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О. Н. ВАСИЛЬКОВА

САХАРНЫЙ ДИАБЕТ

Учебно-методическое пособие
для студентов 5, 6 курсов
факультета по подготовке специалистов для зарубежных стран
учреждений высшего медицинского образования

DIABETES MELLITUS

Teaching workbook
for the 5–6th year students
of the Faculty on preparation of experts for foreign countries
of medical higher educational institutions

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Рецензенты:
доктор медицинских наук, профессор,
заведующий кафедрой эндокринологии
Белорусского государственного медицинского университета
Т. В. Мохорт;
кандидат медицинских наук,
ассистент, выполняющий лечебную работу, кафедры факультетской терапии
Санкт-Петербургского государственного университета
И. Ю. Пчелин

В учебно-методическом пособии затронуты основные вопросы патогенеза, диагностики и лечения сахарного диабета.

Предназначено для студентов 5, 6 курсов факультета по подготовке специалистов для зарубежных стран учреждений высшего медицинского образования.

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INTRODUCTION

KEY POINTS
- Diabetes is common and its incidence is rising.
- Type 2 diabetes is by far the most common accounting for 85–95 % of cases
- Complications in the microvasculature (eye, kidney and nerve) and the macrovasculature are responsible for considerable morbidity and excess mortality.

Diabetes mellitus is a condition of chronically elevated blood glucose concentrations which give rise to its main symptom of passing large quantities of sweet-tasting urine (diabetes from the Greek word meaning 'a siphon', as the body acts as a conduit for the excess fluid, and mellitus from the Greek and Latin for honey). The fundamental underlying abnormality is a net (relative or absent) deficiency of the hormone insulin. Insulin is essentially the only hormone that can lower blood glucose.

Diabetes is common and is becoming more common. Age-adjusted prevalence is set to rise from 5.9 % to 7.1 % (246–380 million) worldwide in the 20–79 years age group, a 55 % increase. The relative proportions of type 1 to type 2 vary from 15:85 for Western populations to 5:95 in developing countries.

Demographics

Type 1 diabetes and type 2 diabetes differentially impact populations based on age, race, ethnicity, geography, and socioeconomic status.

Genetics

Both type 1 and type 2 diabetes are polygenic diseases where many common variants, largely with small effect size, contribute to overall disease risk. Disease heritability, defined as sibling-relative risk, is 3 for type 2 diabetes and 15 for type 1 diabetes. The lifetime risk of developing type 2 diabetes is ~40 % if one parent has type 2 diabetes and higher if the mother has the disease. The risk for type 1 diabetes is ~2 % if a mother has type 1 diabetes and higher ~7 % if the father has the disease.

Environmental Influences

Despite the genetic underpinnings of the diseases, the prevalence of both type 1 and type 2 diabetes is increasing globally at a rate that outpaces genetic variation, suggesting that environmental factors also play a key role in both types of diabetes. Common environmental factors are associated with type 1 and type 2 diabetes, including dietary factors, endocrine disruptors and other environmental polluters, and gut microbiome composition. In addition to well-established roles in type 2 diabetes, obesity and insulin resistance may be accelerators of type 1 diabetes. Conversely, islet autoimmunity associated with possible environmental triggers (e.g., diet, infection) may have a role in a subset of people diagnosed with type 2 diabetes.

DIAGNOSIS AND CLASSIFICATION OF DIABETES

KEY POINTS
- WHO and ADA define a cut-off of 7mmol/L in fasting **plasma** glucose concentration to define diabetes.
- Greater standardisation of HbA1c assays has led to a recommendation that HbA1c ≥6.5 % (or 48 mmol/mol) be used as a diagnostic cut-off for diabetes.
- Impaired glucose tolerance and impaired fasting glycaemia are intermediate states of prediabetes (type 2) associated with increased cardiovascular risk.
- Type 2 diabetes is often undiagnosed in the community, and 20 % of newly diagnosed patients already have evidence of diabetes-related CV complications.

The diagnosis of diabetes in an asymptomatic individual should never be made on the basis of a single abnormal glucose value. Verification of the diagnosis with repeat testing is required, unless an individual presents with unequivocal hyperglycaemia along with its classic symptoms. The diagnostic values for diabetes mellitus are shown in Table 1.

The classic symptoms of diabetes such as polyuria, polydypsia and polyphagia occur commonly in type 1 diabetes, which has a rapid development of severe hyperglycaemia and also in type 2 diabetes with very high levels of hyperglycaemia. Severe weight loss is common only in type 1 diabetes or if type 2 diabetes remains undetected for a long period. Unexplained weight loss, fatigue and restlessness and body pain are also common signs of undetected diabetes. Symptoms that are mild or have gradual development could also remain unnoticed.

Organization (WHO) and the American Diabetes Association (ADA) have used a fasting **plasma** glucose (FPG) of 7 mmol/L or higher to define diabetes (Table 1). This originated from epidemiological studies in the 1990 s which appeared to show that the risk of microvascular complications (e. g. retinopathy) increases sharply at a FPG threshold of 7 mmol/L. Lately, however, the notion of a clear glycaemic threshold separating people at high and low risk of diabetic microvascular complications has been called into question. Part of the rationale for switching to HbA1c >6.5 % as a diagnostic test is that moderate retinopathy, in more recent trials, is rare below this HbA1c threshold.

The Oral Glucose Tolerance Test (OGTT) is the most sensitive test for detecting diabetes mellitus.

Indications

- Patients having symptoms suggestive of diabetes mellitus, but fasting blood sugar value is inconclusive (<6.1 mmol/l).

- During pregnancy, excessive weight gaining is noticed, with a past history of big baby (more than 4 kg) or a past history of miscarriage.

- To rule out benign renal glucosuria.

Table 1 — Classification of diabetes and glucose intolerance according to ADA fasting and WHO 2-h glucose criteria

Parameters	Blood sample		
	Plasma	Capillary	Whole
Fasting blood glucose (mmol/L)			
Normal	<6.1	<5.6	<5.6
Impaired fasting glycaemia	6.1–6.9	5.6–6.0	5.6–6.0
Diabetes	≥7.0	≥6.1	≥6.1
2-hour blood glucose			
Normal	<7.8	<7.8	<6.7
Impaired fasting glycaemia	7.8–11.0	7.8–11.0	6.7–9.9
Diabetes	≥11.1	≥11.1	≥10.0

Contraindications

• Person with confirmed diabetes mellitus.

• OGTT has no role in follow up of diabetes. It is indicated only for the initial diagnosis.

• The test should not be done in acutely ill patients.

Patient Preparation

1. The patient should be on balanced diet, containing normal daily requirement of carbohydrates, at least 2–3 days prior to the test.

2. Patients should avoid drugs likely to influence the blood glucose levels, at least 2 days prior to the test.

3. Patient should report to the laboratory after fasting for 12–16 hours. He/She can drink water.

4. All samples of blood should be venous preferably. If the capillary blood from 'finger-prick' is used, all samples should be capillary blood.

Conduction of OGTT

1. A fasting blood sample is obtained.

2. The glucose drink may be chilled or ice chips may be used to make it more palatable. See schedule below for dosage.

3. Note the time when the patient finishes drinking the glucose.

4. Blood samples are taken following the schedule below. All draws, except the initial draw, are timed from the time the patient finishes drinking the glucose.

Non-pregnant adults receive a 75 g dose with a Blood Glucose level at the following intervals: [0 min.] [120 min.].

Gestational 2 hour receive a 75 g dose with a Blood Glucose level at the following intervals: [0min.] [60 min.] [120 min.].

Children (< 12 years) receive a 1.75 g/kg (max 75 g) dose with a Blood Glucose level at the following intervals: [0 min.] [60 min.] [120 min.].

Normal Values and Interpretation of OGTT see in Table 1.

Diabetes can be diagnosed in several ways:

• HbA1c ≥6.5 %.

• A casual (random) plasma glucose level ≥11.1 mmol/L in someone with typical symptoms of diabetes.

• A fasting **plasma** glucose level ≥7.0 mmol/L.

• A plasma glucose level ≥11.1 mmol/L 2 hours after a 75 g load of glucose given by mouth (OGTT).

Classification of diabetes

The current classification of diabetes is based on the aetiology of the disease. There are four categories.

1. Type 1 (b-cell destruction, usually leading to absolute insulin deficiency)

• Autoimmune

• Idiopathic

2. Type 2 (ranges from predominantly insulin resistant, with relative insulin deficiency, to a predominantly insulin-secretory defect, with or without insulin resistance)

3. Other specific types

• Genetic defects of β cell function

• Genetic defects of insulin action

• Diseases of exocrine pancreas

• Endocrinopathies

• Drug induced or chemical induced, e. g. steroids Infections

• Uncommon forms of immune-mediated diabetes

• Other genetic syndromes sometimes associated with diabetes

4. Gestational diabetes

Type 1 diabetes is subdivided into two main types: autoimmune (about 90 % of type 1 patients, in which immune markers, such as circulating islet cell antibodies, suggest autoimmune destruction of the β cells) and idiopathic (where there is no evidence of autoimmunity).

Various clinical and biochemical features can be used to decide whether the patient has type 1 or type 2 diabetes (Table 2). The distinction may be difficult in individual cases.

The category of 'other specific types of diabetes' is a large group of conditions, which includes genetic defects in insulin secretion (such as in maturity-onset diabetes of the young (MODY) and insulinopathies), genetic defects in insulin action (e.g. syndromes of severe insulin resistance), pancreatitis and other exocrine disorders, hormone-secreting tumours such as acromegaly (growth hormone) and Cushing's syndrome (cortisol). Some cases are caused by the administration of drugs such as glucocorticoids. Some genetic syndromes are sometimes associated with diabetes (e. g. Down's syndrome, Klinefelter's syndrome and many more).

Table 2 — Clinical features of type 1 and type 2 diabetes

Type 1 diabetes	Type 2 diabete
• Sudden onset with severe symptoms of thirst and ketoacidosis (vomiting, hyperventilation, dehydration) • Recent, marked weight loss. Usually lean • Spontaneous ketosis • Life-threatening; needs urgent insulin replacement • Absent C-peptide • Markers of autoimmunity present (e. g. islet cell antibodies)	• Usually insidious onset of tiredness, thirst, polyuria, nocturia • No ketoacidosis • Usually overweight or obese; often no recent weight loss • Frequent infections, e. g. urine, skin, chest • Symptoms may be minimal and/or ignored by patient • Often other features of 'metabolic syndrome', e. g. hypertension • C-peptide detectable

Gestational diabetes mellitus, by definition, is any degree of glucose intolerance with onset or first recognition during pregnancy. This definition applies regardless of whether treatment involves insulin or diet modification alone; it may also apply to conditions that persist after pregnancy.

CASE HISTORY

A 66-year-old retired policeman attends his family doctor for a routine blood pressure (BP) check. He has had hypertension for 4 years. He reports incidentally that he has been feeling generally tired and lethargic. On further questioning, he admits to nocturia×3 and volunteers that in recent months he has been taking a glass of water to bed since he often wakes feeling thirsty. The GP notices that he had a cutaneous boil lanced 6 weeks ago. Apart from hypertension, there is no other significant past medical history but his bodyweight has gradually risen (95 kg, Body Mass Index (BMI) 32). He takes an angiotensin-converting enzyme inhibitor, lisinopril 10 mg, for hypertension. His mother had type 2 diabetes, he is a non-smoker and drinks 15 units of alcohol per week. His only exercise is golf, twice per week. The doctor takes a random venous blood sample, which shows a plasma glucose level of 13 mmol/L. Further blood tests show a normal haematology profile, normal electrolytes and renal function, HbA1c 8.3 %, and fasting lipids show total cholesterol 6.6 mmol/L, low-density lipoprotein-cholesterol 4.3 mmol/L, triglycerides 3.9 mmol/L and high-density lipoprotein-cholesterol 0.6 mmol/L. Minor abnormalities of liver function are also noted AST and ALT 2–3×upper limit.

Comment: This man presents with typical symptoms of type 2 diabetes and several risk factors (age, obesity, hypertension, family history). The random plasma glucose, in the context of symptoms, is diagnostic. He has features of the metabolic syndrome, including hypertension, dyslipidaemia (high triglycerides and low HDL-cholesterol) and central obesity, and fatty infiltration of the liver is common in this scenario. The HbA1c is quite high, reflecting chronic hyperglycaemia over at least 8 weeks. Susceptibility to infections is typical.

PATHOPHYSIOLOGY OF DIABETES

Insulin is synthesised in and secreted from the β cells within the islets of Langerhans in the pancreas. The normal pancreas has about 1 million islets, which constitute about 2–3 % of the gland's mass. The main cell types of the pancreatic islets are β cells that produce insulin, α cells that secrete glucagon, δ cells that produce somatostatin and PP cells that produce pancreatic polypeptide. Islet cells interact with each other through direct contact and through their products (e. g. glucagon stimulates insulin secretion and somatostatin inhibits insulin and glucagon secretion).

The insulin molecule consists of two polypeptide chains, linked by disulphide bridges; the A-chain contains 21 amino acids and the B-chain 30 amino acids. Human insulin differs from pig insulin (an animal insulin which was used extensively for diabetes treatment prior to the 1990s) at only one amino acid position (B30).

Insulin is synthesised in the β cells from a single amino acid chain precursor molecule called proinsulin (Figure 1). Synthesis begins with the formation of an even larger precursor, preproinsulin, which is cleaved by protease activity to proinsulin. Proinsulin is packaged into vesicles in the Golgi apparatus of the β cell; in the maturing secretory granules that bud off it, proinsulin is converted by enzymes into insulin and connecting peptide (C-peptide).

