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Background

C01.S1

Diabetes has existed as long as mankind. Hieroglyphs in the Egyptian pyramids and ancient Asian Sanskrit writings describe the symptoms only too familiar today (see  Chapters 2 and 3).


Before the 1920s, when Banting and Best's discovered that insulin could be prepared and injected to alleviate the morbidity caused by Type 1 diabetes, the only treatment for this condition was a near starvation diet until the inevitability of death (Bliss 1982).

The National Service Framework (NSF) for Diabetes records the increase in numbers of people around the world who have been diagnosed with diabetes over the preceding decades. It is estimated that worldwide 246 million people have the disease (International Diabetes Federation 2007) and it is predicted that this will have doubled by the year 2010.

More than 2.5 million people in England have the disease with a disproportionate spread of those with Type 2 diabetes being of South Asian descent, and African and Afro-Caribbean origin (Qualities Outcome Framework 2007). Members of the poorest sectors of society fare the worst with increased risks of morbidity from complications of the disease.

It is estimated that more than half a million people in the UK have Type 2 diabetes without being aware of their condition and at least 50% already have some complications at the time of diagnosis (Diabetes UK, 2008). How to reach those at risk, but undiagnosed earlier is a problem that health practitioners need to have at the forefront of their minds.



Complications of diabetes are the leading causes of blindness in the working-age population, end-stage renal failure and, baring accidents, the greatest number of limb amputations.

Although the risk of developing Type 2 diabetes increases with age and obesity it can occur at any time, with recent significant increases in the numbers of those diagnosed with Maturity Onset Diabetes of the Young (MODY; see  Classification of monogenetic diabetes, p. 14).

Further information

C01.S1.1

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Diabetes UK (2008) Available at  <http://diabetesuk.org> (accessed 19 December 2008).
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The pancreas: overview

001.52

The pancreas is an elongated, leaf-shaped organ, pinkish in colour, lying across the back of the abdomen behind the stomach. The head of the pancreas, the widest part, lies to the right hand side in the curve of the first section of the small intestine, the duodenum.

The body of the pancreas, the tapered left-hand side, extends upwards towards the spleen, ending in the tail section. The pancreatic duct runs along the whole length of the pancreas.

The pancreas is covered with a thin connective tissue capsule that extends inward, partitioning the gland into lobules. It is made up of two types of cells – *exocrine* and *endocrine*. See Figure 1.1.

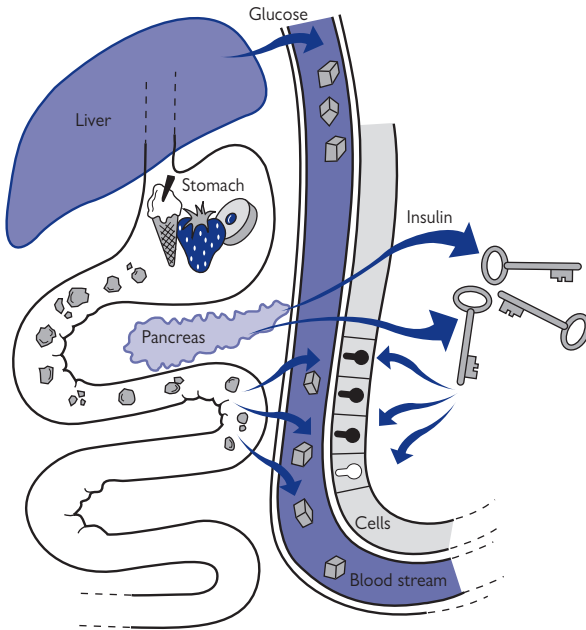


Fig. 1.1 Insulin action on the body. Insulin can be regarded as a key unlocking access to the cells. Reproduced from Matthews D et al (2008), *Diabetes*, with permission from Oxford University Press.

C01.F1

Exocrine functions of the pancreas

C01.S3

Exocrine anatomy

C01.S3.1

The majority of pancreatic cells are *exocrine cells* and their associated ducts. Embedded within this exocrine tissue are approximately 1 million grape-like cell clusters called acini. These are packed with membrane-bound secretory granules containing digestive enzymes, which pass through larger and larger ducts until they flow into the main pancreatic duct and drain into the duodenum.

