An Overview Of DIABETES

Rajib Biswas

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Diabetes

Rajib Biswas
MBBS

Eubios Ethics Institute

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Dedicated to

Tisha and Tirtha, my beloved niece and nephew

Preface

Diabetes affects most families around the world being one of the most important sources of morbidity and mortality. In this overview, Dr. Rajib Biswas provides answers to many questions that all healthcare professionals ask regarding the best way to prevent, diagnosis and treat diabetes, and all its related morbidities. The book is clearly written and increases our knowledge to enable more active professional approaches to disease management.

We are honored to publish this important resource book in cooperation with Rimikri, and hope that it will lead many to a better life. What we can say though is that changes to our diet and lifestyle can substantially reduce the incidence of diabetes. There is not a fixed genetic destiny for this disease. Public health ethics is essential as we combat the epidemic expansion of this disease, and we urge all health care professionals and citizens to take responsibility to make healthy lifestyle choices using wisdom wisely.

Darryl R.J. Macer, Ph.D. (Cantab), Hon.D, MPH
President, American University of Sovereign Nations
http://www.ausn.info
Director, Eubios Ethics Institute, New Zealand, Japan and Thailand
http://www.eubios.info
Email: darryl@eubios.info

About

Eubios Ethics Institute

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Introduction

Diabetes is one of the largest global health emergencies. Advances are taking place in better understanding, preventing and treating diabetes and its complications every day. It is a crucial duty of the healthcare professionals dealing with diabetes patients to keep track with these advances so that they can come up with the best service possible. In this book, I have discussed both the basics and advanced understandings regarding diabetes from its anatomical and physiological background to its disease process, diagnosis, complications, treatment and prevention.

I believe the clear understanding of the disease process is a prerequisite not only for better diabetes care but also for adapting the effective prevention strategies that could help halt the inexorable rise of type 2 diabetes.

I wholeheartedly invite constructive criticism from readers, so that any error can be corrected in future edition.

Rajib Biswas

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1 Introduction
Diabetes: A global emergency

Diabetes is one of the largest global health emergencies of the 21st century. Each year more and more people live with this condition. Diabetes of all types can lead to complications in many parts of the body and can increase the overall risk of dying prematurely. In addition to the 415 million adults who are estimated to currently have diabetes, there are 318 million adults with impaired glucose tolerance, which puts them at high risk of developing the disease in the future. Effective tools are available to prevent type 2 diabetes and to improve management to reduce the complications and premature death that can result from all types of diabetes.[8,13]

Definition

Diabetes mellitus is a clinical syndrome characterised by an increase in plasma blood glucose (hyperglycaemia).[1]

Or, Diabetes mellitus (DM) is a syndrome of chronic hyperglycaemia due to relative insulin deficiency, resistance or both.[5]

Hyperglycaemia results in both acute and long-term problems. Acutely, high glucose and lack of insulin can result in marked symptoms, metabolic decompensation and hospitalisation. Chronic hyperglycaemia is responsible for diabetes-specific 'microvascular' complications affecting the eyes (retinopathy), kidneys (nephropathy) and feet (neuropathy). There is a continuous distribution of blood glucose in the population, with no clear division between people with normal and abnormal values.

Diabetes is a major burden upon health-care facilities in all countries. Globally, diabetes caused 4.6 million deaths in 2011, and health-care expenditure attributed to diabetes was estimated to be at least US$465 billion, or 11% of total health-care expenditure.

Epidemiology

The incidence of diabetes is rising. Globally, it is estimated that 366 million people had diabetes in 2011 (approximately 8.3% of the world population, or 3 new cases every 10 seconds).[1] The International Diabetes Federation (IDF) estimated that 382 million people (8.3% of the global population) had diabetes in 2013, and estimates an increase to 592 million (10.1%) in 2035.[5]

In 2015, according to IDF, 415 million adults are estimated to currently have diabetes and 318 million adults with impaired glucose tolerance.[8]

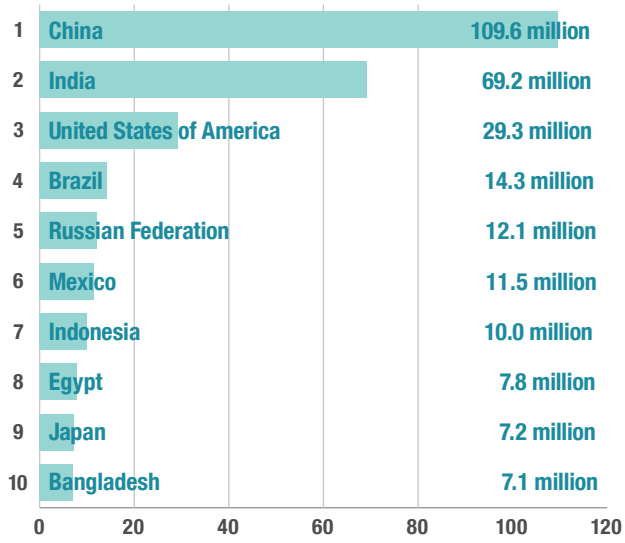


Figure: Top ten countries/territories for number of adults with diabetes.[8]