Insulin and C-peptide are released from the β cell when the granules are transported ('translocated') to the cell surface and fuse with the plasma membrane (exocytosis).
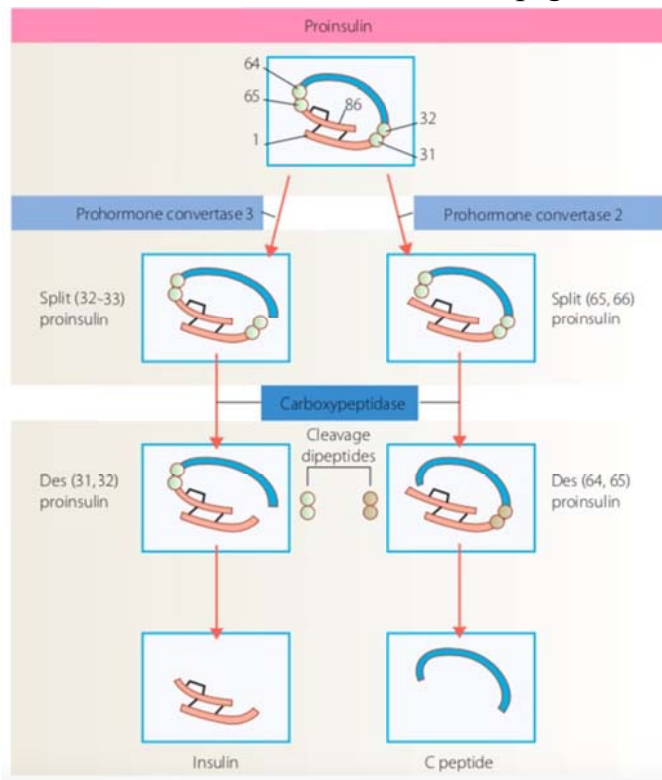
Figure 1 — Insulin biosynthesis and processing. Proinsulin is cleaved on the C-terminal side of two dipeptides. The cleavage dipeptides are liberated, so yielding the 'split' proinsulin products and ultimately insulin and C-peptide

Glucose is the main stimulator of insulin release from the β cell, which occurs in a characteristic biphasic pattern –an acute 'first phase' that lasts only a few minutes, followed by a sustained 'second phase'. The first phase of release involves the plasma membrane fusion of a small, readily releasable pool of granules; these granules discharge their contents in response to both nutrient and

non-nutrient secretagogues. In contrast, second- phase insulin secretion is evoked exclusively by nutrients. Glucose levels below 5 mmol/L do not affect insulin release; half-maximal stimulation occurs at about 8mmol/L. Glucose must be metabolised within the β cell to stimulate insulin secretion (Figure 2). It enters the β cell via the GLUT-2 transporter and is then phosphorylated by glucokinase, which acts as the 'glucose sensor' that couples insulin secretion to the prevailing glucose level. Glycolysis and mitochondrial metabolism produce adenosine triphosphate (ATP), which closes ATP-sensitive potassium (KATP) channels. This in turn causes depolarization of the β cell plasma membrane, which leads to an influx of extracellular calcium through voltage-gated channels in the membrane. The increase in cytosolic calcium triggers granule translocation and exocytosis. The KATP channel is an octamer that consists of four K+-channel subunits (called Kir 6.2) and four SUR-1 subunits.
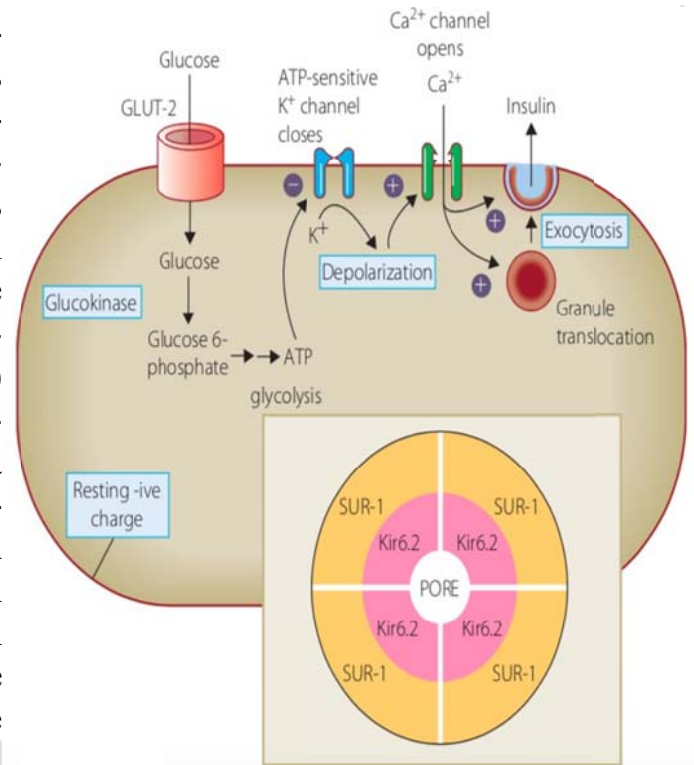
Figure 2 — The mechanism of glucose-stimulated insulin secretion from the β cell. The structure of the KATP channel is shown in the inset

Insulinlowersglucose levelspartlybysuppressing glucose output from the liver, both by inhibiting glycogen breakdown (glycogenolysis) and by inhibiting gluconeogenesis (i.e. the formation of 'new' glucose from sources such as glycerol, lactate and amino acids, like alanine). Relatively low concentrations of insulin are needed to suppress hepatic glucose output in this way, such as occur with basal insulin secretion between meals and at night. With much higher insulin levels after meals, GLUT-4 mediated glucose uptake into the periphery is stimulated.

One model of the evolution of **type 1 diabetes** is that individuals destined to develop the disease are born with genes that confer predisposition and they outweigh any genes with protective effects (Figure 3). Environmental factors then act as triggers of the T cell-mediated autoimmune destructive process, which results in insulitis, β cell injury and loss of β cell mass. As β cell function declines, there is loss of the first-phase insulin response to intravenous glucose, subsequent glucose intolerance (pre- diabetes) and eventually the clinical onset of overt diabetes. An alternative view is that there is a chronic interaction between genetic

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Figure 3 — Depiction of the evolution of type 1 diabetes
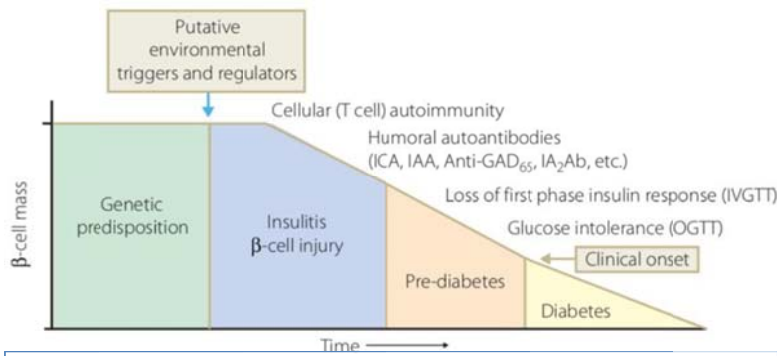
susceptibility, cumulative exposure to environmental factors and immune regulatory processes over the entire period until a critical loss of β cell mass results in insulin deficiency and hyperglycaemia. These events are assumed to proceed more rapidly in children.

Type 2 diabetes develops because of a progressive deterioration of β cell function, coupled with increasing insulin resistance for which the β cell cannot compensate. β-cell mass is thought to be decreased by only 20–40 % in type 2 diabetes and this clearly cannot explain the >80 % reduction in insulin release that is observed. Both insulin resistance and β cell dysfunction are early features of glucose intolerance, and there has been much debate as to whether one is the primary defect and precedes the other. In practice, the contribution of insulin resistance and β cell dysfunction varies considerably between patients, as well as during the course of the disease. Usually, there is a decline in both insulin sensitivity and insulin secretion in patients who progress from impaired glucose tolerance (IGT) to diabetes and undoubtedly environmental and genetic factors contribute to this process (Figure 4).

Figure 4 — Pathogenesis of type 2 diabetes. Both genetic and environmental factors contribute to both insulin resistance and β cell failure

CASE HISTORY

A 25-year-old single, male postgraduate student, whose parents were from Bangladesh, presented to the local genitourinary clinic with penile candida, and was worried he may have contracted a sexually transmitted disease. Urinalysis confirmed glycosuria and a random capillary blood glucose was 13.2 mmol/L. On direct questioning, he said he had been a bit more thirsty lately. He added that his father had just been diagnosed with type 2 diabetes. He used to play first team hockey as an undergraduate but had stopped following a knee injury 18 months ago. Since then his life had become more sedentary, he ate convenience foods more than four times a week and had gained about 12 kg in weight. He now had a waist circumference of 100cm and a BMI of 30kg/m.

Comment: This young man has multiple risk factors for type 2 diabetes. His ethnic background and family history, recent weight gain, dietary changes and lack of exercise are all well validated. We are not given his birthweight but if this was low then he would also fit the picture of the 'thrifty phenotype'. Although his BMI is definitely raised, his height makes this a less reliable measure of obesity than his waist circumference. He also shows the phenomenon of genetic anticipation in that his age at diagnosis is much earlier than that of his father.

DIABETES CONTROL AND ITS MEASUREMENT

KEY POINTS
- Assessment of diabetic control is usually based upon estimates of glycaemia. Capillary blood glucose monitoring is relatively convenient and easy to perform and is a critical adjunct to modern insulin treatment regimens.
- Glycated haemoglobin concentrations estimate average blood glucose over the preceding 8–12 weeks.

'Diabetic control' defines the extent to which the metabolism in the person with diabetes differs from that in the person without diabetes. Measurement usually focuses on blood glucose: 'good' control implies maintenance of nearnormal blood glucose concentrations throughout the day. However, many other metabolites are disordered in diabetes and some, such as ketone bodies, are now more easily measurable and clinically useful, particularly during acute illness or periods of poor blood glucose control.

In addition to blood and urine glucose concentrations, there are indicators of longer term glycaemic control over the preceding weeks using plasma glycated haemoglobin (HbA1c) or fructosamine concentrations.

Capillary blood glucose monitoring

Single blood glucose measurements are of little use as an assessment of overall control in type 1 diabetes because of unpredictable variations throughout the day and from day to day, although they are important in order to detect hypoglycaemia. In order to assess control more meaningfully, serial, timed blood glucose samples are usually needed. Self-monitoring of capillary blood glucose by patients at home using special enzyme-impregnated reagent strips and a meter is now an integral part of modern diabetes management, especially for those who are on insulin therapy.

Urine glucose monitoring

Glycosuria occurs when blood glucose levels exceed the renal threshold for glucose (usually 10mmol/L). However, urine glucose testing is unreliable in the

assessment of blood glucose control because renal threshold varies between and within patients. Fluid intake can affect urine glucose concentrations and importantly, the result does not reflect blood glucose at the time of the test but over the duration that the urine has accumulated in the bladder. A negative urine test cannot distinguish between hypoglycaemia, normoglycaemia and modest hyperglycaemia.

Glycated haemoglobin

Haemoglobin A comprises over 90 % of most adult haemoglobin and is variably glycated by the non-enzymatic attachment of sugars. As the average life span of the red cell is 90–120 days, the percentage glycated haemoglobin is a reflection of glycaemic control over the 8–12 weeks preceding the test. The recommended frequency of testing of HbA1c is twice per year in stable patients and 4–6 times for those undergoing treatment changes.

Fructosamine

Serum fructosamine is a measure of glycated serum protein, mostly albumin, and is an indicator of glycaemic control over the preceding 2–3 weeks (the lifetime of albumin). Colorimetric assays for fructosamine, which are now adapted for automated analysers, give a normal reference range of 205–285 µmol/L. It has potential advantages over HbA1c, particularly in situations such as haemoglobinopathies or pregnancy when the glycated haemoglobin is hard to interpret. However, standardisation is difficult: uraemia, lipaemia, hyperbilirubinaemia and vitamin C use can affect the assay, and there may be an effect of high or low circulating blood proteins.

Urine and blood ketone measurements

Ketones can be measured in urine using a colorimetric test or in capillary blood using an electrochemical sensor similar to those now used for glucose. Blood ketone testing should be available in acute medical and obstetric assessment units as well as for in-patients with diabetes with intercurrent illnesses and perhaps as a means of monitoring response to treatment for diabetic ketoacidosis.

Continuous glucose monitoring systems

Continuous glucose monitoring (CGM) systems consists of a small disposable sensor inserted into the skin, a transmitter connected to the sensor by a sensor mount wirelessly transmits results to a receiver and displays results. The sensor measures the glucose in interstitial fluid and will need to be calibrated or matched with actual blood glucose values at regular intervals during the CGM wear. It can be used whether insulin pump therapy uses, multiple daily insulin injections, other diabetes medications or diet and exercise and works 24 hours a day. It can also include alarms to indicate when glucose levels are too high or too low.

MANAGEMENT OF TYPE 1 DIABETES

> KEY POINTS
> • The objective of insulin treatment is to try and reproduce the physiological pattern of insulin production using subcutaneous injections. This usually entails multiple daily injections of short-intermediate- or long-acting insulins, together with regular capillary blood glucose testing.
> • Continuous subcutaneous insulin infusion can improve glycaemia and reduce hypoglycaemia in patients struggling on conventional therapy.

Modern management of type 1 diabetes comprises a package of measures including

- multiple daily injections for a more physiological insulin replacement;
- assessment of glycaemic control using blood glucose self-monitoring as well as clinic tests such as glycated haemoglobin (HbA1c);
- insulin dosage adjustment according to diet and exercise;
- a healthy diet and carbohydrate counting;
- and intensive diabetes education.

Insulin replacement

The objective of insulin replacement is to mimic the insulin secretion pattern in the person without diabetes with multiple subcutaneous injections. In the person without diabetes, there is normally a rapid increase in

plasma insulin after meals, triggered by glucose absorption into the bloodstream. This surge in insulin limits postprandial glycaemia by stimulating hepatic and peripheral glucose uptake. During fasting and between meals, insulin measurements drop to much lower levels (often called basal or steady state) which are sufficient to maintain blood glucose in the range 3.5–5.5 mmol/L. Even after a prolonged fast, it is possible to detect circulating insulin.

For practical reasons, insulin is usually injected subcutaneously and regimens comprise short-acting (soluble, regular or analogue) insulin to simulate the normal mealtime surge, together with a longer acting insulin which is used to provide the background or basal concentration. This combination is called the 'basal-bolus' regimen or multiple daily injection (MDI) therapy (Figure 5).
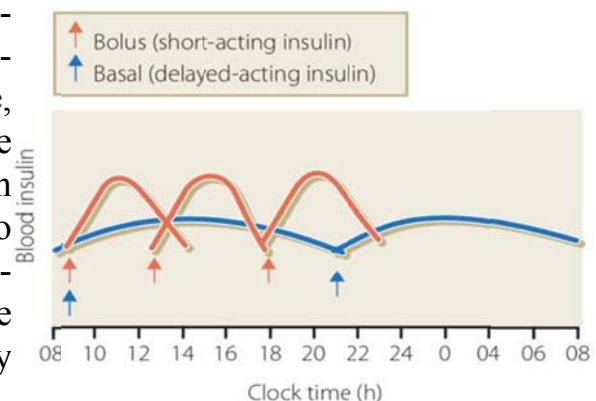

Figure 5— Basal-bolus insulin regimen

Until the 1980s, insulin was extracted and purified from animal sources. Porcine and bovine insulins are still available but have been largely replaced by human sequence insulin produced from genetically engineered bacteria. Recently modified human insulin molecules (so-called analogues) have now been developed. Essentially insulins can be divided up into short-acting and intermediate- to long-acting preparations and those are listed in Table 3.

