurs (dip stick positive, >300mg/day) progressive renal damage is likely. The rate of decline in renal function is accelerated by hypertension.

The preferred method for assessment of albuminuria in patients with diabetes is urinary ACR measurement in a first morning void spot specimen.

Key Practice Points

- Albumin/creatinine ratio (ACR) using early morning spot urine sample is required.
- Dipstick with a multistick prior to transportation to pathology to exclude conditions that may affect the result (eg urinary tract infection).
- A random spot urine sample for ACR is acceptable if a first void specimen is not possible.
- A positive test should be repeated on a first void sample to confirm persistence of albuminuria.
- Albuminuria is said to be present if at least 2 out of 3 results are positive (repeat tests should ideally be first morning specimens if the first test was random).[23]
- Dipstick for protein in the urine is now no longer recommended as the sensitivity and specificity are not optimal.

Note: It is important to test urine with ‘multistick’ to ensure the absence of infection. Infections will reduce the reliability of the result. Retest once the condition has been treated.

For further information and a consumer fact sheet ‘Albuminuria’, visit the Kidney Health Australia website.

Glomerular Filtration Rate (GFR)

GFR is accepted as the best overall measure of kidney function. It can be estimated (eGFR) from serum creatinine using prediction equations. eGFR is automatically reported (using the CKD-EPI equation) with requests for serum creatinine in individuals aged >18 years.

The CKD-EPI equation has been shown to have greater accuracy and precision for eGFR when compared to the Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault formulae.

Key Practice Point

> Further investigation of reduced eGFR is only required if the eGFR is <60 mL/ min/1.73 m2.

> If eGFR is <60 mL/min/1.73 m2, retest within 7 days and consider clinical situations where eGFR results may be unreliable and/or misleading or acute kidney damage.[23]

For further information and consumer fact sheet 'eGFR – estimated glomerular filtration rate', visit the Kidney Health Australia website.

Staging of CKD

The Kidney Health GP guidelines (2015) recommend that CKD is staged by combining Kidney Function Stage (stage 1-5) with description of kidney damage (albuminuria) and clinical diagnosis to specify CKD fully (eg stage 2 CKD with microalbuminuria, secondary to diabetic kidney disease).[23] (Figure 2)

Figure 2.

		Albuminuria Stage		
Kidney Function Stage	GFR (mL/ min/1.73m²)	Normal (urine ACR mg/ mmol) Male: < 2.5 Female: < 3.5	Microalbuminuria (urine ACR mg/ mmol) Male: 2.5-25 Female: 3.5-35	Macroalbuminuria (urine ACR mg/ mmol) Male: > 25 Female: > 35
1	≥90	Not CKD unless haematuria, structural or pathological abnormalities present		
2	60-89			
3a	45-59			
3b	30-44			
4	15-29			
5	<15 or on dialysis			

Refer to colour-coded Clinical Action Plans for management strategies

Ref: Chronic Kidney Disease Management in General Practice, Kidney Health Australia 2012

Note: 'For people with CKD, the combination of low GFR and albuminuria places them at greater risk of CKD and CVD progression at all ages than those with just one of low GFR or albuminuria'.[23]

Management of CKD

People can make improvements to their health and reduce their risk of and/or progression of CKD disease by making lifestyle changes.

Smoking

> Stop smoking using counselling

> Nicotine replacement therapy or other medication.

For further information visit the Quitline website.

Waist Circumference and Body Mass Index (BMI)

> Limit energy intake to maintain a healthy weight.

> Ideal weight should be BMI < 25 kg/m2 and waist circumference < 94 cm in men (< 90 cm in Asian men) or < 80 cm in women (including Asian women).

Nutrition

> Consume a varied diet rich in vegetables, fruits, wholegrain cereals, lean meat, poultry, fish, eggs, nuts and seeds, legumes and beans, and low-fat dairy products.

> Limit salt to <6 g salt per day (<100 mmol/day)

> Limit foods containing saturated and trans fats.

For further information nutrition, please refer to the Australian Dietary Guidelines for Adults (2013)[18] and the Evidence Summary - *'Nutrition and Diabetes'*.

Physical Activity

> At least 30 minutes moderate physical activity on most or preferably every day of the week.

