

# Laboratory Testing in Diabetes



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# Key points

- Fasting morning venous glucose is the best initial test for diagnosing diabetes.
- An oral glucose tolerance test is reserved for people with equivocal fasting glucose results.
- Patients with impaired glucose tolerance or impaired fasting glucose benefit from lifestyle intervention and annual review.
- HbA<sub>1c</sub> is the best test of glycaemic control in diabetes.
- Patients with diabetes benefit from aggressive monitoring and management of all cardiovascular risk factors.

***“....the human and economic costs of diabetes can be reduced by prevention, particularly early detection.....”***

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# Introduction

The prevalence of diagnosed diabetes in New Zealand is estimated to be 3 - 4% and is higher among Māori (5 - 10%), Pacific Island peoples (4 - 8%) and people of Asian origin (4%). In New Zealand, 115, 000 people were estimated to have diabetes in the year 2000, but this is predicted to increase to over 160, 000 by 2021 (NZGG, Diabetes, 2003).

## Type 1 diabetes

- Most frequently affects children and adolescents.
- Symptoms include excessive thirst, excessive urination, weight loss and lack of energy.
- Daily insulin injections required for survival.

## Type 2 diabetes

- Occurs mainly in adults.
- Usually people have no early symptoms.
- People may require oral hypoglycaemic drugs and may also need insulin injections.

## Type 1 diabetes

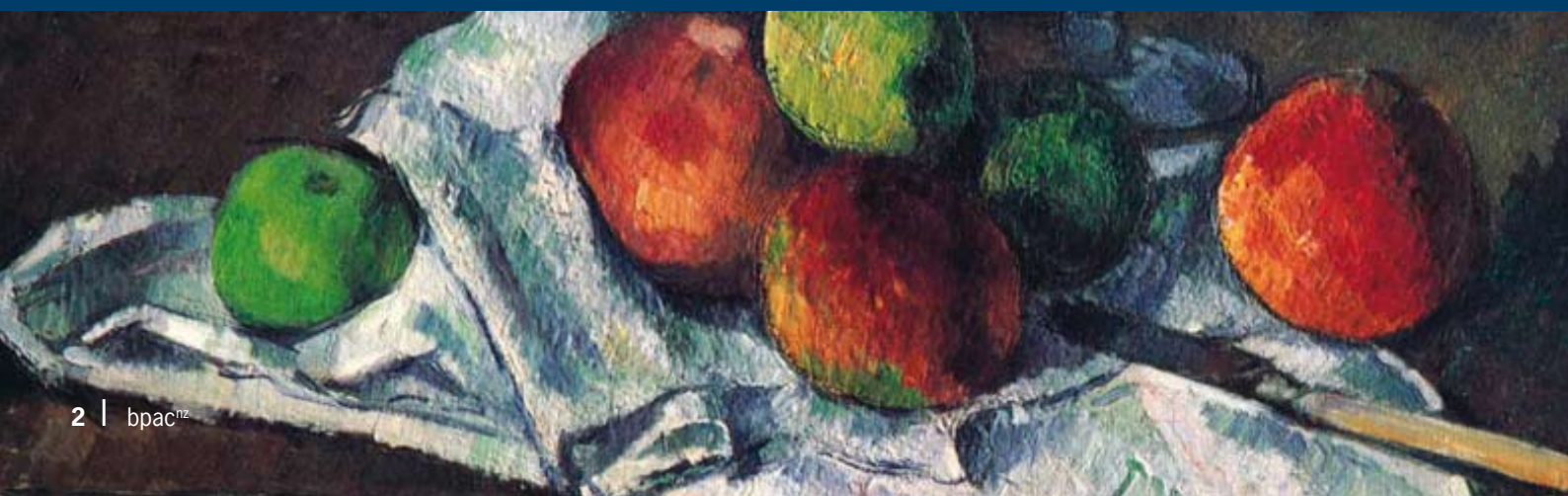
Type 1 diabetes mellitus develops most frequently in children and adolescents. About 5% to 10% of people with diabetes have type 1 diabetes, and it accounts for 3% of all new cases of diabetes each year. The exact cause of type 1 diabetes is not known, but is thought to be autoimmune. Patients require daily insulin injections for survival.