Exocrine physiology

C01.S3.2

Secretions from the exocrine cells are vital to enable food to be completely digested:

- As chyme, the bolus of partially digested food, enters the small intestine it is acidic and needs to be *neutralized* to protect the duodenal mucosa.
- Proteins, fats and starch need to be further broken down before they can be absorbed into the blood stream.

Secretion of bicarbonate (a base) and water:

- Secreted from the endothelia cells that line the pancreatic duct.
- Vital for neutralizing the acidity of the chyme.

Protein digestion

C01.S3.3

- Facilitated by the two major pancreatic proteases, trypsin and chymotrypsin.
- Proteases are synthesized and packaged into secretory vesicles as the proenzymes trypsinogen and chymotrypsinogen.
- Inactive as proenzymes to preserve protein of the pancreatic cells.

Fat digestion

C01.S3.4

- Triglyceride, or neutral lipid, cannot be directly absorbed across the intestinal mucosa.
- First digested into a 2-monoglyceride and two free fatty acids.
- Pancreatic lipase performs this hydrolysis, delivered into the duodenum as a constituent of pancreatic juice.

Starch digestion

C01.S3.5

- Amylase (technically alpha-amylase) is the enzyme that hydrolyses starch to maltose.
- The major source of amylase is pancreatic secretions, although amylase is also present in saliva.

In addition, the pancreas produces other digestive enzymes including:

- Ribonuclease.
- Deoxyribonuclease.
- Gelatinase.
- Elastase.



Endocrine functions of the pancreas

C01.S4

Endocrine anatomy

C01.S4.1

Humans have approximately 1 million *endocrine* cells, called the *Islets of Langerhans*, which comprise five cell types.

Three major cell types are:

- Alpha cells, which secrete *glucagon*.
- Beta cells, which produce *insulin*.
- Delta cells, which secrete the hormone *somatostatin* (also produced by other endocrine cells).

The central part of each islet is occupied by beta cells, and the alpha and delta cells cover this hub.

The Islets have a very good vascular supply receiving 10–15% of the pancreatic blood flow, although they make up only 1–2% of the total pancreatic mass. The pancreas is served by the:

- Gastro-duodenal arteries.
- Branches of the splenic artery.
- The splenic vein and artery run superiorly and posteriorly.
- The mesenteric vein lies in the angle between the head and body of the pancreas.

This facilitates secreted hormones to pass readily into the general circulation.

The secretion of insulin and glucagon are controlled by both parasympathetic and sympathetic neurons.

Endocrine physiology

C01.S4.2

The three hormones secreted by the endocrine tissue in the pancreas regulate the levels of glucose in the blood. They are:

- **Insulin**, which lowers blood glucose (BG) levels.
- **Glucagon**, which promotes the release of glycogen from the liver, raising BG levels.
- **Somatostatin**, which prevents the release of the other two hormones.

Insulin and glucagon are critical participants in glucose homeostasis and serve as acute regulators of blood glucose concentration (see Fig. 1.2).

Insulin is enormously important – a deficiency in insulin or deficits in insulin responsiveness lead to diabetes mellitus.