The recommended injection sites are the subcutaneous tissue of the abdomen, upper outer thighs, upper outer arms, and buttocks (Figure 6). Insulin absorption is fastest in the abdomen and slowest in the thigh and buttocks although it can be accelerated from these sites by exercise or taking a sauna or warm bath. Short-acting insulin is usually given into the abdomen, which is less affected by exercise, and longer acting insulins into the thigh.
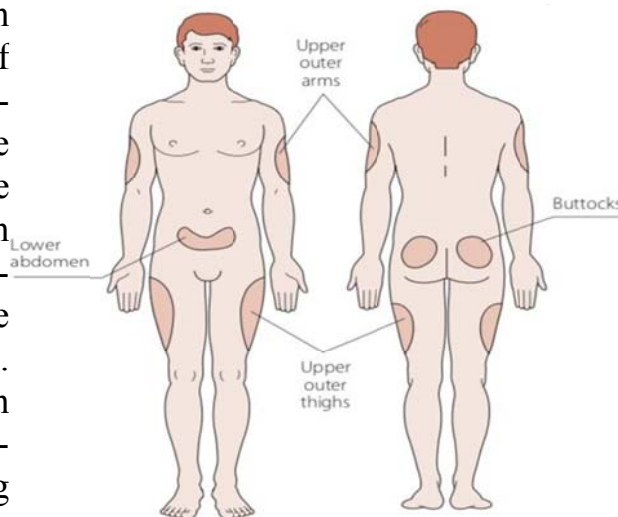
Figure 6 — Suitable sites for subcutaneous insulin injection

Repeated injection into the same subcutaneous site may, in the long term, give rise to an accumulation of fat (lipo-hypertrophy) because of the local trophic action of insulin. Lipohypertrophy can be unsightly and can affect insulin absorption. In order to prevent lipohypertrophy, patients should be advised to rotate the site of injection. It is important to remember that lipohypertrophic areas become relatively painless and are thus often favoured by patients who may inadvertently make the problem worse. For this reasons inspection of injection sites is an important part of the annual patient review.

Table 3 — Main types of insulin preparations

Type	Brand Name	Onset (length of time before insulin reaches bloodstream)	Peak (time period when insulin is most effective)	Duration (how long insulin works for)
Rapid-acting	Humalog Novolog Apidra	10–30 min	30 min–3 hours	3–5 hours
Short-acting	Regular (R)	30 min–1 hour	2–5 hours	Up to 12 hours
Intermediate-acting	NPH (N)	1.5–4 hours	4–12 hours	Up to 24 hours
Long-acting	Lantus Levemir	0.8–4 hours	Minimal peak	Up to 24 hours

Insulin Delivery Devices

There are a number of devices that can be used to deliver insulin, including syringes, insulin pens, jet injectors, and insulin pumps. No single device or type of device works well for everyone. The decision of which to use may be based on a person's insulin regimen, ability to manipulate or operate a particular device, visual ability, insurance coverage or ability to afford a particular device and related supplies, occupation, and daily schedule or leisure-time activities.

Syringes. The most common method of insulin delivery is by syringe. Medical syringes are relatively small, are disposable, and have fine needles with special coatings that make injecting as easy and painless as possible.

Insulin pens. Insulin pens look similar to oversized ink pens, making them a potentially convenient and discreet way of carrying insulin.

Jet injectors. Another option that has been available for several years is insulin jet injectors. Jet injectors use a mechanism to produce high-pressure air to deliver a fine spray of insulin through the skin. Once the appropriate dose of insulin has been loaded into the injector, it is placed against the skin and the trigger, or button, is pushed. The high pressure causes the insulin to vaporize and penetrate the skin so that it reaches the subcutaneous tissue. Some bruising may occur from injections using a jet injector, but bruising can be minimized by adjusting the pressure (setting) of the spray. The pressure may have to be adjusted differently for different injection sites.

Inhaled insulin. Inhaled insulin was approved by the Food and Drug Administration in January 2006, but the only inhaled insulin to reach the market so far — Exubera — was discontinued in October 2007. Other drug companies are working to gain approval of their products by the Food and Drug Administration.

External insulin pump. Insulin pumps are becoming more popular as the technology improves and additional features are added. Some pumps are now available that work in conjunction with continuous glucose monitors that can alert the user to high or low blood glucose levels if programmed to do so. The pump user programs the insulin pump to deliver insulin at a slow, continuous (basal) rate as well as in supplemental (bolus) doses before meals and to correct for high blood glucose. Basal and bolus dosing most closely resembles how the pancreas releases insulin in a person without diabetes. Many people are willing to put in the work necessary to use an insulin pump because it gives them more flexibility with respect to food choices and the timing of meals and activities, while helping to achieve tighter control of their blood glucose.

Bread units (BU)

People who suffer from diabetes mellitus, and therefore require insulin, can use this measurement unit to compare the blood-sugar-effectiveness of carbohydrates in different foods.

According to German dietary regulations, one bread exchange unit (1 BU) corresponds to a quantity of food that contains 10–12 grams of digestible and,

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therefore, blood-sugar-effective carbohydrates — present in different forms of sugar and starch.

BU allows to determine the necessary quantity of insulin. One BU can correspond, for example, to the carbohydrate content of the following foods: 25 g bread, 65 g potatoes, 100 g apples, 250 g milk.

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1 BU contains 10–12 g carbohydrate = raises bg by about 2.5 mmol/l.
1 g of carbohydrate = 4 kcal.
Daily carbohydrates (kcal): 4 = Daily carbohydretes (g)
Daily carbohydrates (g): 10 = Daily amount of BUs.
Insulin dose should be calculated as follows:
1 BU in the morning = 2 IUs of insulin 1 BU in the afternoon = 1 IUs of insulin 1 BU in the evening = 1.5 IUs of insulin

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Calculating Insulin Dose
Total Daily Insulin Requirement:
The general calculation for the body's daily insulin requirement is:
Total Daily Insulin Requirement (in units of insulin) = 0.55 X Total Weight in Kilograms

Example:
• Assume your weight is 70 Kg

Total daily insulin dose = 0.55 x 70 Kg = 38.5 units of insulin/day

If body is very resistant to insulin, it may require a higher dose. If body is sensitive to insulin, it may require a lower insulin dose.

Basal/Background and Bolus Insulin Doses
Next, you need to establish the basal/background dose and carbohydrate coverage dose (insulin to carbohydrate ratio).

Basal/background insulin dose:
Basal/background Insulin Dose = 40–50 % of Total Daily Insulin Dose
Example:
Basal/background insulin dose = 50 % of TDI (38.5 units) = 19.25 units of either long acting insulin, (such as glargine or detemir) or rapid acting insulin if you are using an insulin pump (continuous subcutaneous insulin infusion device).

Carbohydrate counting
Step 1: work out the amount of carbohydrate
All packaging labels have nutritional information about the calorie, protein, fat, carbohydrate and sugar content of the food. Most labels show the information per 100g and others per portion (or both).

CRACKER BREAD

NUTRITION		
Typical Values	Per cracker (approx. 33g)	Per 100g
Energy	315kj/75kcal	954kj/227kcal
Protein	0.6g	1.9g
Carbohydrate (CHO)	11.7g	35.5g
Of which sugars	0.4g	1.2g
Of which starch	11.3g	34.3g

For example — the label for the cracker bread gives us the amount of carbohydrate per cracker, therefore if we were to have 1 cracker, it would be 11.7 g CHO — the figure found in the first column next to carbohydrate. If we were having 3 crackers, the total amount would be 3 x 11.7 = 35.1 g (or 35 g).

To calculate the amount of carbohydrate in a food that you have weighed — Carbohydrate content of your serving = Total Weight of food (g) x CHO content per 100g ÷ 100

Step 2: calculate the insulin dose to cover food:
a) Insulin for food:
Once we have learnt how to identify and count carbohydrates in meals, we will be given something called an insulin to carbohydrate ratio. This helps to calculate how much insulin matches with the carbohydrate in our meal. Each person has their own ratio. For example:

1 unit insulin for every 10 g carbohydrate

Example:
Breakfast meal = 50 g carbohydrate Ratio = 1 unit insulin: 10g carbohydrate
Bolus dose = Total carbohydrate (50g) ÷ Ratio (10) = 5 units insulin

b) Extra insulin to correct high blood glucose levels:
If blood glucose level is high we can give extra insulin to bring blood glucose back into target or goal range. We can do this by giving extra rapid acting insulin at meal times and at other times.
Correction factor:
A correction factor is how much 1 unit of quick acting insulin will lower blood glucose level. Each person has their own individually calculated correction factor. For example one person may find that 1 unit of quick acting insulin lowers the blood glucose by 3 mmol/L, whereas for another person 1 unit lowers blood glucose by 5mmol/L.
Correction bolus:
The formula that is used to calculate a correction bolus (CB) is:

$$CB = \frac{\text{Current blood sugar} - \text{target blood sugar}}{\text{Correction factor}}$$

Example:

Pre-meal blood glucose level: 16 mmol/L Target blood glucose level: 6 mmol/L Correction factor: 2 mmol/L

CB = (16mmol – 6mmol) ÷ 2 = 5 units quick acting insulin.

Guideline and caution for using correction boluses:

• Check blood sugar 2–3 hours after correction bolus to check it has worked.

• Do NOT give correction bolus if blood sugar is less than target range.

• Do NOT correct if it has been less than 2 hours since last correction bolus.

• If a correction bolus is given between meals the dose may need to be lower than usual.

Final step: Combine the insulin dose for the food and/or correction dose:

Insulin: carbohydrate ratio = 1 unit of insulin or every 10 g of carbohydrate

Total carbohydrate at breakfast = 20 g.

Carbohydrate bolus = 20 g /10 g = 2 units quick acting insulin

Correction factor:

Pre-meal blood glucose level = 14 mmol

Target blood glucose level = 6 mmol

Correction factor = 2 mmol.

Correction bolus = (14–6) ÷ 2 = 4 units quick acting insulin

Therefore, we need IN TOTAL:

2 unit (for food) + 4 units (to correct high blood glucose) = total dose of 6 units quick acting insulin before eating.

Glycaemic targets

Glycaemic targets published in the USA (American Diabetes Association) are shown in Table 4.

Table 4 — Summary of glycemic recommendations for many nonpregnant adults with diabetes

HbA1c	< 7.0 %*
Preprandial capillary plasma glucose	4.4–7.2 mmol/L*
Peak postprandial capillary plasma glucose†	< 10.0 mmol/L*

* More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD (cardiovascular disease) or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. †Postprandial glucose may be targeted if HbA1c goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

The dawn phenomenon and the Somogyi effect —two phenomena of morning hyperglycaemia

Morning hyperglycaemia in diabetic subjects may be caused by the dawn phenomenon, or the Somogyi effect, or poor glycaemic control. The dawn phenomenon occurs when endogenous insulin secretion decreases or when the effect of the exogenous insulin administered to the patient the day before disappears, together with a physiological increase in insulin-antagonistic hormones. The Somogyi effect is present in the case of excessive amounts of exogenous insulin. The dawn phenomenon is more common than the Somogyi effect. To diagnose these phenomena, it is useful to measure plasma glucose levels for several nights between 3 a.m. and 5 a.m. or use a continuous glucose monitoring system. Although their treatment differs, the best way of preventing both the dawn phenomenon and the Somogyi effect is an optimal diabetes control with insulin therapy.

MANAGEMENT OF TYPE 2 DIABETES

KEY POINTS
- Key components of management include dietary and lifestyle adjustment to avoid or treat obesity; pharmacological and non-pharmacological strategies to lower glucose levels; and treatments to reduce CV risk, in particular BP and cholesterol reduction.
- Regular exercise, independently of weight loss, improves insulin sensitivity and CV outcomes.
- Type 2 diabetes is metabolically progressive: HbA1c rises with duration of disease, despite escalating therapy, mainly due to a progressive decline in β cell function.
- Glucose-lowering therapies work primarily by increasing insulin secretion (sulphonylureas, miglitinides, DPP-4 inhibitors) or increasing peripheral and hepatic insulin sensitivity (biguanides, glitazones).
- Insulin analogues, bariatric surgery and GLP-1 agonists (exenatide, liraglutide) are creating more choices as part of combination therapy to achieve lower HbA1c targets in different patient subgroups.

Lifestyle modification

The starting points and mainstays of treatment for type 2 diabetes are diet and other modifications of lifestyle, such as increasing exercise and stopping smoking. The major aims are to reduce the weight of obese patients and improve glycaemic control, but also to reduce risk factors for cardiovascular disease (CVD), such as hyperlipdaemia and hypertension, which accounts for 70–80 % of deaths in type 2 diabetes.

Weight loss is achieved by decreasing total energy intake and/or increasing physical activity and thus energy expenditure. Gradual weight loss is preferred – not more than 0.5–1 kg/week. For effective weight loss and improvement in glycaemic control, the amount of energy restriction is more important than dietary composition, though compliance may be greater with high monounsaturated fat diets.

Metabolic progression: effects on treatment

There is a progressive decline in β cell function and insulin sensitivity in type 2 diabetes, which results in deteriorating glycaemic control and the constant need to revise and intensify treatment. Diet and exercise are sufficient to achieve adequate glycaemic control in < 10 % of type 2 patients; when control worsens, an oral hypoglycaemic agent is generally introduced. The particular drug treatment used in an individual patient with type 2 diabetes is decided on the basis of clinical judgement about the balance of β cell impairment and insulin resistance in that particular case. Overweight and obese patients are likely to be insulin resistant: here, the insulin sensitiser metformin is a logical first choice. Thin patients generally have substantial β cell failure, and sulphonylureas (which stimulate insulin secretion) are likely to be effective. β cell function declines at about 4 % per year, so sulphonylureas are less effective later in the disease. About 50 % of type 2 diabetic patients need insulin within 6 years of diagnosis, although newer agents are providing alternative options for combination therapy.

Pharmacologic Therapy for Type 2 Diabetes (Table 5).