For further information, refer to Australia's Physical Activity and Sedentary Behaviour Guidelines (2014)[20] and the Evidence Summary - *'Physical Activity'.*

Alcohol

> Limit alcohol intake to 2 standard drinks per day.

For further information, refer to the current Australian Guidelines to reduce the risk of drinking alcohol National Alcohol Guidelines (2009).[22]

Blood Pressure (BP)

Reducing blood pressure to below target levels is one of the most important goals in management of CKD. In people with CKD, blood pressure lowering therapy should begin with either ACE inhibitor or ARB.

> Combined therapy of ACE inhibitor and ARB is not recommended.

> Maximum tolerated dose of ACE inhibitor of ARB is recommended.

> Hypertension may be difficult to control and multiple medications are frequently required.

> Assess risk of atherosclerotic events and consider treating with an antiplatelet agent unless there is an increased bleeding risk.

For further information and consumer fact sheet 'Cardiovascular disease and chronic kidney disease' and 'Blood pressure and chronic kidney disease', visit the Kidney Health Australia website.

Serum Lipids (Cholesterol, Lipoproteins and Triglycerides)

In adults with newly identified CKD, evaluation with a fasting lipid profile is recommended.

> Consider secondary causes and specialist evaluation if severely elevated fasting lipid levels (LDL cholesterol >4.9mmol/L or triglycerides >11.3mmol/L).

> Follow up measurement of lipid levels is not required for the majority of patients.

> If aged >50 years with any stage of CKD (irrespective of lipid levels):

Statin if eGFR is > 60mL/min/1.73m2

Statin or statin/ezetimibe combination if eGFR is ≤60 mL/min/1.73m2.

> If aged <50 years with any stage of CKD (irrespective of lipid levels):

Statin if presence of diabetes and one or more of: coronary disease, previous ischaemic stroke or estimated 10 year incidence of fatal or non-fatal myocardial infarction above 10%.

Glycaemic Control

Glycaemic control significantly reduces the risk of developing microalbuminuria, macroalbuminuria and/or overt nephropathy in people with diabetes.

Glycated haemoglobin (HbA1c) goals in patients with diabetes should be tailored to the individual, balancing the improvement in microvascular complications with the risk of hypoglycaemia. Generally the goal of therapy is a HbA1c value of <7.0% (53mmol/moL) for most patients.

Glycaemic targets are generally set somewhat higher (eg, HbA1c <8% or 64mmol/moL) for older patients and those with comorbidities or a limited life expectancy and little likelihood of benefit from intensive therapy. Tight glycaemic control (HbA1c <6% or 42mmol/moL) may be indicated for individual patients with type 1 diabetes and during pregnancy.

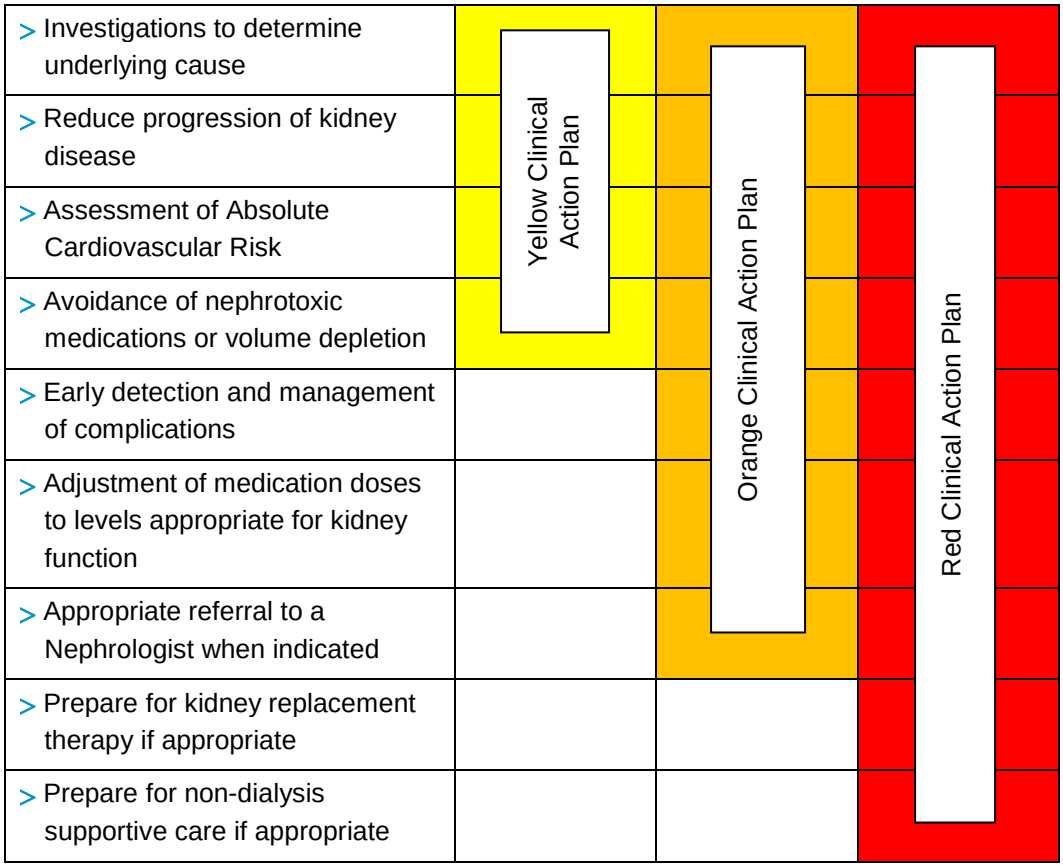
Some medications may need to be reduced in dose or ceased in CKD.