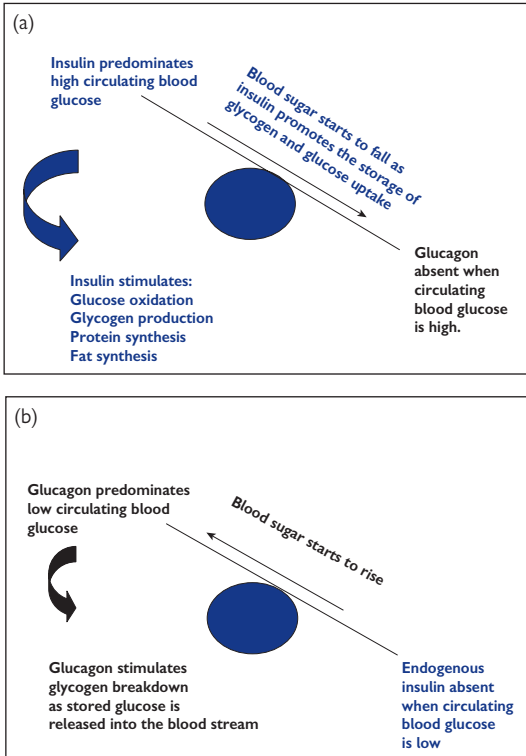


Fig. 1.2 Blood glucose regulation. (a) Fed state post-prandial. (b) Fasting state pre-prandial or after having missed a meal.

001.F2

Hormones

C01.S5

Insulin

C01.S5.1

A small protein composed of two peptide chains, A and B chains:

- The A chain consists of 21 amino acids.
- The B chain of 30 amino acids.
- Synthesized in significant quantities only in B cells in the pancreas.

Glucagon

C01.S5.2

This is the counter regulatory hormone to insulin:

- A linear peptide of 29 amino acids.
- Synthesized as proglucagon within the alpha cells of the pancreas.
- Secreted in response to:
 - hypoglycaemia;
 - elevated blood levels of amino acids;
 - exercise (it is not clear whether it is exercise *per se* or the accompanying exercise-induced depletion of glucose).

When BG levels fall, glucagon is secreted. It facilitates the rise in BG levels in two ways:

- Glucagon stimulates breakdown of glycogen stored in the liver.
- Glucagon activates hepatic gluconeogenesis (production of glucose).
Gluconeogenesis is the pathway by which non-hexose substrates, such as amino acids are converted to glucose.

Glucagon also appears to have a minor effect of enhancing lipolysis of tri-glyceride in adipose tissue, which could be viewed as an additional means of conserving blood glucose by providing fatty acid fuel to most cells.

Somatostatin

C01.S5.3

This was first discovered in hypothalamic extracts and identified as a hormone that inhibited secretion of growth hormone. Subsequently, somatostatin was found to be secreted by a broad range of tissues including:

- Pancreas.
- Intestinal tract.
- Central nervous system (outside the hypothalamus).

Effects on the pancreas

C01.S5.1

- Inhibits secretion of insulin and glucagon.
- Suppresses pancreatic exocrine secretions.



Diabetes: an overview

C01.S6

Definition

C01.S6.1

Diabetes is a group of metabolic conditions, which are chronic and progressive, and are all characterized by an elevated blood glucose level. It impacts on almost every aspect of life, and affects the psychological and physiological well being of those who have been diagnosed with the condition.

Chronic hyperglycaemia causes damage to the eyes, kidneys, heart, blood vessels, and nervous tissue.

Current classification

C01.S6.2

The World Health Organization (WHO) reclassified diabetes in 1999 when the terms Type 1 and Type 2 diabetes were reintroduced.


The classification of diabetes is based on the underlying cause (Table 1.1) within the categories Type 1, Type 2 gestational diabetes, and other types.

Type 1

C01.S6.3

This is an autoimmune disease resulting from islet β cell destruction and is associated with:

- Pancreatic islet cell deficiency.
- Anti-glutamic acid decarboxylase (GAD) antibodies.
- Islet cell antibodies.
- Insulin antibodies.

People with Type 1 diabetes are prone to ketoacidosis (see  Diabetic ketoacidosis, p. 172).

Type 2

C01.S6.4

This comprises between 75 and 95% of all cases of diabetes, and is classified with defective insulin secretion or action.

It is associated with:

- Insulin resistance.
- Insulin secretion deficit.
- Or a combination of both.

Further information

C01.S6.5

Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. (2003) Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* **26**, S5–20.