Table 5 — Major classes of drug used in the treatment of type 2 diabetes (excluding insulins)

Class	Compounds	Cellular mechanisms	Primary physiological action(s)	Advantages	Disadvantages
Biguanides	Metformin	Activates AMP-kinase	↓ Hepatic glucose production	- Extensive experience - Rare hypoglycemia - ↓ CVD events - Relatively higher A1C efficacy	- Gastrointestinal side effects (diarrhea, abdominal cramping, nausea) - Vitamin B_{12} deficiency - Contraindications: eGFR < 30 mL/min/ 1.73 m^2, acidosis, hypoxia, dehydration, etc. - Lactic acidosis risk (rare)
Sulfonylureas	2nd generation Glyburide Glipizide Glimepiride	Closes Katpchannels on β-cell plasma membranes	↑ Insulin secretion	- Extensive experience ↓ Microvascular risk - Relatively higher A1C efficacy	- Hypoglycemia - ↑ Weight

Class	Compounds	Cellular mechanisms	Primary physiological action(s)	Advantages	Disadvantages
Meglitinides (glinides)	Repaglinide Nateglinide	Closes Katpchannels on β-cell plasma membranes	↑ Insulin secretion	- ↓ Postprandial glucose excursions - Dosing flexibility	- Hypoglycemia - ↑ Weight - Frequent dosing schedule
TZDs	Pioglitazone Rosiglitazone	Activates the nuclear transcription factor PPAR-γ	↑ Insulin sensitivity	- Rare hypoglycemia - Relatively higher A1C efficacy - Durability - ↓ Triglycerides (pioglitazone) - ↓ Risk of stroke and MI in patients without diabetes and with *insulin resistance* and history of recent stroke or TIA, pioglitazone)	- ↑ Weight - Edema/heart failure - Bone fractures - ↑ LDL-C (rosiglitazone)
α-Glucosidase inhibitors	Acarbose Miglitol	Inhibits intestinal α-glucosidase	Slows intestinal carbohydrate digestion/absorption	- Rare hypoglycemia - ↓ Postprandial glucose excursions	- Generally modest A1C efficacy - Gastrointestinal side effects(flatulence, diarrhea) - Frequent dosing schedule
DPP-4 inhibitors	Sitagliptin Saxagliptin Linagliptin Alogliptin	Inhibits DPP-4 activity, increasing postprandial incretin (GLP-1, GIP) concentrations	- ↑ Insulin secretion (glucose dependent) - ↓ Glucagon secretion (glucose dependent)	- Rare hypoglycemia - Well tolerated	- Angioedema/urticaria and other immune-mediated dermatological effects - Acute pancreatitis - ↑ Heart failure hospitalizations (saxagliptin; alogliptin)
Bile acid sequestrants	Colesevelam	Binds bile acids in intestinal tract, increasing hepatic bile acid production	- ↓ Hepatic glucose production - ↑ Incretin levels	- Rare hypoglycemia - ↓ LDL-C	- Modest A1C efficacy - Constipation -↑ Triglycerides - May ↓ absorption of other medications

Class	Compounds	Cellular mechanisms	Primary physiological action(s)	Advantages	Disadvantages
Dopamine-2 agonists	Bromocriptine (quick release)	Activates dopaminergic receptors	- Modulates hypothalamic regulation of metabolism - ↑ Insulin sensitivity	- Rare hypoglycemia - ↓ CVD events	- Modest A1C efficacy - Dizziness/syncope - Nausea - Fatigue - Rhinitis
SGLT2 inhibitors	Canagliflozin Dapagliflozin Empagliflozin	Inhibits SGLT2 in the proximal nephron	- Blocks glucose reabsorption by the kidney, increasing glucosuria	- Rare hypoglycemia-↓ Weight -↓ Blood pressure - Associated with lower CVD event rate and mortality in patients with CVD (empagliflozin)	- Genitourinary infections - Polyuria - Volume depletion/hypotension/dizziness - ↑ LDL-C - ↑ Creatinine (transient) - DKA, urinary tract infections leading to urosepsis, pyelonephritis
GLP-1 receptor agonists	Exenatide Liraglutide Albiglutide Lixisenatide Dulaglutide	Activates GLP-1 receptors	-↑ Insulin secretion (glucose dependent) -↓ Glucagon secretion (glucose dependent) -Slows gastric emptying ↑ Satiety	- Rare hypoglycemia -↓ Weight -↓ Postprandial glucose excursions -↓ Some cardiovascular risk factors -Associated with lower CVD event rate and mortality in patients with CVD (liraglutide LEADER)	-Gastrointestinal side effects (nausea/vomiting/diarrhea) -↑ Heart rate -Acute pancreatitis -C-cell hyperplasia/medullary thyroid tumors in animals -Injectable - Training requirements

CVD, cardiovascular disease; GIP, glucose-dependent insulinotropic peptide; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; PPAR-γ, peroxisome proliferator–activated receptor γ; PROactive, TIA, transient ischemic attack; TZD, thiazolidinedione.

Metformin monotherapy should be started at diagnosis of type 2 diabetes unless there are contraindications. Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death. Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on HbA1c, weight, and cardiovascular mortality. Metformin may be safely used in patients with esti-

mated glomerular filtration rate (eGFR) as low as 30 mL/min/1.73 m^2, and the FDA recently revised the label for metformin to reflect its safety in patients with eGFR ≥ 30 mL/min/1.73 m^2. Patients should be advised to stop the medication in cases of nausea, vomiting, or dehydration. In patients with metformin contraindications or intolerance, consider an initial drug from another class depicted in Figure 7 under "Dual Therapy" and proceed accordingly. When HbA1c is ≥ 9 %, consider initiating dual combination therapy (Figure 7) to more expeditiously achieve the target HbA1c level. Insulin has the advantage of being effective where other agents may not be and should be considered as part of any combination regimen when hyperglycemia is severe, especially if catabolic features (weight loss, ketosis) are present. Consider initiating combination insulin injectable therapy (Fig. 8) when blood glucose is ≥16.7 mmol/L or HbA1c is ≥10 % or if the patient has symptoms of hyperglycemia (i. e., polyuria or polydipsia). As the patient's glucose toxicity resolves, the regimen may, potentially, be simplified.

CASE HISTORY

A 54-year-old man with a 5-year history of type 2 diabetes presents to his GP for annual review. This shows BMI 32, BP 156/94 mmHg and HbA1c 7.8 % (Table 6) using a maximum-tolerated dose of metformin 1g bid and gliclazide 80 mg bid. He has background retinopathy and a history of previous myocardial infarction. He takes some exercise, but is limited by arthritis. There have been no significant hypos, LDL-cholesterol is 3.1 mmol/L using a statin. He has some symptoms of tiredness and nocturia.

Comment: If there is no further scope to improve his compliance with diet and exercise, this man will require additional therapy in view of his established complications. Options would include adding basal insulin, exenatide, pioglitazone or a DPP-4 inhibitor. The NICE recommendation for exenatide is at BMI > 35; insulin and, to a lesser extent, pioglitazone may worsen his obesity, and a DPP-4 inhibitor is an option, either instead of the SU (if hypos were a problem) or as add-on therapy.

Table 6 — Diabetes control managements (ADA 2018)

Diagnostic Test	Target Value	Comment
HbA1c	**< 7 %**	• Reasonable target for most non-pregnant adults
	< 8 %	• Possibly appropriate for selected patients • History of severe hypoglycemia • Limited life expectancy • Advanced micro/macrovascular disease
	< 6.5 %	• Possibly appropriate for selected patients • Without hypoglycemia/adverse effects of therapy • Long life expectancy • Without significant micro/macrovascular disease

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy**

Monotherapy   **Metformin**   **Lifestyle Management**

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy   **Metformin +**   **Lifestyle Management**

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy   **Metformin +**   **Lifestyle Management**

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin§	or GLP-1-RA	or Insulin§	or GLP-1-RA
or Insulin§	or Insulin§		or Insulin§		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).
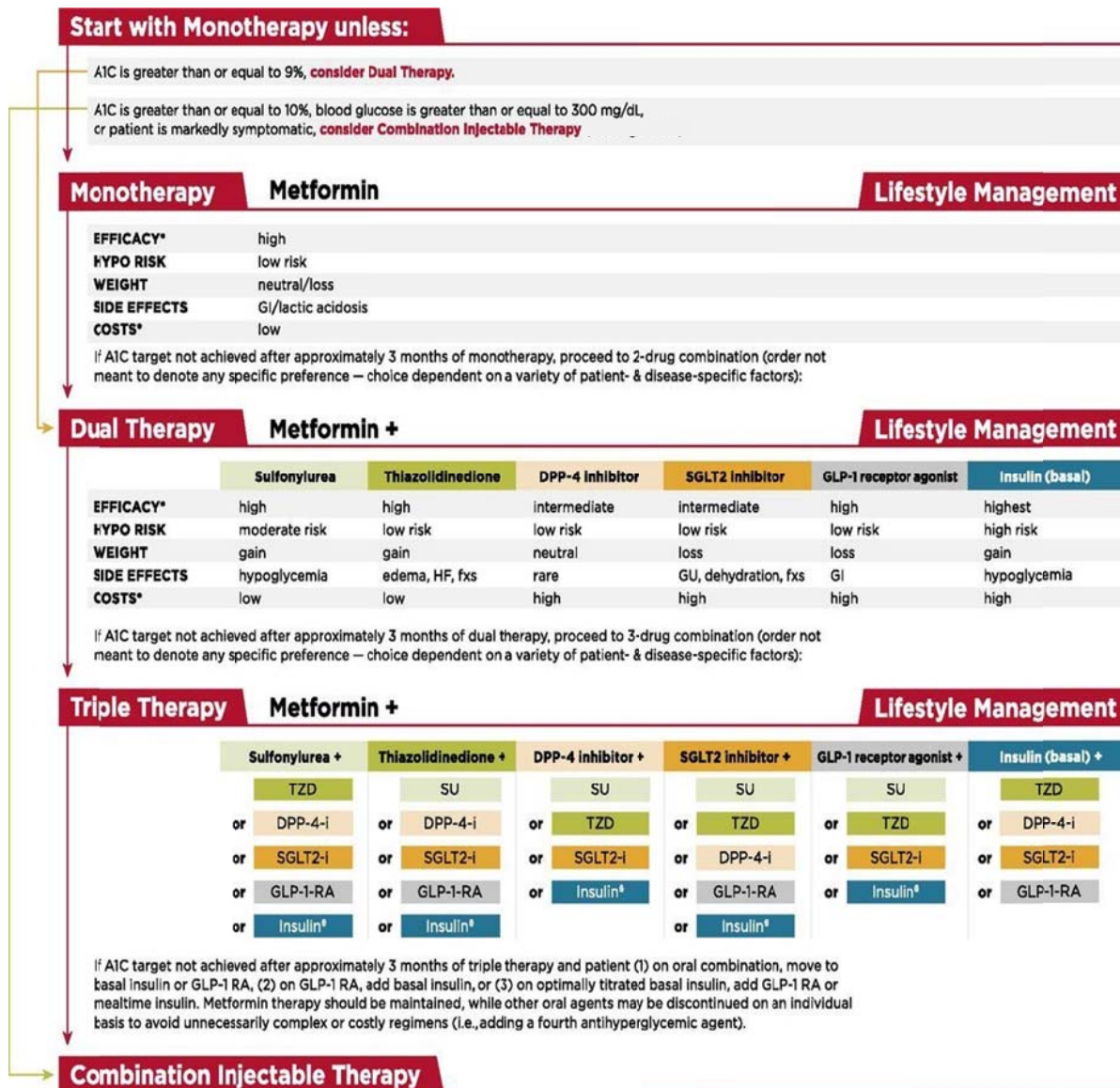
Combination Injectable Therapy

Figure 7 — Antihyperglycemic therapy in type 2 diabetes: general recommendations. The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic therapy for patients with type 2 diabetes are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances). DPP-4-i, DPP-4 inhibitor; fxs, fractures; GI, gastrointestinal; GLP-1 RA, GLP-1 receptor agonist; GU, genitourinary; HF, heart failure; Hypo, hypoglycemia; SGLT2-i, SGLT2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. Adapted with permission from Inzucchi et al

For very obese patients with type 2 diabetes (BMI >35), bariatric surgery is an increasingly recognised treatment option. The results with laparascopic adjustable gastric banding or gastric bypass demonstrate significant weight loss (often >20 kg) and improved glycaemic control.

It is common for many patients with type 2 diabetes to progress from treatment by diet alone to monotherapy with metformin or a sulphonylurea, then to a combination of the two, before finally starting insulin. Insulin can be given alone or in combination with oral agents. A single daily injection of basal insulin can be given as add-on to oral therapy (e.g. at bedtime), and twice-daily injections. When obesity and insulin resistance predominate, the doses may range up to 2–3 U/kg (Figure 7, 8).

Initiate Basal Insulin
Usually with metformin +/- other noninsulin agent

Start: 10 U/day or 0.1–0.2 U/kg/day
Adjust: 10–15% or 2–4 units once or twice weekly to reach FBG target
For hypo: Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10–20%

If A1C not controlled, **consider combination injectable therapy**

Add 1 rapid-acting insulin injection before largest meal

Start: 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount
Adjust: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

Add GLP-1 RA

If not tolerated or A1C target not reached, change to 2 injection insulin regimen

If goals not met, **consider changing to alternative insulin regimen**

Change to premixed insulin twice daily (before breakfast and supper)

Start: Divide current basal dose into ⅔ AM, ⅓ PM or ½ AM, ½ PM
Adjust: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

If A1C not controlled, **advance to basal-bolus**

If A1C not controlled, **advance to 3rd injection**

Add ≥2 rapid-acting insulin injections before meals ('basal-bolus')

Start: 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by same amount
Adjust: ↑ dose(s) by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

If goals not met, **consider changing to alternative insulin regimen**

Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)

Start: Add additional injection before lunch
Adjust: ↑ doses by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%
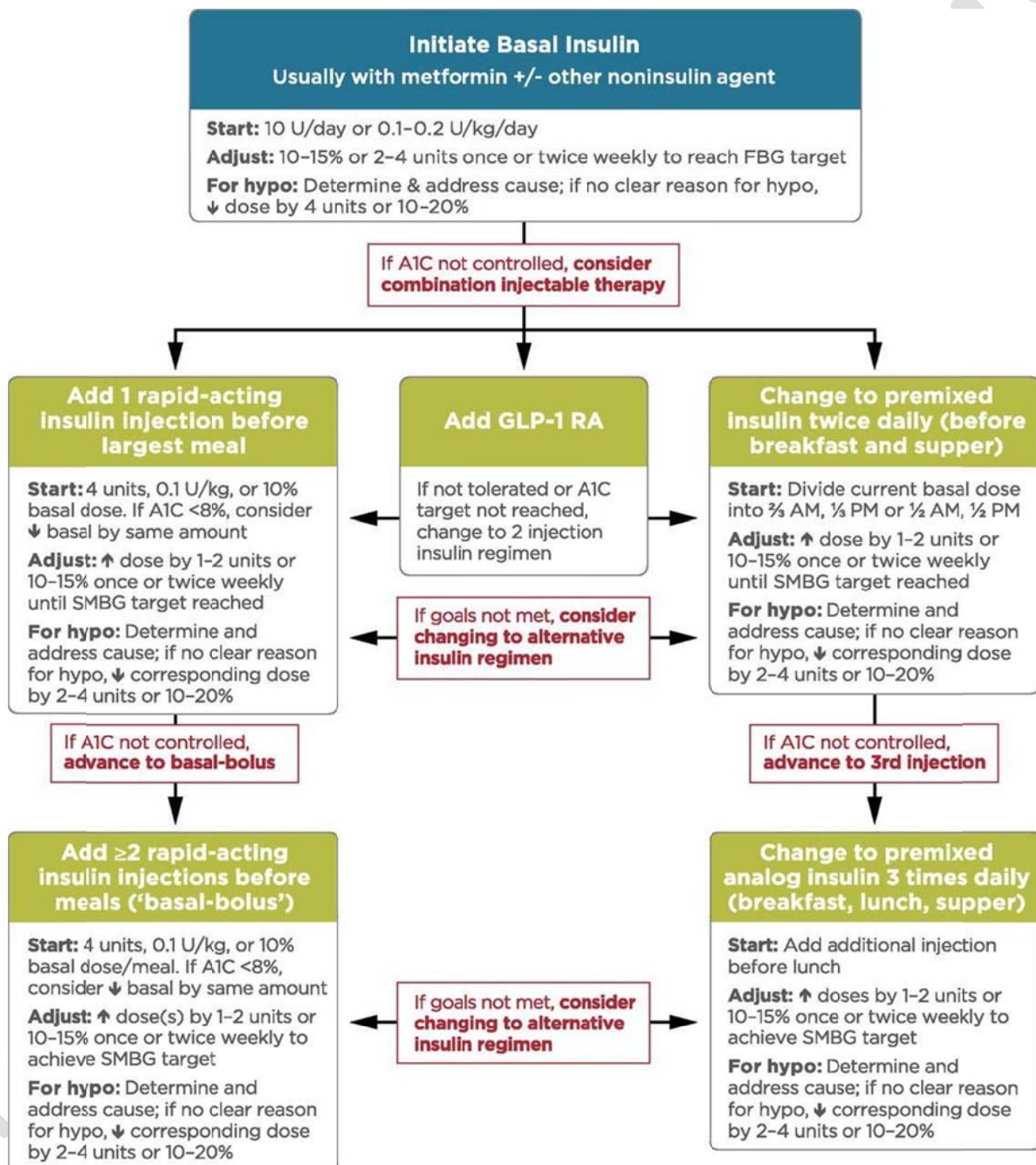
Figure 8 — Combination injectable therapy for type 2 diabetes. FBG, fasting blood glucose; GLP-1 RA, GLP-1 receptor agonist; hypo, hypoglycemia. Adapted with permission from Inzucchi et al

ACUTE COMPLICATIONS OF DIABETES MELLITUS AND ITS MANAGEMENT

KEY POINTS
- Diabetic ketoacidosis is a state of severe uncontrolled diabetes characterized by hyperglycaemia, hyperketonaemia and metabolic acidosis in the face of absolute insulin deficiency.
- Frequency may be increasing and it accounts for 50 % of deaths in people with type 1 diabetes under 24 years of age.
- Treatment requires fluid and electrolyte infusions with careful potassium replacement, and insulin by intravenous infusion, intramuscular or subcutaneous injection (in milder cases).
- Hyperosmolar hyperglycaemic state is characterized by extreme hyperglycaemia and dehydration without acidosis. Treatment is similar to that for diabetic ketoacidosis but mortality is higher.
- Lactic acidosis is a rare serious metabolic crisis that may be more frequent in people with diabetes. Treatment requires intravenous bicarbonate infusion in addition to rehydration, and mortality is high.
- Fear of hypoglycaemia is a major barrier to achieving optimum glycaemic control in patients with diabetes.
- IM or SC glucagon can be administered in an emergency setting to treat hypoglycaemia if the patient is unable or unwilling to take glucose orally.