For further information HbA1c, please refer to the Evidence Summary - '*Monitoring blood glucose and ketones'.*

CKD Action Plans

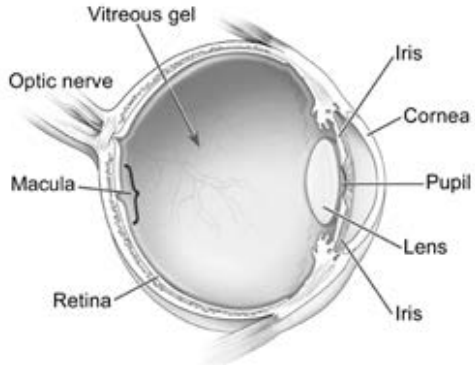
Kidney Health Australia has developed three colour coded action plans which outline information pertaining to the management options of CKD. The management will depend on the stage of CKD (Figure 3).

Figure 3. Kidney Health Australia Action Plans



Diabetic retinopathy

The retina detects light and converts it to signals sent through the optic nerve to the brain.



Diabetic retinopathy (DR) occurs as a result of microvascular disease of the retina. DR can cause blood vessels in the retina to leak fluid or haemorrhage, distorting vision.[25] In its most advanced stage, new abnormal blood vessels proliferate on the surface of the retina, which can lead to scarring and cell loss in the retina.

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

Risk

People with all types of diabetes are at risk for DR. Between 25 and 44% of people with diabetes have some form of DR at any point in time.[26] All people with diabetes are at risk of developing DR but the duration of diabetes is the strongest factor that determines the prevalence.

Women who develop or have diabetes during pregnancy (eg pre-existing type 1 or type 2 diabetes or gestational diabetes) may have rapid onset or worsening of DR.

The most important systemic factor associated with increased risk of DR is glycaemic control, followed by control of blood pressure and blood lipids.[26] People with diabetes are also at an increased risk of glaucoma and cataracts.

Screening

The early stages of diabetic retinopathy usually have no symptoms. As the disease often progresses unnoticed until it affects vision, screening is essential from diagnosis.

Bleeding from abnormal retinal blood vessels can cause the appearance of “floating” spots. These spots sometimes clear on their own. But without prompt treatment, bleeding often recurs, increasing the risk of permanent vision loss.

Macular oedema can develop at all stages of retinopathy. It typically presents with the gradual onset of blurring of near and distant vision in patients with diabetes who have other evidence of microvascular eye disease (eg peri-macular microaneurysms).

DR is detected during a comprehensive dilated eye exam that includes:

- Visual acuity testing. This eye chart test measures a person’s ability to see at various distances.
- Tonometry. This test measures pressure inside the eye.
- Pupil dilation. Drops placed on the eye’s surface dilate the pupil, allowing a physician to examine the retina and optic nerve.
- Optical coherence tomography (OCT). This technique is similar to ultrasound but uses light waves instead of sound waves to capture images of tissues inside the body. OCT provides detailed images of tissues that can be penetrated by light, such as the eye.