Table 1.1 Diabetes Types 1 and 2 compared

	Type 1	Type 2
Phenotype	Onset mainly in childhood and adolescence	Onset mainly after 40 years of age; however, increase in numbers of cases in the young
	95% develop the disease before the age of 25	Risks rise steeply with age. 1 in 20 of those over 65 years have Type 2 diabetes. 1 in 5 of those over 85 years of age
	Often thin or unintentionally losing weight.	Often obese
	Ketoacidosis often a presenting feature	Not prone to ketoacidosis
	Absolute insufficiency of insulin, therefore requires insulin replacement to survive	Relative insufficiency of insulin or insulin resistance, therefore does not need insulin replacement to survive
	Pancreatic damage caused by an autoimmune attack	No autoimmune attack on the pancreas
Treatment	Insulin injections are essential treatment, alongside healthy diet and exercise	Staged approach: 1 Healthy diet 2 Regular exercise 3 Weight loss if indicated 4 Hypoglycaemic/anti-diabetic medication 5 Insulin injections
Genotype	Increased prevalence in relatives	Increased prevalence in relatives
	Identical twin study >50% concordance	Identical twin study above 70% concordance
	Equal presentation men and women	More women, especially those who have had gestational diabetes. Increase prevalence in those of South Asian, African, African Caribbean, Hispanic, and Middle Eastern descent

C01.T1

Classification of monogenetic diabetes 001.57

Diabetes caused by inherited monogenetic defects in beta cell function, previously called maturity onset diabetes of the young (MODY), is found mainly in those under 25 years of age. It is characterized by mild hyperglycaemia. In contrast to Type 2 diabetes, insulin action remains unimpaired, but insulin secretion is reduced. Inheritance follows an autosomal dominant pattern which means a parent with MODY has a 50% chance of passing it on to their offspring (autosomals are one of the 22 non-sexually specific chromosomes).

Each type of MODY is caused by a single gene not working properly (monogenetic). The first MODY gene was identified in 1992 (Hattersley et al 1992), and there are more than 6 known genes, each causing a different form of monogenetic diabetes (Fajans et al 2001). The defective genes are responsible for the body's glucose sensor (glucokinase) and factors that control the production of insulin in the beta cells of the Islets of Langerhans in the pancreas (HNF-1alpha, HNF-1beta, HNF-4alpha, IPF-1, and NEURO-D1).

The different types of MODY make up between 2 and 5% of the population of people who have diabetes, but who do have endogenous insulin. MODY X refers to those where a particular genetic mutation has not yet been identified.

HNF-4alpha or HNF-4a (MODY 1) 001.57.1

This rare type is caused by a mutation of the *HNF-4* gene on chromosome 20q and has an effect similar to MODY3.

Glucokinase (MODY 2) 001.57.2

- Causes between 10 and 65% of MODY.
- Causes mild diabetes that rarely leads to complications.
- Often treated with meal planning and diet alone.
- Often diagnosed in childhood or pregnancy.

HNF-1alpha or HNF-1a (MODY 3) 001.57.3

Caused by mutations on chromosome 12, HNF-1alpha is the most commonly found MODY (WHO 1999).

- Causes between 20 and 75% of MODY.
- Causes progressive diabetes.
- Potential for complications of diabetes to develop.
- Usually diagnosed after puberty.
- Sensitive to sulphonylureas.

IPF-1 (MODY 4) 001.57.4

Rare form of MODY producing relatively mild diabetes.

HNF-1beta (MODY 5) 001.57.5

Rare form of MODY associated with kidney disease.

Further information

001.57.6

- Fajans S, Bell G, Polonsky K. (2001) Molecular mechanisms and clinical pathophysiology of Maturity Onset Diabetes of the Young. *N Engl J Med* **345**, 971.
- Hattersley AT, Turner RC, Permutt MA, et al (1992) Linkage of Type 2 diabetes to the glucokinase gene. *Lancet* **339**(8805), 1307–10.
- World Health Organization (1999) *Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus*. Geneva: World Health Organization.

Genetic testing

C01.S8

It is estimated that 1% of people with diabetes in the UK (about 20,000 people) have monogenetic diabetes (Shepherd 2001).