DIABETIC KETOACIDOSIS

Diabetic ketoacidosis (DKA) is a state of severe uncontrolled diabetes caused by insulin deficiency. It is characterised by hyperglycaemia, hyperketonaemia and metabolic acidosis, and has been somewhat arbitrarily divided into mild, moderate and severe based upon biochemical and clinical features (Table 7).

Table 7 — Diagnostic criteria for DKA and HHS

	DKA (plasma glucose >13.9 mmol/L)			HHS (plasma glucose >33 mmol/L)
	Mild	**Modearte**	**Severe**	
Arterial pH	7.25–7.30	7.00–7.24	<7.00	≥7.30
Serum bicarbonate, mmol/L	15–18	10–15	<10	≥18
Urine ketones	Positive (2+)	Positive (>2+)	Positive (>2+)	Small (<1+)
Serum osmolality, mOsm/kg	Variable	Variable	Variable	>320
Anion gap	≥10	≥12	≥12	≤12

Osmolality = 2 [serum Na+] + plasma glucose (mmol/L) In this situation serum urea is ignored. Anion gap = [serum Na+] − [serum Cl− + HCO3−] (mmol/L) [normal ≤9].

NB: plasma glucose levels can be near normal in pregnant women with DKA. Mental state varies with severity but coma is an ominous development in DKA.

Although DKA mainly occurs in type 1 patients, it can occur in African American and Hispanic people who subsequently can be managed without insulin and thus behave as type 2 diabetes. This phenomenon is now termed 'ketosis-prone type 2 diabetes'; it can account for 25–50 % of African American or Hispanic cases of DKA. Their clinical characteristics are shown below.

Features of ketosis-prone type 2 diabetes mellitus:
- Acute presentation.
- Mean age > 40 years Male preponderance.
- BMI ≥ 28 (for African American, less for Hispanic and Taiwanese).
- Mostly newly diagnosed with diabetes.
- Strong family history of type 2 diabetes HbA1c at presentation > 12 %.
- Autoimmune markers for type 1 diabetes negative.
- Fasting C-peptide detectable.
- Most do not require long-term insulin therapy.

The most common precipitating factor is intercurrent infection (19–56 %) but it is important to remember that a polymorphonucleocytosis is common in DKA, probably secondary to physiological stress, and does not necessarily imply sepsis, infection, insulin error/omission, newly diagnosed diabetes, cardiovascular (myocardial infarction, stroke), pancreatitis, pulmonary embolism, alcohol excess, steroid use. The frequency of cause will vary according to age and ethnicity.

Pathophysiology

Relative or absolute insulin deficiency in the presence of catabolic counterregulatory stress hormones (particularly glucagon and catecholamines, but also growth hormone and cortisol) leads to hepatic overproduction of glucose and ketones. Lack of insulin combined with excess stress hormones promotes lipolysis, with the release of non-esterified fatty acid from adipose tissue into the circulation. In the liver, fatty acids are partially oxidised to the ketone bodies acetoacetic acid and 3-hydroxybutyric acid, which contribute to the acidosis, and acetone (formed by the non-enzymatic decarboxylation of acetoacetate). The latter is volatile and excreted via the lungs.

Hyperglycaemia results from increased glycogenolysis secondary to glucagon excess; gluoconeogenesis as a result of increased lipolysis and proteolysis;

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diminished peripheral uptake of glucose due to absent insulin stimulated uptake; and utilisation of alternative fuels such as non-esterified fatty acid and ketone bodies in preference to glucose.

Hyperglycaemia causes an osmotic diuresis that leads to dehydration and loss of electrolytes. Sodium depletion is worsened because of diminished renal sodium reabsorption due to insulin deficiency. Metabolic acidosis leads to the loss of intracellular potassium in exchange for hydrogen ions, and insulin deficiency also results in potassium loss from cells. These processes can result in high circulating plasma potassium.

The symptoms of DKA include:
• Increasing polyuria and thirst
• Weight loss
• Weakness
• Blurred vision
• Acidotic (Kussmaul) respiration
• Abdominal pain, especially in children
• Leg cramps
• Nausea and vomiting
• Confusion and drowsiness
• Coma (10 % of cases)

Abdominal pain can occur, particularly in the young, and should resolve within 24 hours. If not, alternative causes should be looked for. Physical signs include dehydration, hypotension, tachycardia and hypothermia. Acidosis stimulates the respiratory centre, which results in deep and rapid (Kussmaul) respirations. The smell of acetone on the patient's breath (similar to nail-varnish remover) may be obvious to some, but many people are unable to detect it.

Treatment

Diabetic ketoacidosis is a medical emergency. A rapid history, physical examination and bedside blood and urine tests should allow a provisional diagnosis in the emergency department and avoid treatment delays. Immediate bedside investigations should include blood glucose concentration and a test for the presence of urine or blood ketones with reagent strips, followed by laboratory measurements of blood glucose, urea, Na+, K+, Cl−, bicarbonate (for calculation of the anion gap), arterial blood pH and gas tensions, blood count, and blood and urine cultures. Venous pH could suffice if an arterial sample is difficult to obtain.

Initial treatment involves rehydration, usually with isotonic saline (0.9 %) with appropriate supplements. Although initial serum potassium levels may be normal or even high, there will be an overall deficiency, and replacement should commence more or less immediately at 20 mmol/L unless there is significant renal failure or hyperkalaemia > 5.2 mmol/L. Serum potassium will fall with treatment as a result of correction of acidosis and insulin administration, both of

which increase cellular uptake. Careful and regular monitoring of serum potassium is essential as treatment-induced hypokalaemia is a significant cause of cardiac dysrhythmia and even death.

Regular/soluble insulin is usually given by continuous infusion, US guidelines suggest a dose of 0.1 unit/kg body-weight/hour. They also suggest a priming IV bolus of a similar amount but there is no evidence to suggest that this influences outcome or recovery. Alternatively, insulin can be given by hourly IM injection if there is no infusion pump available. Recently, regular SC injection of short-acting insulin analogues in a dose of 0.2 unit/kg bodyweight every 2 hours has been shown to be as effective as IV infusion in mild to moderate DKA.

The overall treatment goal is a reduction in blood glucose of no more than 3–5 mmol/L/h and osmolality by 3 mOsm/kg/h. The role of intravenous bicarbonate is controversial. There is no proven benefit in patients with an arterial pH ≥ 6.9. There are good theoretical reasons why IV bicarbonate should not be given and its use has been associated with the development of cerebral oedema. The American Diabetes Association guidelines suggest 100 mmol diluted and given over 2 hours in patients with a pH < 6.9 or in whom the acidosis is felt to be contributing to their clinical status. Although phosphate and magnesium depletion are also present, there is no evidence that routine replacement is of benefit. However, serum phosphate levels < 0.35 mmol/L can cause muscle weakness and myocardial dysfunction and need correction. Similarly, serum magnesium levels < 0.7 mmol/L should also be treated.

Complications of diabetic ketoacidosis:
• Cerebral oedema.
• Respiratory distress syndrome.
• Thromboembolism.

HYPEROSMOLAR HYPERGLYCAEMIC STATE

Hyperosmolar hyperglycaemic state (HHS) used to be called hyperosmolar non-ketotic hyperglycaemic coma, or HONK, but is now termed HHS because mild ketosis can be present and because not all patients are comatose. The diagnostic criteria are contrasted with DKA in Table 7.

It tends to occur gradually and is often associated with drug use (notably thiazide and loop diuretics, β-blockers, steroids and major psychotropic agents). Because of its gradual onset with thirst, many patients inadvertently compound the problem by drinking fruit juices or fluids high in glucose. Precisely why ketosis is not a feature in HHS is not known but because there is only a relative deficiency of insulin, portal venous concentrations may be enough to prevent hepatic ketogenesis, but peripheral insulin levels are insufficient to stimulate glucose uptake.

Around 25 % of patients with HHS have newly diagnosed diabetes. Mortality is high (5–20 %), partly because of age and underlying cause – often cardio-

vascular disease or serious infection. In addition, thromboembolic complications may occur secondary to the marked hyperosmolality and some guidelines recommend prophylactic heparinisation.

Treatment is similar to DKA, with rehydration the key. Patients may present with significant hypernatraemia (serum sodium > 150 mmol/L) in which case either 0.45 % (half normal or hypotonic saline) or 5 % (isotonic) dextrose can be used. The low concentration of glucose in this solution should not exacerbate hyperglycaemia which will correct more by rehydration. Only 1–2 litres of hypotonic saline should be used as otherwise a too rapid reduction in osmolality may cause pulmonary or cerebral oedema. Many patients can be managed ultimately without insulin once they are metabolically stable.

LACTIC ACIDOSIS

This is a rare but very serious and life-threatening metabolic crisis that is said to occur more frequently in people with diabetes. There are two types (type A- anaerobic and type B-aerobic) and their causes are listed in Table 8.

Table 8 — Causes of lactic acidosis

Type A (anaerobic)		Type B (aerobic)	
Shock —	Cardiogenic Endotoxic (septic) Hypovalaemic	Systemic disease	Diabetes Neoplasia Hepatic failure Renal failure
Heart failure Asphyxia Carbon monoxide poisoning		Drugs	Biguanides Ethanol/methanol Salicylate overdose Inborn errors of metabolism

Most patients present with a profound metabolic acidosis with a massive anion gap. Treatment is of the underlying condition (which often determines outcome) and large volumes of IV bicarbonate are often required. Dichloroacetate can also be used to block lactate production but its use is confined to specialist centres. Most patients require ITU monitoring and care.

CASE HISTORY

A 32-year-old woman with type 1 diabetes was 30 weeks pregnant. She had been unwell with dysuria and vague abdominal pain, and felt nauseous. She presented to the obstetric day unit where she was found to be slightly breathless and mildly febrile (37.9 °C), and urinalysis showed 3+ ketones, trace proteinuria and glycosuria 55mmol/L. Her capillary blood glucose was 11.9 mmol/L. A diagnosis of urinary tract infection was made, she was commenced on oral cefalexin and discharged.

Twelve hours later she was brought to the accident and emergency department severely breathless and vomiting with severe abdominal pain. She was tachycardic (pulse 120/min, regular), hypotensive (BP 90/50 mmHg lying, 70/40 mmHg sitting), dehydrated and unwell. Laboratory plasma glucose was 35.6 mmol/L, blood 3-hydroxybutyrate was 8.1mmol/L. Arterial pH was 7.0.

She was commenced on IV saline and insulin. She made a rapid recovery over the next 24 hours. Her abdominal pain settled, fetal ultrasound was normal. She was delivered by elective caesarean section at 36 weeks gestation.

Comment: Pregnancy is considered to be a proketotic state. Serum bicarbonate routinely falls in normal pregnancy; the normal range is 16–19 mmol/L. This means that DKA can occur at a relatively low blood glucose; cases of normoglycaemic DKA have been described. The clues were the heavy ketonuria and her breathlessness. After this case, new guidelines were drawn up that mandated serum electrolyte samples and whole-blood ketone tests in all diabetic women presenting with ketonuria to the obstetric unit irrespective of the blood glucose result.

Urinary tract infection rarely occurs without either positive urinary nitrite or leucocytes; proteinuria alone is not diagnostic.

HYPOGLYCAEMIA

Hypoglycaemia is a common side effect of treatment with insulin and oral antidiabetic drugs, especially sulphonylureas, and is a major factor preventing patients with type 1 and 2 diabetes from achieving near normoglycaemia. The brain is dependent on a continuous supply of glucose, and its interruption for more than a few minutes leads to central nervous system dysfunction, impaired cognition and eventually coma. The brain cannot synthesise glucose or store more than 5 minutes supply as glycogen. At normal or high circulating glucose concentrations, blood-to-brain glucose transport exceeds the rate of brain glucose metabolism but as glucose levels fall, blood-to-brain glucose transport becomes limiting to brain glucose utilisation. Hypoglycaemia is more common in young children and may be responsible for the cognitive impairment and lowered academic achievement in children diagnosed with diabetes under the age of 5 years — the developing brain is especially sensitive to hypoglycaemia.