## Type 2 diabetes

Type 2 diabetes is more common than type 1 diabetes. Type 2 diabetes results from the combination of insulin resistance (resistance by body tissues to the action of insulin), and an insulin secretory defect.

Type 2 diabetes occurs mainly in adults although it is now also increasingly found in children and adolescents. Most people with type 2 diabetes, however, have no early symptoms and are only diagnosed several years after the onset of the condition, when various diabetic complications are often already present.

People with type 2 diabetes may require oral hypoglycaemic drugs and may also need insulin injections.



# People at high risk of diabetes

Unfortunately the risk factors for diabetes, unlike those for cardiovascular disease, have not been quantified. This means that clinicians must assess risk from the wide range of factors associated with increased risk.

## Factors associated with increased risk for diabetes include:

- Māori, Pacific or Indian ethnicity
- Increasing age
- Metabolic syndrome (see Table 1)
- Impaired glucose tolerance
- Polycystic ovary syndrome
- History of gestational diabetes or having a baby over 4 kg
- Family history of diabetes
- Physical inactivity
- Increased BMI
- Central obesity
- Hypertension
- Adverse lipid profile
- Elevated LFTs
- Patients taking some drugs e.g. prednisone or anti-psychotic drugs (haloperidol, chlorpromazine, and newer atypical anti-psychotics).

Table 1. *Definition of Metabolic Syndrome* (NZGG, Cardiovascular, 2003)

Three or more of the following risk factors listed below are required for a diagnosis of metabolic syndrome.

Risk Factor	Defining Level
Waist circumference*	Men $\geq$ 100 cm Women $\geq$ 90 cm
Triglycerides	$\geq$ 1.7 mmol/L
HDL cholesterol	Men $<$ 1.0 mmol/L Women $<$ 1.3 mmol/L
Blood pressure	SBP $\geq$ 130 or DBP $\geq$ 85
Fasting glucose	$\geq$ 6.1 mmol/L

\*It is likely that people of Indian ethnicity will have features of the metabolic syndrome at lesser waist circumferences than people of European, Māori or Pacific ethnicity.

People with the metabolic syndrome are at increased risk of diabetes, cardiovascular disease, sub-fertility and gout despite only moderate elevation in individual risk factors.

# Prevention and identification

**IGT** = Impaired  
Glucose  
Tolerance

**IFG** = Impaired  
Fasting  
Glucose

(See Table 4)

## Opportunities for prevention

Both impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) refer to metabolic stages intermediate between normal glucose homeostasis and diabetes. People with IGT or IFG have an increased risk of progressing to diabetes. Lifestyle interventions delay and prevent the onset of diabetes underlining the importance of early identification in all racial groups.

## Identification of diabetes

Almost one half of people who have diabetes do not know it and one quarter will have microvascular complications (e.g. retinopathy or nephropathy) at diagnosis, and have increased risk of macrovascular disease. This raises the question of how best to identify people with undiagnosed diabetes.

The New Zealand Guidelines Group (NZGG) recommends testing for diabetes with a fasting morning venous glucose as part of a cardiovascular risk assessment programme. Recommendations are tabled below:

Table 2. NZGG recommendations for cardiovascular risk assessment (NZGG, Cardiovascular, 2003)

Population group	Age to commence testing	
	Men	Women
Asymptomatic people without other known risk factors	45 years	55 years
Māori, Pacific peoples and people from the Indian subcontinent	35 years	45 years
People with other known cardiovascular risk factors or at high risk of developing diabetes	35 years	45 years

**“...if clinical suspicion is high; testing should be performed at any age....”**

# How to test

## Blood Glucose

The NZGG currently recommends fasting morning venous glucose as the best test for the diagnosis of diabetes.