The comprehensive dilated eye examination aims to undercover:

- changes to blood vessels

> leaking blood vessels or warning signs of leaky blood vessels, such as fatty deposits

> swelling of the macula (eg macula odema)

> changes in the lens

> damage to nerve tissue.

If severe DR is suspected, a fluorescein angiogram may be used to look for damaged or leaky blood vessels. In this test, a fluorescent dye is injected into the bloodstream and pictures of the retinal blood vessels are taken as the dye reaches the eye.

Stages of Diabetic retinopathy

Diabetic retinopathy may progress through four stages:[26]

1. **Mild non-proliferative retinopathy**. Small areas of balloon-like swelling in the retina's tiny blood vessels, called microaneurysms, occur at this earliest stage of the disease. These microaneurysms may leak fluid into the retina.

2. **Moderate non-proliferative retinopathy**. As the disease progresses, blood vessels that nourish the retina may swell and distort. They may also lose their ability to transport blood. Both conditions cause characteristic changes to the appearance of the retina and may contribute to DME.

3. **Severe non-proliferative retinopathy**. Many more blood vessels are blocked, depriving blood supply to areas of the retina. These areas secrete growth factors that signal the retina to grow new blood vessels.

4. **Proliferative diabetic retinopathy (PDR)**. At this advanced stage, growth factors secreted by the retina trigger the proliferation of new blood vessels, which grow along the inside surface of the retina and into the vitreous gel, the fluid that fills the eye. The new blood vessels are fragile, which makes them more likely to leak and bleed. Accompanying scar tissue can contract and cause retinal detachment - the pulling away of the retina from underlying tissue, like wallpaper peeling away from a wall. Retinal detachment can lead to permanent vision loss.

Diabetic macular oedema

This is the build-up of fluid (oedema) in a region of the retina called the macula. The macula is important for the sharp, straight-ahead vision that is used for reading, recognizing faces, and driving.

It is the most common cause of vision loss among people with diabetic retinopathy. About half of all people with DR will develop macular oedema. Although it is more likely to occur as DR worsens, diabetic macular oedema can happen at any stage of the disease.

Management

People can have severe eye disease without any symptoms and therefore early detection of sight-threatening retinopathy by regular eye exams is the key to reducing visual loss and blindness from DR.

Screening for DR can be done by;

> general practitioners

> physicians

> endocrinologists

> optometrists and

> ophthalmologists.

The Australian Diabetes Society Guidelines for the management of diabetic retinopathy (2008) recommends:

- People with diabetes should have a dilated fundus examination by a trained examiner, with adequate sensitivity and specificity, at the time diabetes is diagnosed and at least every two years thereafter.
- Children with pre-pubertal diabetes onset should be screened at puberty, unless earlier examination is needed.
- Women with diabetes who are planning a pregnancy should have a comprehensive eye examination prior to conception. Women with diabetes who become pregnant should have a comprehensive eye examination in the first trimester and, if DR is found, they need close follow-up throughout pregnancy.
- If no retinopathy is present when examined at the diagnosis of diabetes, eye examinations are recommended at least every two years thereafter.
- Indigenous Australians or those of non-English speaking backgrounds, those with longer duration of diabetes, or patients with poor glycaemic, hypertension or blood lipid control, or with renal disease, have higher risk of DR or visual loss and should be considered for annual examinations.
- Once any non-proliferative DR is detected, further examinations should be conducted annually or at 3-6 monthly intervals, depending on the level of DR.
- Urgent ophthalmological review must be arranged if there is sudden deterioration in vision.
- Laser treatment is effective in preventing further vision loss but will not restore vision that has already been lost.[26]

Refractive changes

Can occur because of high blood glucose levels.

Cataracts

Can occur prematurely for people with diabetes.

Key practice points

- ensure screening at appropriate times
- address modifiable risk factors
- include overall eye health check which assesses for refractive changes to cataracts.

Peripheral and autonomic neuropathy

Neuropathy can be peripheral or autonomic.

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

Peripheral neuropathy

Neuropathy can affect the sensory nerves in the peripheries causing a myriad of symptoms such as pain, tingling, numbness or pins and needles. Sensory loss can result in the person being unable to sense pain, cold, touch and vibration. If motor nerves are affected there can be resultant weakness, loss of muscle fibres and reduced reflexes.[25]

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.