Iatrogenic hypoglycaemia often causes physical and psychosocial morbidity and sometimes causes death (the 'dead- in-bed' syndrome may be due to cardiac arrhythmias secondary to nocturnal hypoglycaemia). In the person without diabetes, hypoglycaemia is limited in part by inhibition of insulin release from the pancreatic β cells and stimulation of glucagon from the α-cells. The major

physiological responses to hypoglycaemia occur as a result of activation of neurones in the ventromedial region of the hypothalamus and elsewhere in the brain; these neurones sense the lowered plasma glucose levels, activate the autonomic nervous system and stimulate pituitary counterregulatory hormone release (Figure 9). Glucagon and epinephrine (adrenaline) release are probably the main factors that limit hypoglycaemia and ensure glucose recovery in normal subjects.
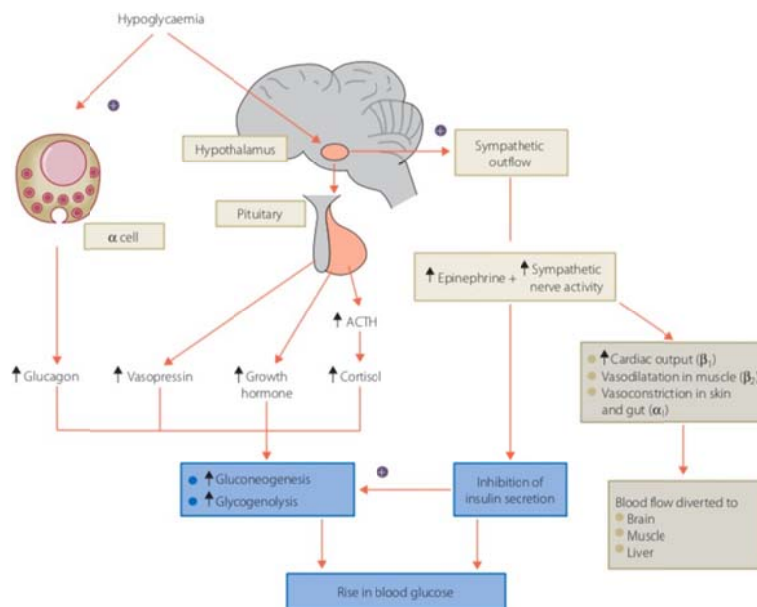

Figure 9 — Major components of the counterregulatory and sympathetic nervous system responses to hypoglycaemia. Vasopressin has weak counterregulatory effects on its own, but acts synergistically with the other hormones

The physiological responses to a falling plasma glucose level produce a range of symptoms that help individuals to recognise hypoglycaemia and take corrective action. Hypoglycaemic symptoms can be classified as **'autonomic'**, caused by activation of the sympathetic or parasympathetic nervous system (e. g. tremor, palpitations or sweating), or **'neuroglycopenic'**, caused by the effects of glucose deprivation on the brain (e. g. drowsiness, confusion and loss of consciousness). Headache and nausea are probably non-specific symptoms of malaise. Autonomic symptoms are prominent in subjects with a short duration of diabetes, but diminish with increasing duration of diabetes.

In patients with type 1 diabetes, episodes of asymptomatic hypoglycaemia are common: plasma glucose levels may be in the region of 2.8–3.3 mmol/L 10 % of the time. Patients experience an average of two episodes of symptomatic hypoglycaemia per week, and one episode of severe disabling hypoglycaemia per year; 2–4 % of deaths among people with type 1 diabetes are attributed to hypoglycaemia. Hypoglycaemia causes unpleasant symptoms, e. g. anxiety, palpitations, sweating, and the neurological consequences include behavioural changes, cognitive dysfunction, seizures and coma.

The initial response to hypoglycaemia is the acute release of counterregulatory hormones (in particular, glucagon and epinephrine) which occurs at a plasma glucose concentration of about 3.6–3.8 mmol/L. Autonomic symptoms develop at about 3.2 mmol/L, before cognitive function starts to deteriorate at around 3 mmol/L.

Most episodes of hypoglycaemia can be self-treated by ingestion of glucose tablets or 20g of carbohydrate in the form of juice, biscuits or a meal. Parenteral therapy is needed when a hypoglycaemic patient is unable or unwilling (because of neuroglycopenia) to take carbohydrate orally.

Intramuscular glucagon is used by family members of patients with type 1 diabetes, but glucagon is less useful in type 2 diabetes because it stimulates insulin secretion as well as glycogenolysis. Suspected severe hypoglycaemia (e.g. in a diabetic patient with impaired consciousness or coma) should be confirmed by blood glucose testing. It should be treated immediately with oral glucose or, if the patient is unconscious or unable to swallow safely, with intravenous glucose or intramuscular or subcutaneous glucagon injection (Figure 10). Patients usually recover within minutes.
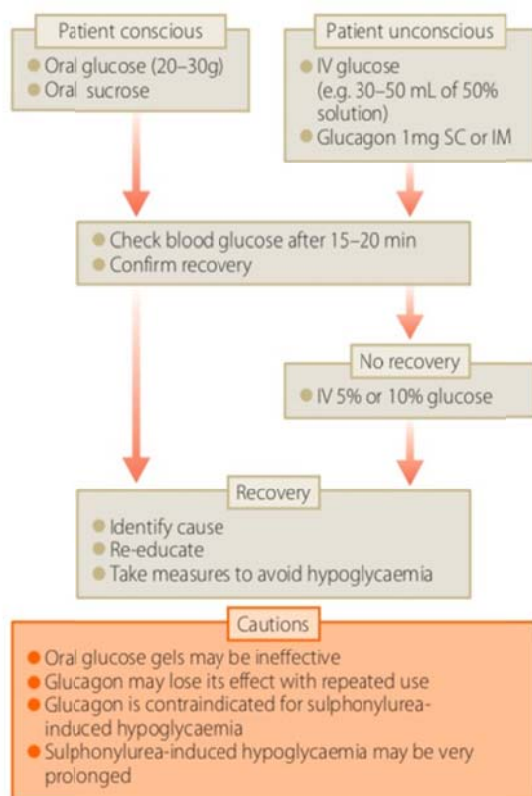
Figure 10 — Algorithm for treating acute hypoglycaemia in patients with diabetes.

CASE HISTORY

A 36-year-old woman with a 25+ year history of type 1 diabetes presents with recurrent severe hypoglycaemia, often in the early hours of the morning. She has multiple microangiopathic complications, including proliferative retinopathy (treated by laser photocoagulation), painful neuropathy, microalbuminuria and gastroparesis. HbA1c is 8.4 % using a basal-bolus insulin regimen. She has considerable anxiety about hypoglycaemia, having embarrassed herself at work with odd behaviour associated with a hypo. She has mostly lost her awareness of hypoglycaemic symptoms, and is reluctant to modify her insulin doses (in order to improve HbA1c) because of the risk of hypos. On admission to hospital, she reports at least six severe hypos in the past year requiring third-party assistance.

Comment: Hypoglycaemia unawareness is common among patients with long-duration type 1 diabetes, especially when autonomic dysfunction is present. Fear of severe hypoglycaemia, associated with behavioural disturbance and altered cognition, is an understandable barrier to improving glycaemic control, yet because of advanced microvascular complications, this woman would benefit from lower HbA1c levels in the long term. This is a complex management problem. She would be a candidate for continuous subcutaneous insulin infusion using a pump.

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CONTROL AND COMPLICATIONS

KEY POINTS
• Tissue complications of diabetes can be specific, microvascular damage to the eye, kidney or peripheral nerve (retinopathy, nephropathy or neuropathy), or non-specific macrovascular accelerated atherosclerosis.
• Conclusive evidence now links the level of hyperglycaemia to development of microvascular complications and glycaemic correction can prevent or slow their progression.
• The evidence for macrovascular disease is much less secure. Hyperglycaemia causes complications by several potential mechanisms including activation of the polyol and hexosamine pathways, and production of advanced glycation end-products. Each of these processes results in the generation of reactive oxygen species, so oxidative stress may represent the final common path towards complications.

Much of the impact of chronic diabetes results from the development of tissue complications, mainly microvascular (retinopathy, nephropathy and neuropathy) and macrovascular disease (atherosclerosis). Microangiopathy is characterised by progressive occlusion of the capillary lumen with subsequent impaired tissue perfusion, increased vascular permeability and increased production of extracellular material by perivascular cells, resulting in basement membrane thickening. There is strong evidence that microvascular disease is related to the duration and severity of hyperglycaemia in both type 1 and type 2 diabetes.

Microvascular complications occur in cells and tissues which are unable to limit glucose transport in the face of hyperglycaemia (particularly the retina, the mesangium in the kidney and Schwann cells). Several metabolic pathways and secondary messengers have been implicated in these tissues and the main ones are dealt with here.

Polyol pathway

In this pathway, the rate-limiting enzyme, aldose reductase, reduces glucose to its sugar alcohol, sorbitol. This is then oxidised by sorbitol dehydrogenase into fructose. Aldose reductase is a ubiquitous enzyme found in many tissues but specifically nerve cells, retinal cells, the glomerulus and kidney tubule, and blood vessel walls. The pathway is normally inactive but in the presence of hyperglycaemia there is increased flux leading to accumulation of intracellular glucose and glucose-derived substances, such as methylglyoxal and acetol, which can rapidly glycate proteins. Sorbitol does not diffuse easily across cell membranes and damage may occur because of osmotic stress (currently thought to be less likely although may be operative in the lens of the eye in the formation of cataract). Alternative mechanisms involve decreased levels of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), and increases in nicotina-

mide adenine dinucleotide plus hydrogen (NADH). The result of these changes is activation of protein kinase C and the promotion of advanced glycation end-product formation. Moreover, these changes result in increased oxidative stress.

Advanced glycation endproducts

Advanced glycation endproducts (AGEs) are formed by the reaction of glucose and other glycating compounds, such as methylglyoxal, with proteins (an analagous process to the formation of glycated haemoglobin), and other long-lived molecules, such as nucleic acids. Early glycation products are reversible, but eventually they undergo irreversible change through cross-linking.

Advanced glycation endproducts can cause damage and ultimately complications of diabetes in two ways; firstly, as a result of cross-linkage of matrix proteins, such as collagen and laminin, leading to thickening and stiffening of blood vessels which can affect permeability and elasticity. Secondly, AGE-modified circulating proteins bind to specific receptors (RAGEs – three subtypes have now been described) on several types of cell, including monocyte/macrophages, glomerular mesangial cells and endothelial cells. This binding leads to the generation of reactive oxygen species, activation of secondary messengers such as protein kinase C (PKC), release of transcription factor NFκB and stimulation of cytokine and growth factor production, which can result in inflammatory cell adhesion (via increased VCAM-1), procoagulant protein expression and increased vascular permeability (via VEGF).

Secondary messengers

Protein kinase C is an enzyme that phosphorylates several target proteins. It exists in many isoforms and is activated by diacylglycerol which is a direct product of increased glucose flux and increased glycolysis. Overactivity of PKC has been implicated in increased vascular permeability and blood flow, particularly in the retina. Interest in this pathway has been stimulated by the development of a PKC β inhibitor, ruboxistaurin, which was shown in experimental animals to reduce the development of retinopathy. Trials in humans have shown benefit in advanced eye disease but confirmatory studies are awaited.
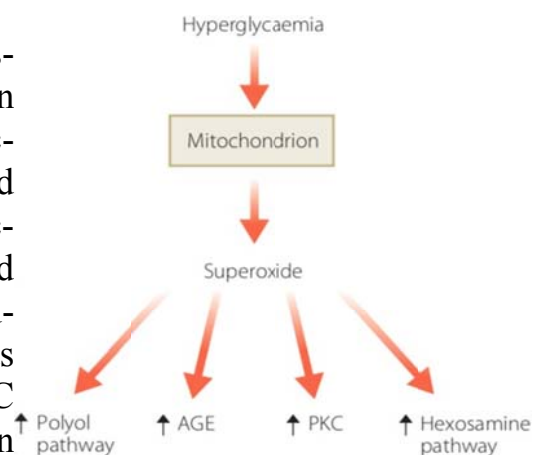

Figure 11 — Superoxide links glucose and diabetic complications

Hexosamine pathway

An increased flux of glucose can result in activation of the hexosamine pathway. Fructose-6-phosphate is diverted from glycolysis to form UDP-N-

acetylglucosamine, which is used in the synthesis of glycoproteins. The rate-limiting step in the conversion of glucose to glucosamine is regulated by glutamine: fructose-6-phosphate amidotransferase (GFAT). It is thought that glycation of transcription factors by N-acetylglucosamine increases the activity of many genes. Amongst these are TGF-β (a key profibrogenic cytokine), acetyl CoA carboxylase (the rate-limiting enzyme for fatty acid synthesis and which might increase insulin resistance) and plasminogen activator inhibitor-1 (PAI-1) which promotes thrombosis.

All the mechanisms listed above have a common effect of increasing reactive oxygen species and thus increasing oxidative stress (Figure 11). Some workers feel that this is the final common path which underpins the development of all diabetes complications.

DIABETIC EYE DISEASE

KEY POINTS
- Diabetic eye disease primarily affects the retina, but other structures can also be involved.
- Pathological damage to the microvasculature leads to retinal ischaemia and proliferative retinopathy, but macular oedema and maculopathy are the main causes of visual loss.
- Prevention of retinopathy development is critical; glycaemic control, blood pressure lowering and renin angiotensin system blockade are of proven benefit.
- Medical therapies for prevention of progression of retinopathy have shown promise but photocoagulation remains the cornerstone of treatment.
- Screening for diabetic retinopathy using digital fundus photography is now recommended by many national guidelines.

Ocular complications can be divided into **extraocular and intraocular** complications. Extraocular complications include inflammation of the eyelid (blepharitis), yellowish deposits of fat underneath the skin (xanthelasma) extraocular muscle palsy, especially involving the III (oculomotor nerve) and VI (abducense nerve) cranial nerves, and microaneurysms of the conjunctiva. To the ocular complications belongs reduced corneal sensitivity resulting in recurrent corneal epithelial damage, glaucoma and disturbed visual function. Among the ocular complications mention must be made of alterations of lens leading to myopia and early development of cataracts, as well as diabetic retinopathy and anterior ischemic optic neuropathy (AION).

Conjunctival bacterial infections occur in 80–90 % of patients with diabetes, resulting in a decreased number of goblet cells which may lead to keratosis.

Microaneurysms in the bulbar conjunctiva are more common in diabetic individuals. There is a change in tear film composition, leading to reduced corneal sensation, which results in increased risk of corneal damage.

Tear break up time, which is a minimum of 20 seconds in healthy individuals, significantly diminishes as a result of damage to tear film disposition and stability in the corneal surface.

Superficial corneal inflammation (punctate keratitis) and **recurrent corneal erosions** have also been linked to decreased corneal sensitivity and poor adhesion between epithelial cells and the basal membrane.

Diabetic individuals may find it difficult to use contact lenses, as the cornea may become **oedematous and epithel damage** may occur. One of the most serious complications of diabetes is the **neovascularisation** of the iris. This alteration is usually first observed at the pupillary margin but it can involve the entire iris surface and filtration angle. Neovascularisation arises from hypoxia caused by retinal capillary damage. It is reported up to 60 % of proliferative retinopathies.

In diabetic patients the pupils may be more narrow (miotic) and may have weaker reaction to topical mydriatics originating in diminished innervations of pupil dilatator muscle due to diabetic neuropathy.

The occurrence of **Uveitis** (inflammation of the iris or ciliary body) is also more common in diabetes. Neovascularisation of the iris results in neovascular glaucoma. The newly growing vessels block the drainage of aqueous fluid through the anterior chamber angle, causing elevation of intraocular pressure. The pupil may become irregularly shaped; the eyes become red and painful leading to loss of visual acuity if not treated (e. g. by normalising intraocular pressure).