While other specimens are sometimes used for measuring glucose, they should not be used for diagnostic purposes. There is confusion regarding the relationship between capillary samples (i.e. fingerprick) and venous samples. Although equivalence values have been published by WHO to allow comparison between different samples, these are difficult to demonstrate in practice. (Colagiuri, 2003)

Finger prick results are usually lower than plasma glucose and the results are more variable (less precise), therefore finger prick samples should not be used for diagnostic purposes.

## Urine Glucose

Urine glucose should not be used in New Zealand for the diagnosis of diabetes.

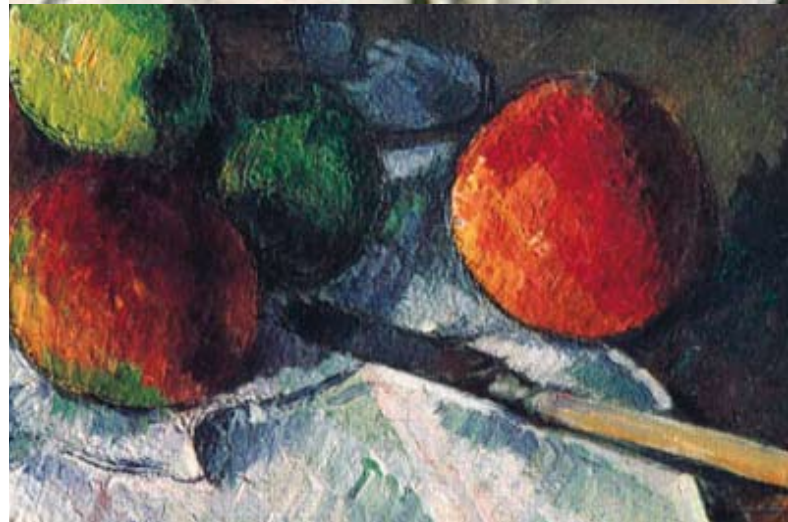
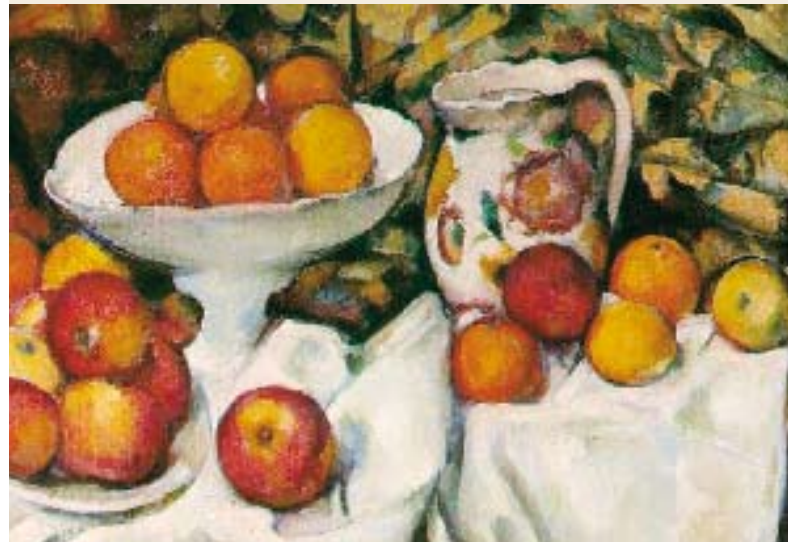
## HbA<sub>1c</sub>

HbA<sub>1c</sub> is not recommended as a diagnostic test for diabetes by the NZGG or any other national organisation at this time. Its role remains in monitoring overall glycaemic control.

While there is some evidence to suggest HbA<sub>1c</sub> is being used as an initial screening test in New Zealand (Kenealy, 2004), some experts have strong concerns around this practice due to lack of correlation between HbA<sub>1c</sub> and glucose levels.