For more information, refer to the Evidence Summary - *'Foot care'*.

Autonomic neuropathy

Autonomic neuropathy refers to damage that has occurred within the autonomic nervous system. It may affect several organs, signs and symptoms may be non-specific and it often goes undiagnosed. Diagnosis will depend on the organ affected and treatment will vary depending on clinical history and assessment.

Table 1 highlights the clinical indications of autonomic neuropathy, possible signs and symptoms and treatment.[25, 27]

Key practice points

- Neuropathy can present with a range of symptoms.
- Table 1 provides an overview of the types of neuropathy, signs and symptoms and management.

Table 1: Clinical indications of autonomic neuropathy

	Signs and symptoms	Treatment
Gastrointestinal (gastroparesis)	> impaired gastric emptying > diarrhoea > constipation > faecal incontinence	> consult dietitian > small light frequent meals that are low in fat and contain only soluble fibre which to assist gastric emptying > incretin-based therapies and GLP1 analogues (eg Exenatide) should be avoided as they can delay gastric emptying > diabetes medication timing may need to be adjusted – discuss with doctor > an Insulin:Carbohydrate Ratio offers adjustment of rapid acting meal related insulin and flexibility with timing and meal size. > medication may be required for patients who continue to have symptoms of gastroparesis despite dietary modification (eg prokinetics, metoclopramide, cisapride, macrolide antibiotics and antiemetics).

Genitourinary	> delayed/incomplete bladder emptying > stress incontinence > silent urinary infection > nocturia > erectile dysfunction > retrograde ejaculation > reduced vaginal lubrication with arousal in women	> urinary catheterisation and self catheterisation may be required > medications may be required > manage erectile dysfunction with medications or implantable devices > lubricants can assist women during intercourse > check urine for asymptomatic infection.
Neurological	> hypo unawareness	> raising BGL targets may be necessary as a safety measure > frequent BGL testing will be required. > a period of avoiding hypoglycaemia may restore awareness.
Cardiovascular	> silent MI > postural hypotension > resting tachycardia > exercise intolerance	> ensure person is aware that chest discomfort in any location as well as unexplained fatigue, confusion, tiredness, oedema, haemoptysis, nausea/vomiting, diaphoresis, cough or dyspnoea should be investigated for possible silent MI > seek medical advice before starting an exercise regimen > encourage sitting on the edge of the bed for a few minutes before standing > support stockings or medications may be useful.
Lower limbs	> reduced sweating > reduced blood flow > reduced pain perception > redness	> consult podiatrist > foot risk assessment > education and support to reduce the risk of ulceration and infection.
General	> excessive sweating > heat intolerance > dry skin	> provide support and information about management of symptoms.

Other potential complications for the person with diabetes

Sexual health

Men

Diabetes can have physical effects that cause erectile dysfunction (ED). ED may also be an early warning sign of CVD. It is important to inquire about this in the annual screening because the prevalence of erectile problems in men over 40 years old with diabetes may be as high as 50%.[14] Intensive glycaemic control reduces the development of ED.

ED can result from neuropathy, impaired blood flow to the penis, or psychologic factors; several of these factors are present in most cases. It is important to differentiate psychogenic from organic erectile impotence. Several treatments for men with are available including:

- psychosexual counselling to discuss the quality and stability of the man's sexual relationship and to explore the expectations of both the man and his partner.
- phosphodiesterase inhibitors are considered the first-line therapy for are cyclic GMP phosphodiesterase five (PDE-5) inhibitors (sildenafil, vardenafil, tadalafil) that prolong the vasodilatory effect of nitric oxide to initiate and maintain an erection.[14]

Women

The effects of diabetes on female sexual functioning, is not well documented. Older women with type 2 diabetes may complain of impairment in vaginal lubrication with arousal which may be age related or due to pelvic autonomic neuropathy. Explanation and use of lubricants may be useful.[14, 25] Other issues particularly for women may include;

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, nitrite, leucocytes). A urine culture and antimicrobial susceptibility testing should be performed to guide treatment.

Psychosocial

There is evidence that a range of psychological and social factors can impact on the ability of people with diabetes to manage their condition. Whether the burden of managing diabetes causes psychological and social problems or vice versa, however, is unclear.