Refractive changes are common in diabetes because significant plasma glucose fluctuations (in uncontrolled diabetes) induce shifts in glucose concentration of aqueous humour which leads to swelling of the lens. Glycosylation of lens proteins results in a decrease in the lens's transparency.

Patients with diabetes have a 2 to 4 times greater risk of developing **cataracts** than do non-diabetic people. Cataracts typically tend to develop earlier and the risk increases with age, duration of diabetes, uncontrolled diabetes (high HbA1c) and kidney disease. The only effective treatment of a matured cataract is surgery.

Macular edema, which is actually the swelling or thickening of the central retina, is often (in 7 %) found while examining diabetic patients. Epidemiological data indicate that it is the major cause of vision loss in diabetic individuals. Treatment of diabetic macular edema includes Argon laser photocoagulation of the fundus, as well as the proper management of systemic risk factors such as hyperglycaemia, hypertension and hyperlipidaemia.

Extensive laser photocoagulation may result in complications like central and paracentral scotoma (visual field loss), colour vision changes or loss, or occasionally secondary retinal neovascularisation. In these cases anti VEGF treatments are recommended, such as intravitreal administration of bevacizumab, ranibizumab, pegaptanib, or aflibercept.

Attempts have been made to administer glucocorticosteroids. Triamcinolon, fluocinolone and dexamethasone can be used intravitreally for the treatment of diabetic macular edema.

DIABETIC RETINOPATHY

Essentially, diabetic retinopathy can be classified as non-proliferative (now often split into background and pre-proliferative) and proliferative. The earliest pathological features are thickening of the retinal capillary basement membrane, loss of tight junctions in the retinal endothelium, and loss of pericytes which are the contractile cells enveloping the capillaries and which control vessel calibre and thus perfusion (Figure 12).
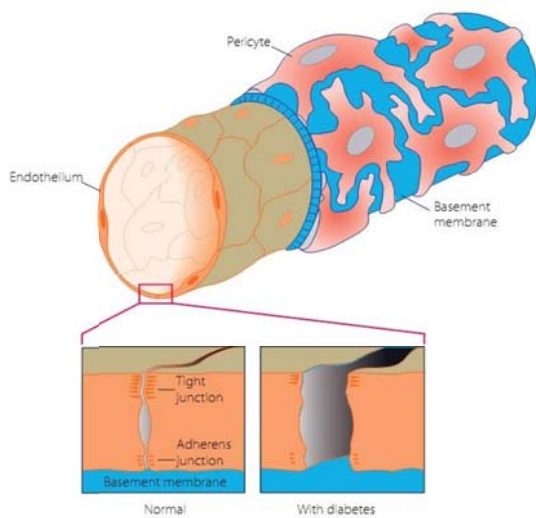
Figure 12 — Structure of the retinal microvasculature. The endothelial cells are normally joined by tight junctions, which constitute much of the blood — retinal barrier; these separate in diabetes, causing increased vascular permeability. Other abnormalities in diabetes include thickening of the basement membrane and fallout of both the endothelial cells and the contractile pericytes

Physiologically, an increase in retinal blood flow is an early feature of diabetes and it is possible that this creates mechanical stress that leads to endothelial separation and pericyte loss. The first noticeable lesions on ophthalmoscopy are microaneurysms which appear as small red dots varying in size from 20 to 200 μm in diameter. They are blind pouches arising from capillaries, probably from weakened endothelial cell junctions adjacent to an area of pericyte loss. Microaneurysms are rarely sight threatening (unless occurring in the macula) and can seem to disappear although this is probably a result of thrombosis within the aneurysm or closure of the feeding capillary. Capillary closure is a feature of advancing retinopathy and the resultant ischaemia is a driver for subsequent proliferation. Haemorrhages can occur superficially when they tend to be flame shaped (limited by nerve fibres) or deep (blot or round shaped and indicative of underlying ischaemia). Hard exudates are the result of leakage of lipid rich proteins into the retina. They appear as discrete yellow-creamy white patches which are often ring-shaped or circinate around a central area of ischaemia and capillary leakage. Capillary closure causes microinfarcts in the nerve fibre layer and these appear as indistinct white patches and are termed cotton wool spots (previously known as soft exudates).

More advanced ischaemia results with the development of intraretinal microvascular abnormalities (IRMAs), which are clumps of small irregularly branching vessels within the retina, and venous dilatation, beading (segmental dilatation resembling a string of sausages), loops and reduplication, sometimes into multiple loops resembling a four-leafed clover. New vessel growth or neovascularisation is the hallmark of proliferative retinopathy and results from the local release of growth factors (such as vascular endothelium-derived growth factor; VEGF) in response to ischaemia. These vessels are fragile, fine outgrowths from retinal veins and grow forward into the vitreous. Because of this, they are prone to shear stress and rupture, resulting in preretinal or vitreous haemorrhage and sudden visual loss. New vessels are associated with fibrous bands that can cause traction retinal detachment or tearing of vessels, leading to further haemorrhage. Sometimes the haemorrhage remains encapsulated between these fibrous bands, the retina and the vitreous, leading to a fluid level and a flat-topped (boat-shaped) appearance. Tractional detachment results in 'tenting' or folding of the retina with grey-white bands and occasional tears. Ophthalmic ultrasound is often helpful at detecting detachment, particularly if the retina is obscured by haemorrhage. The most common cause of visual loss, however, is maculopathy which results from ischaemia and subsequent oedema of the central retina. Focal maculopathy is usually associated with areas of circinate or star-shaped exudate within one optic disc diameter of the macula.

Diffuse macular oedema results from ischaemia and causes thickening of the retina. It is harder to detect clinically and needs either stereo ophthalmoscopy or optical coherence tomography (OCT) which can generate clear images of the retina and accurate estimates of thickness.

Treatment of retinopathy
Glycaemic control
All studies demonstrated the benefit of glycaemic control for the primary prevention of new retinopathy, and secondary prevention of progression of existing retinopathy.

However, as previously mentioned, rapid improvement in glycaemia can result in an early worsening of retinopathy.

Blood pressure control
Post hoc analysis suggested a 13 % decrease in the aggregate microvascular endpoint (combination of retinopathy requiring photocoagulation, vitreous haemorrhage and/or fatal or non-fatal renal failure) for every 10 mmHg reduction in blood pressure.

Lipid-lowering agents
The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study found a significant reduction in the need for laser therapy in 9 795 patients

with type 2 diabetes treated for 5 years. This effect was independent of blood lipid levels and is unexplained. Absolute numbers of patients were small and the indications for laser therapy were not specified so interpretation of these data is difficult. No consistent effect of statin therapy on retinopathy has been reported.

Growth hormone inhibitors

The observation of a regression in proliferative retinopathy in a woman with Sheehan's syndrome (postpartum hypopituitarism) and the subsequent clinical trials (in the days before photocoagulation) of hypophysectomy in patients with advanced eye disease established a potential link between growth hormone and neovascularisation. Octreotide (a somatostatin analogue that blocks growth hormone release) has been shown to decrease progression of severe non- proliferative or early proliferative retinopathy but had serious GI side effects.

Intravitreal steroids

Both triamcinolone (by injection) and fluocinolone (by implant) have been shown to reduce macular oedema and improve visual acuity but with the serious side effects of glaucoma and cataract formation. Many patients required multiple steroid injections and some developed infections. The long-term benefits and safety of these treatments need to be established.

VEGF inhibitors

These agents have been shown to benefit patients with 'wet' age-related macular degeneration which shows some similarities with diabetes-related macular oedema.

Laser photocoagulation

Meta-analysis shows that panretinal laser photocoagulation reduces the risk of blindness in eyes with proliferative retinopathy by 61 %, and this has now become the cornerstone of treatment of advanced disease. Focal laser photocoagulation can be effective for more discrete neovascularisation or ischaemia.

> ### CASE HISTORY
>
> A 29-year-old woman with type 1 diabetes and coeliac disease had a profound fear of hypoglycaemia. Consequently, she maintained high blood glucose levels and her HbA1c was consistently above 9 %. Because of developing retinopathy, she elected to try CSII. There was a dramatic improvement in blood glucose control without hypoglycaemia and her HbA1c came down to 6.5 % over 6 months. Regular ophthalmic assessments were scheduled but she missed two appointments. Four months later she presented with acute vitreous haemorrhage in her right eye secondary to advanced proliferative retinopathy. Extensive panretinal photocoagulation has prevented further haemorrhage and preserved vision in her left eye, but she now requires vitreoretinal surgery on the right for traction detachment.
>
> **Comment:** This case demonstrates the potential for rapid worsening of retinopathy with glycaemic improvement. It is essential to arrange frequent eye examinations in this and similar situations (such as pregnancy) and also to impress upon the patient their importance. Panretinal photocoagulation is best carried out before neovascularisation and haemorrhage.

Vitrectomy

Surgical vitrectomy in advanced eye disease results in sustained benefit in terms of visual acuity, with 6/12 (20/40) or greater vision in at least 25 % of eyes at 4 years. Improved operative technique with intraoperative imaging has greatly advanced the field and is likely to have improved outcomes.

Surveillance and screening

Regular retinal examination is recommended by all national guidelines. The ADA suggests expert examination within 5 years of diagnosis of all with type 1 diabetes aged >10 years and as soon as possible after diagnosis of type 2 diabetes. The best periodicity thereafter is controversial. The ADA suggests that review could be every 2 or more years if there are several annual assessments with no retinopathy. Studies from Liverpool in the UK suggest that there is a minimal likelihood of progression from no retinopathy to significant change requiring therapy in less than 2 years in patients with type 2 diabetes.

DIABETIC NEPHROPATHY

KEY POINTS
- Diabetic nephropathy is a clinical diagnosis based upon the presence of albuminuria in a person with diabetes.
- Classic staging based upon albuminuria does not map clearly to the current classification of chronic kidney disease. Once patients develop clinical nephropathy (urinary albumin concentration > 300 mg/L), their renal function declines toward end-stage renal failure.
- Patients with nephropathy have an increased cardiovascular mortality, which increases further as proteinuria and renal function worsen.
- The pathological features are of glomerular basement membrane thickening and diffuse glomerulosclerosis, both secondary to matrix protein accumulation. Both metabolic and haemodynamic factors play a role in pathogenesis.
- Tight glycaemic control can prevent nephropathy developing but once it is established, the cornerstone of treatment is blood pressure lowering, primarily with agents that block the renin-angiotensin system.
- Diabetes is the biggest single cause of end-stage renal failure requiring renal replacement therapy.

Diabetic nephropathy is a clinical diagnosis based upon the detection of proteinuria in a patient with diabetes in the absence of another obvious cause such as infection. Many of these patients will also be hypertensive, have retinopathy and, in advanced stages, renal impairment.

Persistent albuminuria in the microalbuminuric range is now widely accepted as a positive diagnosis for diabetic nephropathy (Table 9).

Table 9 — Definition of diabetic nephropathy by albuminuria and test

Urine specimen	Microalbuminuria	Clinical nephropathy
Timed overnight collection	20–199 ng/min	> 200 μg/min
24-hour collection	30–299 mg/d	≥ 300 mg/d
Albumin concentration	20–300 mg/L	> 300 mg/L
Albumin/creatinine ratio (Europe)	Men 2.5–30 mg/mmol Women 3.5–30 mg/mmol	> 30 mg/mmol > 30 mg/mmol
USA	Both 30–300mg/g	> 300 mg/g

National Institute of Health and Clinical Excellence (NICE) guidance suggests that positive tests for microalbuminuria should be confirmed within 3–4 months before making a diagnosis of nephropathy.

Classically, patients were considered to progress relentlessly from normoalbuminuria through microalbuminuria to clinical nephropathy. It is now recognised that patients with microalbuminuria may spontaneously revert to normoalbuminuria, up to 50 % in some series of type 1 patients. Moreover, albuminuria can increase during periods of poor glycaemic control (and then decrease with glycaemic correction), and reduce with antihypertensive therapy (notably drugs which block the renin-angiotensin system (RAS)).

An international classification of chronic kidney disease (CKD) has now been widely adopted, but unfortunately it does not map precisely to staging of diabetic nephropathy based upon albuminuria (Table 10).

Table 10 — Stages of chronic kidney disease (CKD) and their mapping to diabetic kidney disease (DKD)

Stage	Defining eGFR (mL/min/ 1.73 m^2)	Other required features	Patients with diabetes Normo-albuminuria	Micro-albuminuria	Clinical nephropathy
1	> 90	Abnormal urinalysis and/or renal imaging	At risk for DKD	Likely DKD (type 1) Possible DKD (type 2)	DKD
2	60–89	Abnormal urinalysis and/or renal imaging	At risk for DKD	Likely DKD (type 1) Possible DKD (type 2)	DKD
3A	45–59	None	Likely DKD (type 1)	DKD (type 1)	DKD
3B	30–44	None	Possible DKD (type 2)	Likely DKD (type 2)	DKD
4	15–29	None	Probable DKD	DKD	DKD
5	< 15 or RRT	None	DKD	DKD	DKD

RRT, renal replacement therapy.
Abnormal urinalysis = albuminuria and/or haematuria.

The new staging is based upon GFR as estimated (eGFR) from a plasma creatinine concentration using a formula derived from the Modification of Diet in Renal Disease (MDRD) Study.

eGFR (mL min 1.73 m^2) = 175 × [serum creatinine (μmol L) × 0.0113$^{-1.154}$] × age (years)$^{-0.203}$
If female multiply by 0.742
If African American multiply by 1.21

This formula uses a serum creatinine assay aligned to an international reference method. It has not been specifically validated in people with diabetes, in other ethnic subgroups such as South Asians or Chinese/Japanese, in children or in pregnancy. Alternative formulae for estimating creatinine clearance (not GFR) exist, such as Cockroft–Gault, and for GFR using serum cystatin C. Both have their advocates but although cystatin C has advantages, it is expensive and not widely available in the UK.

The earliest pathological feature is thickening of the glomerular capillary basement membrane due to an accumulation of matrix material, which is detectable within 5 years of diabetes onset in patients with type 1 diabetes. Increasing proteinuria is preceded and accompanied by further accumulations of matrix material (mostly type IV collagen and laminin) in the mesangium (called diffuse glomerulosclerosis), due to both overproduction and reduced breakdown and clearance. Ultimately this process obliterates the capillary and reduces filtration, leading to renal failure.

Arteriolar hyalinosis leading to glomerular ischaemia, glomerular epithelial cell (podocyte) loss and tubulointersti tial inflammation and fibrosis are also features of advanced nephropathy.

Metabolic and haemodynamic factors combine to stimulate the release of profibrogenic cytokines such as transforming growth factor β (TGF-β) and connected tissue growth factor, as well as decreasing matrix degradation by inhibition of enzymes such as metalloproteinases. In experimental and human diabetes, renal blood flow is increased and there is a relative dilatation of the afferent compared to the efferent glomerular arteriole. This leads to an increase in glomerular capillary pressure which has been closely related to thedevelopmentof glomerulosclerosis in diabetic animals. Angiotensin II blockade relaxes the efferent arteriole and lowers intraglomerular capillary pressure (Figure 13).