## Testing for diabetes

- Fasting morning blood glucose is the best initial test.
- Urine glucose and HbA<sub>1c</sub> should not be used for diagnosis.



## People with symptomatic hyperglycaemia

For people with symptomatic hyperglycaemia, a single fasting glucose of:

**≥ 7.0 mmol/L**

or a random glucose of:

**≥ 11.1 mmol/L**

is diagnostic of diabetes.

Symptomatic hyperglycaemia may have an acute onset, usually in younger people with type 1 diabetes, or a more insidious onset, usually in older people with type 2 diabetes. The usual symptoms of hyperglycaemia are thirst, polyuria and weight loss but hyperglycaemia can also cause fatigue, lack of energy, blurring of vision or recurrent infections, such as candida.

In clinical practice, when symptoms are typical of diabetes, a single fasting plasma glucose level of ≥7.0 mmol/L or 2 h post-glucose or casual postprandial plasma glucose level of ≥11.1 mmol/L is diagnostic. If symptoms are equivocal or the patient is ill or stressed for other reasons (e.g. infection or trauma), an additional glucose, (preferably fasting) on a day when the patient has recovered is needed.

**“fasting glucose test should be performed when the patient is well...”**

### Action following fasting venous plasma glucose

Criteria have been recommended by NZGG for the diagnosis of diabetes, IGT and IFG.

Table 3. *Criteria for the interpretation of fasting glucose* (NZGG, 2003)

Normal		Diabetes		
Fasting glucose result	< 5.5	5.5 - 6.0	6.1 - 6.9	≥ 7.0
Interpretation	Normal result	Borderline result	IFG	Diabetic
Action	Retest in five years or three years for those at risk.	OGTT for those at increased risk of diabetes. Re-test annually those with IFG or IGT.	Assess with OGTT. Re-test annually	Two results ≥ 7.0 mmol/L on two different days are diagnostic of diabetes. OGTT is not required.

OGTT is not required for people with a fasting glucose result ≥ 7.0 mmol/L (in which case a second fasting sample is required) or a fasting glucose result of < 5.5 mmol/L.

## Interpretation of the glucose tolerance test

A 75 gram oral glucose tolerance test (OGTT) is used to follow up people with equivocal results who may have diabetes, IFG or IGT.

Table 4. *Diagnosis of diabetes, IGT and IFG using OGTT*

	Fasting mmol/L		2 hours post load mmol/L
Normal	< 5.5	and	< 7.8
IFG	6.1 – 6.9	and	< 7.8
IGT	< 7.0	and	7.8 – 11.0
Diabetes mellitus	≥ 7.0	and/or	≥ 11.1
GDM	≥ 5.5	and/or	≥ 9.0

## Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) increases the risk of many foetal and maternal complications in pregnancy and the development of type 2 diabetes later in life (Kjos, 1999). Screening is currently recommended for all women between 24 - 28 weeks gestation or earlier if the woman is thought to be at high risk, for example because of previous GDM, marked obesity or family history. In women at high risk of developing GDM, preconception screening is strongly recommended.

### Screening for GDM using 50 gram load

Currently in New Zealand, for the initial screening for GDM, a 50 gram glucose load is given to the patient with a single blood glucose estimation after one hour. There is no need for the patient to fast. Most laboratories now provide the glucose in the form of a carbonated drink, although previously the glucose load was prepared from 'Polycose' powder, hence the common name 'Polycose test'. If the one hour blood glucose is ≥ 7.8 mmol/L, a two hour OGTT is performed.