The Royal Devon and Exeter Hospital (RD&E) has funding for a project that delivers further training regarding monogenetic diabetes and genetic testing to 18 experienced diabetes specialist nurses. Each nurse will be based in a different region of the UK and will offer:

- Updating to local diabetes teams regarding monogenetic diabetes and the genetic tests available.
- Assistance identifying which families are likely to have monogenic diabetes.
- Advice regarding the most appropriate diagnostic genetic test to use.

They can also discuss implications with the families and guide follow-up for the family members once the results are received.

Predictive testing

C01.S8.1

It is possible to test individuals who have a parent with MODY to see if they have inherited the impaired gene, and this is called predictive testing.

- If a parent has MODY then there is a 50% (1:2) chance that their offspring will have the same the gene and will go on to develop diabetes.
- A predictive genetic test looks at the genetic code to see if the same genetic changes are present.
- A venous blood sample is sent to the RD&E for examination.
- Results either positive or negative are available in 4–8 weeks:
 - *positive* – the person is likely to develop diabetes at some time in the future and regular blood glucose checks should be undertaken;
 - *negative* – the risk factors for developing diabetes are the same as for the rest of the population.

Why test?

- If a differential diagnosis is made this will lead to the provision of optimal treatment.
- Mistakes can be made by teams who do not have the experience or latest information regarding the implications of the different types of MODY, for example:
 - people with HNF-1alpha (MODY 3) are sensitive to sulphonylureas and often achieve better glycaemic control on a small dose of these compared with insulin injections.
 - mutations within the glucokinase gene (MODY 2) cause mild, stable hyperglycaemia, which does not require treatment, but in children may be misdiagnosed as Type 1 diabetes.

Further information

C01.S8.2

Shepherd M. (2001) Recognising maturity onset diabetes of the young. *J Diabetes Nurs* 5(6), 168–72.

Shepherd M, Sparkes AC, Hattersley AT. (2001) Genetic testing in Maturity Onset Diabetes of the Young (MODY): a new challenge for the diabetes clinic. *Pract Diabetes Internat* 18, 16–21.

Disease-related diabetes

C01.S9

Diseases of exocrine function

C01.S9.1

- Pancreatitis.
- Pancreatectomy following trauma or surgery.
- Neoplasia.
- Pancreatic destruction, for example, with cystic fibrosis.
- Fibrocalculous pancreatopathy.
- Haemochromatosis (a disease of iron storage).

C01.S9.2

Diseases of the endocrine system

C01.S9.2.1

Cushing's syndrome

- Increases the production of glucose by the liver.
- Increases insulin resistance at the peripheral tissue level.
- Resulting in increased blood glucose.

C01.S9.2.2

Acromegaly

- Usually caused by a tumour in the pituitary gland, which causes excess growth hormone to be produced.
- Growth hormone increases insulin resistance.
- Over half of patients with acromegaly have hyperinsulinemia and glucose intolerance.

C01.S9.2.3

Pheochromocytoma

- Excess epinephrine, a 'fight or flight' hormone is secreted, often because of a pheochromocytoma, a tumour of the adrenal gland.
- Fight or flight response mobilizes glucose production in order to fuel the activity.
- Epinephrine acts on adrenoreceptors and increases insulin resistance.
- Inhibits insulin secretion and increases the breakdown of fat and glycogen to glucose in the liver.
- This can result in diabetes.

C01.S9.2.4

Glucagonoma

Rare tumours of the pancreatic alpha cells may increase glucagons levels resulting in impaired glucose regulation.

C01.S9.2.5

Somatostatinoma

- Excess somastatin secretion caused by a rare pancreatic tumour affecting the pancreatic delta cells.
- Inhibits insulin secretion and results in impaired glucose regulation.

Drug and chemical interactions

C01.S10

Many medications prescribed for specific purposes can inhibit the effect of insulin, not causing diabetes, but acting as a trigger in those with a predisposition to develop it.

Some hormones when given in large doses can impair the action of insulin, e.g. glucocorticoids and thyroid hormones.

It is important to check the current edition of the British National Formulary (BNF) for full details of drug interactions and contra-indications.

Patients who need to take contraindicated medications will need to be aware of the additional risks of hyperglycaemia. Appropriate monitoring is required in order to be able to react to unsafe blood glucose levels.