These changes in structure and capillary pressure underpin the development of albuminuria. The glomerular capillary has an inherent size and molecular charge selectivity. In structural terms the endothelium lining the capillary is fenestrated and has a complex glycocalyx of proteins on its surface. The glomerular basement membrane (GBM) is a meshwork of mainly type IV collagen which is cross-linked in a lattice formation. Finally, the epithelial surface comprises the podocytes which have a series of interdigitating foot processes.

The glomerular barrier normally retains most circulating proteins of the size and charge of albumin. Glycation of the glycocalyx proteins, disruption of

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the GBM lattice by matrix accumulation, and podocyte loss allow filtration of increas ing amounts of albumin and larger macromolecules which characterise progressive nephropathy. There is evidence that the increased presentation of proteins in the filtrate to tubular cells leads to tubulointerstial inflammation and fibrosis, contributing to declining GFR.
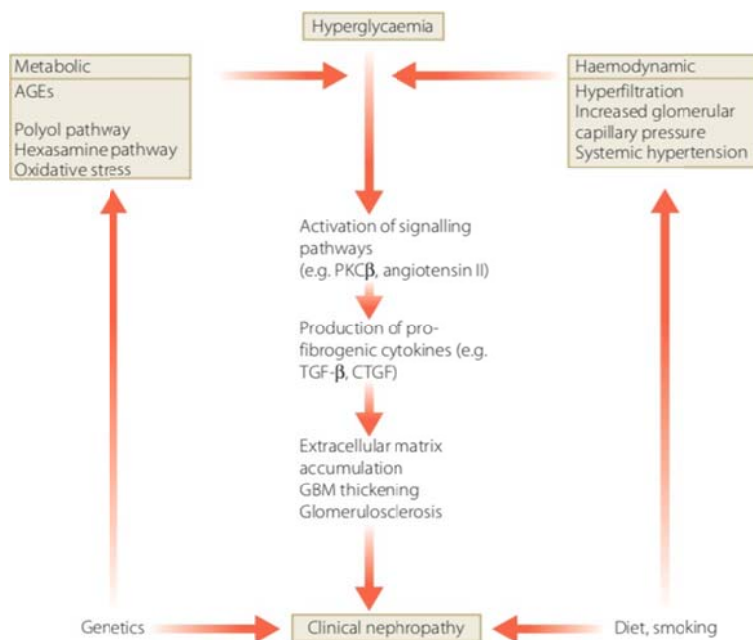

Figure 13 — Schematic diagram illustrating how metabolic and haemodynamic factors combine to cause glomerulosclerosis. PKCβ, protein kinase C β; GBM, glomerular basement membrane; TGF-β, transforming growth factor β; CTGF, connective tissue growth factor

Factors associated with the development of diabetic nephropathy
• Glycaemia
• Diabetes duration
• Hypertension
• Hyperfiltration
• Ethnicity
• Genetics
• Diet (protein intake)

Management
Glycaemic control

There is very little evidence to suggest that it can prevent or delay the progress of nephropathy once it is established. This is probably because after nephropathy has been initiated (by largely glucose-dependent mechanisms), it is continued by pathways that are no longer sensitive to changes in glycaemia. Intriguingly, though, in a small group of type 1 pancreas transplant recipients, renal pathology improved in their native kidneys after 10 (but not 5) years of normoglycaemia, implying that not only is complete normalisation of blood glucose required, but also the lesions take almost as long to resolve as they do to develop. Good glycaemic control, however, will continue to benefit other complications such as retinopathy.

Blood pressure

Target blood pressure for people with diabetes has been set at <130/80 mmHg by most guidelines, with some suggesting < 120/75 in those with nephropathy and proteinuria >1 g/day. Improved control of blood pressure is probably the main reason why the median duration of clinical nephropathy prior to ESRD has risen from 7 to 14 years since 1980.

Because of the involvement of angiotensin II in the glomerular haemodynamic changes in diabetes, agents which block the RAS feature as first- line therapy in most guidelines. These drugs also reduce albuminuria which would help ameliorate any tubulointerstitial insult caused by increased protein trafficking across the tubular epithelium.

However, there is little evidence that RAS blockade can prevent primary development of microalbuminuria in type 1 diabetes and may only be effective in patients with type 2 diabetes who are already hypertensive or at high cardiovascular risk.

Protein restriction

In experimental diabetes, dietary protein restriction reduces albuminuria and progression to renal failure. A systematic review has shown a modest reduction in the rate of decline of GFR in type 1 diabetes with a restriction of dietary protein intake to 0.7–1.1 g/kg bodyweight/day. For type 2 diabetes the data were not significant. The National Kidney Foundation guideline recommends a dietary protein intake of 0.8 g/kg bodyweight/day for diabetic patients and CKD stages 1–4.

Anaemia correction

Anaemia secondary to erythropoietin (EPO) deficiency is a feature of CKD generally and some studies suggest that it occurs earlier at a higher GFR in people with diabetes. Hospital clinic-based surveys suggest prevalence rates of WHO- defined anaemia (<12 g/dL women, <13 g/dL men) of 15–25 %, and many cases were in patients with an eGFR >60mL/min/1.73m^2. Several large trials of anaemia correction using various preparations of EPO have suggested no benefit (and possibly some harm) of achieving a

CASE HISTORY

A 32-year-old man with type 1 diabetes, modest renal impairment (serum creatinine 212 μmol/L) and clinical nephropathy had a BP of 170/110 mmHg when he first presented in 1994. His diabetic control was poor and he would only take insulin once a day in an unusual mixture of lente and ultralente preparations. He was started on enalapril 10 mg with an immediate response; his BP fell to 120/80 mmHg. Although there was an initial increase in his serum creatinine, this stabilised and now 15 years later he is still independent of dialysis. During this time his BP has always been <140/90 mmHg and usually much less than that. He was working until 5 years ago as a scaffolder but had to stop because of postural dizziness due to autonomic neuropathy. His HbA1c has varied between 8 % and 11 % over this time; he is now on twice-daily premixed insulin (after ultralente was withdrawn).

Comment: The renal response to therapy in this man is striking and was achieved despite poor glycaemic control. This underscores the primacy of BP in driving progression of diabetic nephropathy once it is established. The initial increase in serum creatinine is significant but still within a 35 % change that is acceptable when commencing RAS- blocking drugs. His blood pressure response was dramatic which supports the role of angiotensin II in nephropathy-related hypertension.

Although eGFR is a useful reminder of kidney function, a reciprocal serum creatinine chart like this is also helpful in monitoring progression and the impact of any interventions, especially once the level is >150 μmol/L.

haemoglobin concentration >13 g/dL. Below this level, patients feel better but no conclusive impact on rate of decline in GFR or cardiovascular morbidity/mortality has been demonstrated. Current NICE guidance has set an intervention threshold of 11g/dL and a target of 10.5–12.5 g/dL for all patients with CKD and adequate iron stores.

Cardiovascular risk factor management

There are no conclusive trial data to support aspirin or lipid-lowering therapy specifically in diabetic nephropathy. Thus targets are the same as for diabetes generally.

DIABETIC NEUROPATHY

KEY POINTS
• Diabetic neuropathy is a term that encompasses a heterogeneous group of disorders.
• Microvascular disease affecting the small nutrient vessels that supply peripheral nerves (vasa vasorum) results in ischaemic and metabolic neuronal injury.
• Chronic sensorimotor neuropathy is the most common form, typically affecting the stocking distribution of the lower limb, causing painful symptoms, mixed modality sensory loss, small muscle wasting and deformity (e.g. clawed toes).
• Several drug treatments have been tried for painful diabetic neuropathy, but few have any evidence base from controlled trials. Only duloxetine and pregabalin are licensed by the US FDA.

Diabetes is one of the most common causes of peripheral neuropathy, a term that encompasses a heterogeneous group of disorders. In population-based surveys, up to one-third of patients with diabetes have evidence of peripheral neuropathy but many are asymptomatic. Diabetic neuropathy should not be diagnosed solely on the basis of one symptom, physical sign or test; it is recommended that a minimum of two abnormalities
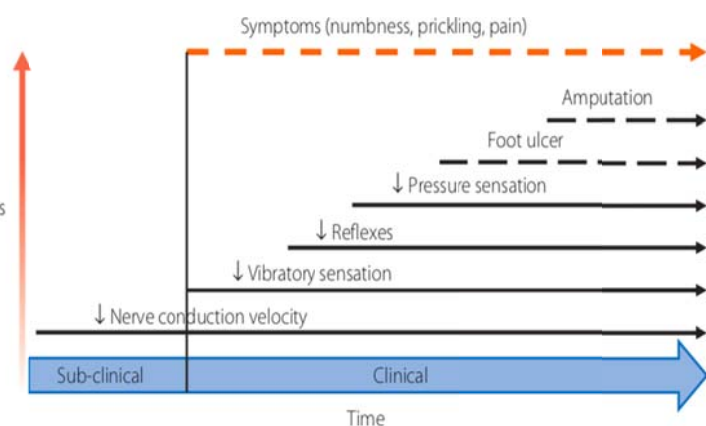

Figure 14 — **Diabetic neuropathy is common and associated with a complex mix of symptoms and signs. With increasing duration of diabetes and associated microangiopathy, diabetic neuropathy may lead to foot ulceration, deformity and/or amputation**

be detected (symptoms, signs or test abnormalities — nerve conduction, quantitative sensory testing or quantitative autonomic testing). Healthy nerves consist of myelinated and unmyelinated nerve fibres or axons. The pathophysiology of diabetic neuropathy is complex, but microvascular disease affecting small vessels (the vasa vasorum) that supply oxygen and nutrients to peripheral nerves results in ischaemic and metabolic neuronal injury via activation of several biochemical pathways, in particular the polyol pathway, non-enzymatic glycation and formation of advanced glycation endproducts (AGEs), activation of diacylglycerol-protein kinase C-β, transcription factors (e.g. NFκB) and mitogen- activated protein kinase (MAPK), and the accumulation of reactive oxygen species (ROS).

Classification of diabetic neuropathy
1. Generalised symmetrical polyneuropathies
  • Sensorimotor (chronic)
  • Acute sensory
  • Hyperglycaemic neuropathy
2. Focal and multifocal neuropathies
  • Cranial nerve
  • Thoracolumbar radiculoneuropathy
  • Focal limb
  • Proximal motor (amyotrophy)
3. Superimposed chronic inflammatory demyelinating neuropathy (CIDP)
4. Autonomic neuropathy

Chronic sensorimotor neuropathy
Chronic sensorimotor neuropathy is the most common form of diabetic neuropathy. This results from the distal dying back of axons that begins in the longest nerves; thus, the feet are affected first in a stocking distribution, and later there may be progressive involvement of the upper limbs. Sensory loss is most evident; autonomic involvement is usual, although it is mostly symptomless. Positive painful symptoms tend to be worse at night. Neurological examination shows a symmetrical sensory loss to all modalities, reduced or absent ankle or knee reflexes, and small muscle wasting of the feet and hands. The foot at high risk of neuropathic ulceration might have a high arch (pes cavus deformity) and clawing of the toes.

Positive sensory symptoms can arise spontaneously or as a response to stimulation, and they are often classified into painful and non-painful descriptors. Numbness and prickling are the most common symptoms, and they usually occur earlier. The prevalence of painful symptoms varies from 3 % to 20 %. The natural history of painful neuropathy is unclear, but there is some suggestion that the intensity of symptoms may subside with worsening quantitative measures of nerve

function. Similarly, the risk factors for painful neuropathy are ill defined. Hypo-aesthetic neuropathy is associated with minimal or negative sensory symptoms, and therefore is best detected by quantitative sensory testing.

Positive symptoms of neuropathy are distressing, often occur at night, are disabling and difficult to treat. Patients with painful peripheral neuropathy often have warm, dry feet because of autonomic involvement, which results in dilated arteriovenous shunts and absent sweating. The most important complications are:

• foot ulceration

• neuropathic oedema, caused by increased blood flow in the foot, which has reduced sympathetic innervation

• Charcot arthropathy, with chronic destruction, deformity and inflammation of the joints and bones of the mid-foot. There is reduced bone density, possibly because of increased blood flow.

Autonomic neuropathy

In patients with long-standing diabetes, numerous abnormalities can be demonstrated in organs that receive an autonomic innervation. Often, autonomic abnormalities are found in those with distal sensory neuropathies. Symptoms are unusual, occurring mostly in those with poorly controlled type 1 diabetes. Common manifestations are gustatory sweating over the face, postural hypotension (systolic blood pressure fall >30mmHg on standing), blunting of physiological heart rate variations, diarrhoea and impotence. Gastroparesis (delayed gastric emptying and vomiting) and bladder dysfunction are rare.

Treatment of diabetic neuropathy

Various topical and systemic therapies have been tried for painful diabetic peripheral neuropathy, but few have been subjected to well-designed randomised controlled trials (RCTs). Acupuncture may be helpful and the antioxidant α-lipoic acid is used in some countries. The US Food and Drug Administration (FDA) has only licensed duloxetine and pregabalin for painful diabetic neuropathy.

Pharmacological options with evidence of efficacy from RCTs for use in patients with painful diabetic peripheral neuropathy

Treatments with positive results from two or more RCTs
• Duloxetine (serotonin-norepinephrine reuptake inhibitor)
• Pregabalin (α-2-δ Ca^{2+} channel modulator)
• Oxycodone (opioid)
• Tricyclic antidepressants (e. g. amitriptyline)

Treatments with evidence of efficacy from a single trial in patients with diabetic neuropathies
• Gabapentin (α-2-δ Ca^{2+} channel modulator) Venlafaxine (SNRI)

- Tramadol
- Carbamazepine and lamotrigine may also be considered

Topical therapies
- Capsaicin cream
- Lignocaine patch

CASE HISTORY

A 55-year-old man with a 6-year history of type 2 diabetes presents to his family doctor with unpleasant symptoms of prickling discomfort, numbness and tingling over both lower limbs and feet. These symptoms often disturb his sleep, and he has noticed excessive discomfort when putting his feet into a warm bath. There are no symptoms in his hands, he is a non-smoker and drinks 6 units of alcohol per week. There are no symptoms to suggest autonomic dysfunction. He has background diabetic retinopathy, and his diabetes is managed with metformin 1g and gliclazide MR 120 mg daily (HbA1c 8.5 %). Clinical examination shows some distal muscle wasting in the feet, but no ulceration. He is unable to feel the 10 g monofilament placed over the metatarsal heads. Pedal pulses are present. His height is 6' 1", BMI 29.

Comment: This patient presents with typical symptoms and signs of diabetic peripheral neuropathy, including allodynia when he puts his feet into warm water. Risk factors include age, duration of diabetes and HbA1c, and peripheral neuropathy is more common in tall people (longer nerves are more susceptible to damage). Alcohol consumption may aggravate his symptoms. He also has evidence of microvascular complications in the eye. Improving HbA1c is important, and his feet are at high risk of ulceration. Appropriate footcare education is needed. This man may also need symptomatic treatment, e.g. pregabalin, gabapentin or amitriptyline would be reasonable choices.

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