### OGTT for diagnosis of GDM

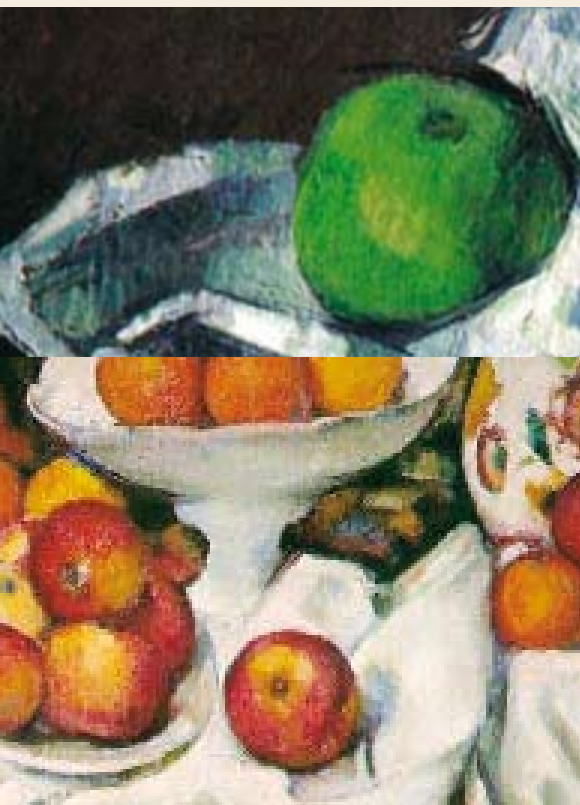
There is no international consensus on the diagnostic criteria for GDM. The diagnostic criteria recommended in New Zealand are indicated in Table 4. It is interesting to note the two hour value recommended in New Zealand is higher than both Australia and the United States. There remains continued debate regarding the best criteria for establishing a diagnosis of gestational diabetes and it depends on interpretation of papers reviewing foetal outcome. It may be that these guidelines will change slightly in the next few years.

# Laboratory tests and monitoring

Laboratory tests play an important role in determining glycaemic control and in preventing and delaying complications of diabetes.

**“...HbA<sub>1c</sub> is the best test of glycaemic control in diabetes...”**

<b>Stable diabetes</b>	Test six monthly
<b>Changes in treatment</b>	Test no more than three monthly



## Target level for HbA<sub>1c</sub>

Any sustained reduction of HbA<sub>1c</sub> is worthwhile because there appears to be a direct relationship between cardiovascular risk and HbA<sub>1c</sub>. In people with diabetes, each 1% decrease in HbA<sub>1c</sub> is associated with a 7% relative reduction in myocardial infarction over 5 years (NZGG, Diabetes, 2003). This relative reduction is significant because people with diabetes have a high absolute risk of cardiovascular disease especially in the presence of other risk factors. There is however no good prospective data demonstrating a reduction in mortality or cardiovascular events when HbA<sub>1c</sub> has dropped below 7%, although studies are being conducted to investigate this.

The goal is to achieve an HbA<sub>1c</sub> as low as possible, preferably less than 7.0%, without causing unacceptable hypoglycaemia. As metformin or glitazones do not cause hypoglycaemia, the target HbA<sub>1c</sub> can be reached more easily. However for people on insulin or sulphonylureas the achievable HbA<sub>1c</sub> is likely to be higher because of the risk of hypoglycaemia. HbA<sub>1c</sub> > 8 mmol/L is a sign of inadequate control for most people.

HbA<sub>1c</sub> targets need to be individualised, taking into consideration the patient's age and co-morbidities.

## Alternatives to HbA<sub>1c</sub>

Occasionally interpretation of HbA<sub>1c</sub> is unreliable in conditions that decrease erythrocyte survival, such as haemolysis, ongoing blood loss or frequent venesections, for example, in haemochromatosis.

In these situations alternatives are either self monitoring of blood glucose, or fructosamine. Fructosamine is no longer used routinely, as HbA<sub>1c</sub> has been found to be much more reliable.

## Self monitoring blood glucose (SMBG)

People who take insulin for type 1 or 2 diabetes should regularly self monitor blood glucose to guide insulin doses and detect and avoid hypoglycaemia.