Glucocorticoids

C01.S10.1

- Raise blood glucose levels by counteracting some actions of insulin.
- Prolonged use of prednisolone may lead to glucose intolerance and diabetes.

Thiazides (diuretics)

C01.S10.2


- Can increase hyperglycaemia in people with Type 2 diabetes.
- Impairing insulin secretion as a result of causing potassium depletion.
- May also increase insulin resistance.

Gestational diabetes

CD1.011

Gestational diabetes (diabetes in pregnancy) affects less than 1 in 20 women.

It is thought that placental hormones increase insulin resistance in the mother leading to elevated blood glucose levels.

- Usually identified in the second trimester.
- If hyperglycaemia persists requires treatment with insulin for the duration of the pregnancy.
- Blood glucose levels return to normal following delivery.
- Usually occurs in subsequent pregnancies.
- Can often be an indicator of Type 2 diabetes in later life (see  Chapter 2, pp. 27–52).
- Severe insulin resistance with circulating antibodies to the insulin receptor is known as Type B insulin resistance.
- Hyperglycaemia can be caused when anti-insulin receptor antibodies bind to the insulin receptor, blocking insulin from its receptors.
- Rarely these autoantibodies can cause hypoglycaemia by mimicking the action of insulin.

Impaired-fasting glucose

C01.S12

Those who have fasting blood glucose above the normal range (less than 6.1mmol/l), but below the diagnostic range for diabetes (greater than 7mmol/l).

A study in Helsinki (Qiao et al 2003) of 2593 people over 10 years showed the risk of progression to diabetes was 1 in 50 for an adult aged 45–64 years with normal fasting glucose, but rose to 1 in 22 for an adult with impaired fasting glucose.

Men and women had the same level of risk.

Further information

C01.S12.1

Qiao Q, Lindström J, Valle T, Tuomilehto J (2003). Progression to clinically diagnosed and treated diabetes from impaired glucose tolerance and impaired fasting glycaemia. *Diabetes Med* **20**, 1027–33.



Diagnosis and diagnostic criteria

C01.S13

Diabetes mellitus

C01.S13.1

WHO (2006) does not discriminate between Types 1 and 2, identifying people with diabetes as 'a group with significantly increased premature mortality and increased risk of microvascular and cardiovascular complications', and the diagnostic criteria for this group as having:

- A fasting plasma glucose ≥ 7.0 mmol/l (126mg/dl).
- Or a 2h plasma glucose ≥ 11.1 mmol/l (200mg/dl).

Type 1 (see Table 1.2)

C01.S13.2

- If classical symptoms present, confirm diagnosis by a single laboratory glucose measurement.
- If classical symptoms not present, confirm diagnosis by two laboratory glucose measurements (NICE 2004).

Diagnosis of diabetes mellitus is made if there are positive tests from any two of the following on different days:

- Symptoms of diabetes mellitus plus random blood glucose concentration above 11mmol/L.¹

or

- Fasting plasma glucose above 7.00mmol/l.

or

- 2h post-prandial blood glucose above 11.1mmol/l following a 75g glucose load (a glucose tolerance test).

Type 2 (see Table 1.3)

C01.S13.3

The National Collaborating Centre for Chronic Conditions updated the NICE National Clinical Guidelines NICE in 2008 describing people with Type 2 diabetes as:

People are normally thought to have Type 2 diabetes if they do not have Type 1 diabetes (rapid onset, often in childhood, insulin-dependent, ketoacidosis if neglected) or other medical conditions or treatment suggestive of secondary diabetes. (NICE 2008)

Gestational diabetes

C01.S13.4

A standard oral glucose tolerance test should be performed. The World Health Organization (WHO) recommends:

- Overnight (8–14h) fasting.
- 75g anhydrous glucose in 200–300ml water.
- Measure plasma glucose fasting and 2h after the glucose loading.
- A diagnosis is made if the fasting blood glucose is above 5.3mmol/l and the 2h post-glucose load is above 8.6mmol/l.