Psychological problems include anxiety, diabetes related distress, eating disorders, cognitive impairment and depression.

Depression and anxiety are common in older children, and adolescents with diabetes. Adolescents with type 1 diabetes are at an increased risk for an eating disorder. Adults aged >65 years with diabetes should be considered a high-priority population for depression screening and treatment.

The person with diabetes must be assessed at diagnosis and their psychological and social situation should be included as an ongoing part of the medical management of diabetes.

For further information on assessment tools and treatment, please refer to the Evidence Summary - '*Psychosocial'.*

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 so that the risk can be minimised.

The International Diabetes Federation Guide: Oral health for people with diabetes recommend:[28]

- Enquire annually as to whether each person with diabetes follows local recommendations for day-to-day dental care for the general population, and (where access permits) attends a dental professional regularly for oral health check-ups.
- Enquire at least annually for symptoms of gum disease (including bleeding) when brushing teeth, and gums which are swollen or red).
- In those people not performing adequate day-to-day dental care, remind them that this is a normal part of diabetes self-management, and provide general advice as needed.
- Advise those not attending for regular dental check-ups on the importance of doing so.
- In those people with possible symptoms of gum disease, advise them to seek early attention from a dental health professional.
- Education of people with diabetes should include explanation of the implications of diabetes, particularly poorly controlled diabetes, for oral health, especially gum disease.

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.

Key practice point

- People with diabetes should be asked about their sexual, psychological and social situation and oral health as part of their annual review.

Summary

Morbidity from diabetes involves both macrovascular (atherosclerosis) and microvascular (retinopathy, nephropathy, and neuropathy) disease. Interventions can limit end organ damage, and therefore patients with diabetes require initial and ongoing evaluation for diabetes-related complications.

Intensive insulin therapy is recommended for the majority of patients with type 1 diabetes, and therefore patients with type 1 diabetes should be referred to an endocrinologist for management of diabetes. For most patients with type 2 diabetes, care can be delivered by primary care providers and their health care teams in coordination with other specialists where appropriate.

Following diagnosis, the recommended screening for type 1 diabetes and type 2 diabetes patients are outlined in Table 2 and Table 3.

Table 2: Recommended complication screening in type 1 diabetes[7]

	When to commence screening	Frequency	Method of screening
Retinopathy	After 2 years duration in adolescents and adults, after 5 years duration and from age 9 years in children.	2nd yearly Annually (high risk, long duration, high A1c, non-proliferative background retinopathy).	Slit lamp biomicroscopy Retinal photography Mydriatic fundoscopy Visual acuity
Nephropathy	After 2 years in adolescents and adults, after 5 years duration from age 9 years in children.	Annually	Timed albumin excretion rate. First morning albumin creatinine ratio. Spot urinary albumin to creatinine ratio.
Neuropathy	Annually	Annually	Physical examination Monofilament Vibration & thermal threshold. Autonomic nerve tests
Lipids	At diagnosis if family history or from 12 years of age.	Every 5 years until puberty, then annually.	Fasting cholesterol, HDL cholesterol, LDL cholesterol and triglycerides.
Blood pressure	At diagnosis	At least annually.	Sphygmomanometer 24 hour BP measurements
Macrovascular disease	In adulthood	At least annually.	Clinical assessment and consider resting ECG.

Table 3: Recommended complication screening in type 2 diabetes[7, 14]

	When to commence screening	Frequency	Method of screening
Retinopathy	At diagnosis	2nd yearly Annually (high risk, long duration, high A1c, non-proliferative background retinopathy).	Slit lamp biomicroscopy Retinal photography Mydriatic fundoscopy Visual acuity
Nephropathy	At diagnosis	Annually	Timed albumin excretion rate. First morning albumin creatinine ratio. Spot urinary albumin to creatinine ratio.
Neuropathy	At diagnosis	Will depend on whether the person is high risk, intermediate or low risk.	Physical examination Monofilament Vibration & thermal threshold. Autonomic nerve tests
Lipids	At diagnosis	Annually	Fasting cholesterol, HDL cholesterol, LDL cholesterol and triglycerides.
Blood pressure	At diagnosis	At least 6 monthly. Will depend on risk factors.	Sphygmomanometer 24 hour BP measurements
Macrovascular disease	At diagnosis	At least annually	Clinical assessment and consider resting ECG.

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