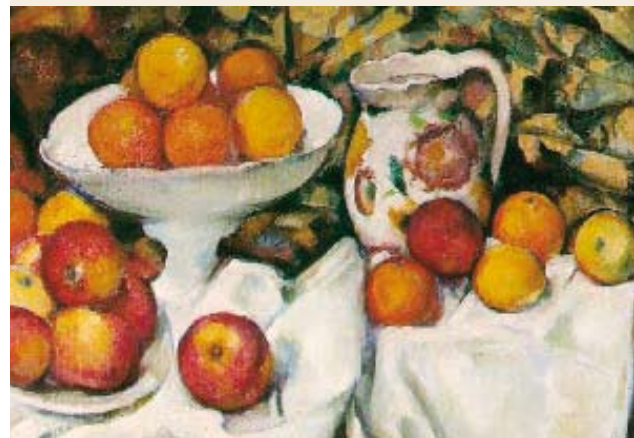
The situation is less clear for people with non-insulin treated type 2 diabetes. It has been demonstrated that SMBG combined with an eating diary and standardised counselling reduced HbA<sub>1c</sub> by 0.5% compared to controls, probably due to its effect as an educational modality (Schwedes, 2002). However SMBG may be associated with higher degrees of distress or worry (Franciosi, 2001). Other studies however have shown no definite effect of self monitoring in patients with stable type 2 diabetes, particularly those on diet or metformin only. As a result, testing is most useful if patients use the results to learn and alter behaviour, or medication.

Home glucose monitoring may therefore be useful as part of a structured educational programme. It may be useful performed intermittently before breakfast or two hours post-prandially, but more regularly at times of medication change, illness or at any time hyper/hypo-glycaemia is suspected.

## Urinalysis for glucose

Urine glucose testing is not necessary or useful.

***“...SMBG is most useful if patients use the results to learn, as part of an overall diabetes education package...”***



# Laboratory tests to prevent and delay complications of diabetes

Parameter	Optimal value
Total cholesterol	< 4 mmol/L
LDL cholesterol	< 2.5 mmol/L
HDL cholesterol	> 1 mmol/L
TC:HDL ratio	< 4.5
Triglycerides	< 1.7 mmol/L
HbA <sub>1c</sub>	< 7 mmol/L

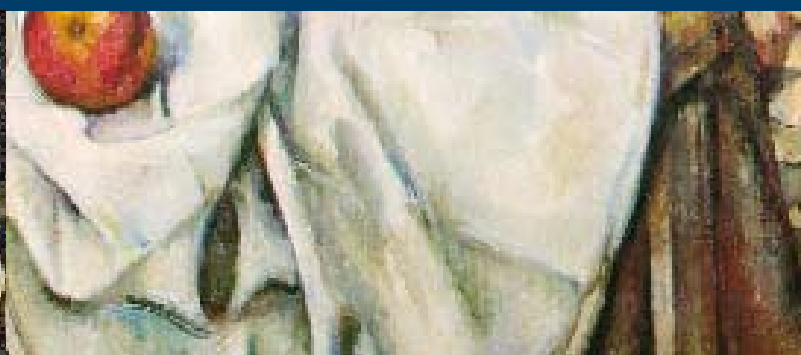
People with diabetes usually die from macrovascular complications of their diabetes; namely cardiovascular disease. This is influenced by all of the commonly recognised risk factors for cardiovascular disease as well as glycaemic control. Fasting lipid levels are measured three monthly until stable and then 6 - 12 monthly thereafter.

Management should be individualised and a less aggressive approach is more appropriate for some people. For example those with less risk factors.

It is important to be aware of all cardiovascular risk factors, for example there is increasing evidence that patients after CABG or angioplasty should aim for LDL cholesterol less than 1.7 mmol/L.

***“There is conclusive evidence that good glycaemic control can substantially reduce the risk of developing complications and slow progression in all types of diabetes. The management of high blood pressure and raised blood lipids are equally important.”***

International Diabetes Federation



# Diabetic renal disease

The best way of testing for diabetic renal disease is by urinary albumin:creatinine ratio (ACR) and serum creatinine with estimated glomerular filtration rate (eGFR). These tests are performed on everyone with diabetes at diagnosis and repeated at least annually – more frequently if there is proteinuria, microalbuminuria or reduced eGFR.