(see  Gestational diabetes, p. 19).

¹ Symptoms include polydipsia, polyuria, recurrent infections, or unexplained or unintended weight loss.

Table 1.2 Signs and symptoms of Type 1 diabetes

Initial signs and symptoms	Reason
Rarely diabetic ketoacidosis (DKA)	It is unusual for patients to present with ketoacidosis unless precipitated by trauma, infection, or surgery
Polyuria (frequently passing urine)	Caused by osmotic diuresis secondary to hyperglycaemia
Polydipsia (thirst)	Caused by the hyperosmolar state and dehydration caused by polyurea
Polyphagia with weight loss	Weight loss with a normal or increased appetite is due to depletion of water, and a catabolic state with reduced glycogen, proteins, and triglycerides
Fatigue and weakness	Due to muscle wasting from the catabolic state of insulin deficiency, hypovolemia ¹ , and hypokalemia ²
Muscle cramps	Due to electrolyte imbalance
Blurred vision	Due to the effect of the hyperosmolar state on the lens and vitreous humor Glucose and its metabolites cause dilation of the lens, altering its normal focal length
Gastrointestinal symptoms: • Nausea • Abdominal discomfort or pain • Changes in bowel habit	Acute fatty liver may lead to distention of the hepatic capsule, causing right upper quadrant pain. Pancreatitis may cause abdominal pain. Abdominal pain often accompanies ketosis.

¹Hypovolemia: decrease in blood plasma volume.
²Hypokalemia: decreased blood potassium levels.

C01.T2

Table 1.3 Diagnostic criteria Type 2, IGT, IFG

Plasma glucose (mmol/l)	Fasting plasma glucose	2h post-glucose tolerance test
Diabetes mellitus	≥7.00	≥11.1
Impaired glucose tolerance (IGT)	>7.00	Between 7.8 and 11
Impaired fasting glucose (IFG)	6.1–7	>7.8
Non-diabetic response	6.1	7.75

NB. In the absence of symptoms, diabetes should only be diagnosed on the basis of two abnormal glucose results. One abnormal result is sufficient if the patient has symptoms.

C01.T3

Further information

001.S13.5

WHO (1999). *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications*. World Health Organization, Geneva.

□ http://www.staff.ncl.ac.uk/philip.home/who_dmc.htm#Diagnosis (accessed 24 November 2007). National Institute for Clinical Excellence (NICE) (2004) *Type 1 diabetes: diagnosis and management of type 1 diabetes in adults*. NICE, London.

WHO (2006) *Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia*. World Health Organization, Geneva.



Differential diagnosis

001.S14

This is the (often mental) checklist of hypothesized alternative diagnoses made in response to a patient's symptoms, history, appearance, and clinical parameters. For example, if a patient has glycosuria (glucose in their urine), it is important to consider the following possible causes.

Endocrine disorders

001.S141

- **Endocrine tumour** causing increased production of growth hormone:
 - glucocorticoids
 - catecholamines
 - glucagon
 - somatostatin.
- **Addison disease.**
- **Graves disease.**
- **Hashimoto thyroiditis.**
- **Acanthosis nigricans** (genetic disorders with insulin resistance).

Drugs

001.S142

- Thiazides.
- Diuretics.
- Phenytoin.
- Glucocorticoids.

Chronic pancreatitis

001.S143

Cystic fibrosis

001.S144

Prader-Willi syndrome

001.S145

- Mental retardation.
- Muscular hypotonia (low muscle tone, and reduced muscle strength).
- Obesity.
- Short stature.
- Hypogonadism (lack of function of the ovaries or testes associated with diabetes mellitus (DM)).

Renal glycosuria

001.S146

Glucose appears in urine despite normal glucose concentration in blood. This glucose may be due to:

- An autosomal genetic disorder.
- Dysfunction of the proximal renal tubule (e.g. Fanconi syndrome, chronic renal failure).
- Increased glucose load on tubules by the elevated glucose filtration rate during pregnancy.

Peripheral neuropathy

001.S147

- Due to alcohol and vitamin B12 deficiency.