## Albumin:creatinine ratio

ACR provides an estimate of daily urinary albumin excretion. A confirmed ACR greater than or equal to 2.5 mg/mmol in men, or greater than or equal to 3.5 mg/mmol in women, indicates microalbuminuria before the development of frank proteinuria. Microalbuminuria cannot be detected on a conventional urinary protein dipstick.

Microalbuminuria is urinary albumin excretion between 30 and 300 mg/day; above 300 mg/day represents proteinuria. It is not only an early marker for kidney disease but is associated with at least a doubling of cardiovascular risk and should prompt aggressive cardiovascular risk management e.g. aspirin, ACE inhibitor, statin.

ACR is best measured in the laboratory using a first morning urine sample where possible when the patient is well; a random urine sample may also be used. An abnormal initial test requires confirmation by testing on two further occasions. If at least one of these tests is positive microalbuminuria has been confirmed.

Table 5. Renal testing in diabetes

ACR mg/mmol (confirmed)			eGFR mL/min/1.73 <sup>2</sup>	Risk	Management
men < 2.5 women < 3.5	and		> 60	2 - 4% per year progress to microalbuminuria.	Annual ACR and eGFR. Good diabetes & BP management.
men ≥ 2.5 women ≥ 3.5	or		< 60	One third progress to overt nephropathy. CVD risk doubled.	Review ACR and eGFR at each visit. Intensive management of glycaemia and CVD risk factors. Use ACE inhibitor and low-dose aspirin. Avoid nephrotoxic drugs. Investigate if suspicious of causes other than diabetes*
> 30	or		< 30	Almost all proceed to end stage renal disease or die prematurely of CVD.	Overt nephropathy Refer specialist

\*Non-diabetic renal disease is suspected when there is absence of diabetic retinopathy in a person with renal disease, there are urinary abnormalities such as haematuria or casts, or when there is renal disease without microalbuminuria or proteinuria.

# Other tests

## Testing of LFTs is recommended for people with diabetes:

- at diagnosis,
- at the start of antidiabetic drug therapy, and
- at any other time indicated by clinical judgement



## Liver function tests

People with type 2 diabetes have a higher incidence of abnormal liver function tests. The most common cause is non-alcoholic fatty liver disease. Mild chronic abnormalities often reflect underlying insulin resistance.

Elevated ALT and GGT are the most frequent abnormality found. Mild chronic elevation, e.g. ALT above the upper limit of the reference range but below 250 U/L for greater than 6 months, is an indication to screen for causes of chronic liver disease, particularly hepatitis B, hepatitis C and haemochromatosis which have increased incidence in type 2 diabetes. Unless there are clinical findings suggesting other causes such as medications, alcohol, autoimmunity, metabolic or hereditary aetiology further investigation is probably not required. Oral antidiabetic therapy may decrease levels as tight glycaemic control is achieved. Elevations above this level or other abnormalities will need to be treated on a case-by-case basis.

Elevation of transaminase levels (ALT and AST) within three times the upper limit of the reference range is not a contraindication for starting oral antidiabetic medication or lipid modifying therapy.

## Other laboratory tests

Type 1 diabetes is an autoimmune disease and is associated with autoimmune thyroid disease. It is probably worthwhile requesting a TSH on people who have been recently diagnosed with type 1 diabetes, and at intervals thereafter. A check of TSH in the context of high LDL cholesterol is worthwhile, particularly in elderly women. Additionally, it is increasingly being recognised that coeliac disease, (silent or symptomatic) occurs in about 5% of people with type 1 diabetes. In patients with non-specific gastrointestinal symptoms or weight loss testing may be indicated. In these patients, testing should include endomysial antibodies and tissue transglutaminase antibodies.

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