Type 1 diabetes

The incidence of type 1 diabetes is also increasing, such that between 1960 and 1996, 3% more children were diagnosed worldwide each year.[1]

Type 1 diabetes is generally more common in countries closer to the polar regions.[1] Finland and other Northern European countries have the highest rates of type 1 diabetes.[5] Finland, for instance, has the highest rate of type 1 diagnosis per year at around 40 per 100 000 of the population, whereas in China the incidence is only 0.1 per 100 000 of the population.[1]

Type 1 diabetes is most common in Caucasians and more people are diagnosed in the winter months.[1]

Type 1 diabetes is a disease of insulin deficiency and is subdivided into type 1A (immunemediated) and type 1B (non-immune-mediated). The great majority of those affected, especially in Western countries, have type 1A disease.[5]

In Europe, the annual increase in the incidence of type 1 diabetes is of the order of 2–3%, and is most marked in children under the age of 5 years. The IDF estimated in 2013 that 0.5 million children aged 0– 14 years are currently affected by diabetes, and the figure is increasing by 3% annually.[5]

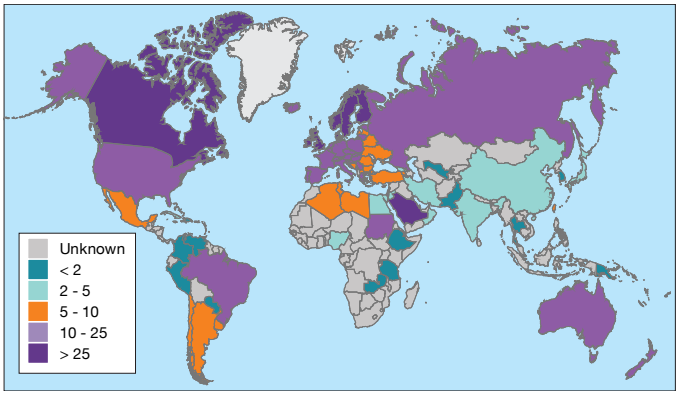


Figure: Estimated new cases of type 1 diabetes (< 15 years) per 100,000 children per year, 2015.

From International Diabetes Federation. IDF Diabetes Atlas, 7th edn. Brussels: International Diabetes Federation; 2015

Type 2 diabetes

The global pandemic of diabetes principally involves type 2 diabetes. The prevalence of which varies considerably around the world, being associated with differences in genetic as well as environmental factors such as greater longevity, obesity, unsatisfactory diet, sedentary lifestyle, increasing urbanization, economic development[1] and also because of better diagnosis.[4] The IDF estimates the global lifetime risk of diabetes at 20%, with the highest rates and most rapid increase in the Middle East, South-east Asia and the Western Pacific.[5]

A pronounced rise in the prevalence of type 2 diabetes occurs in migrant populations to industrialised countries, as in Asian and Afro- Caribbean immigrants to the UK or USA.[1] There are sometimes 2–3-fold differences in prevalence between populations from different ethnic backgrounds who share the same environment.[5]

Type 2 diabetes is now being observed in children and adolescents, particularly in some ethnic groups, such as Hispanics and Afro-Americans.

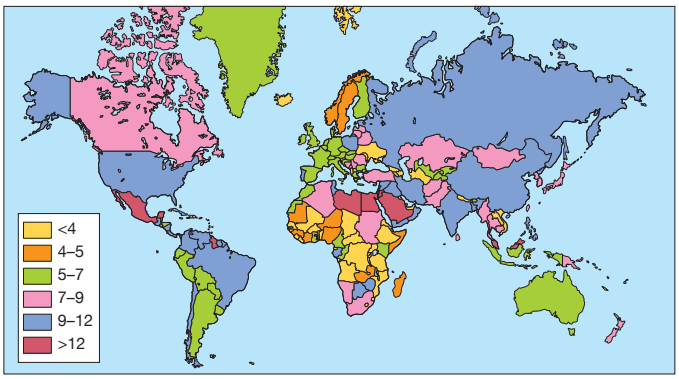


Figure: Prevalence (%) of diabetes in those aged 20–79 years, 2011, based on estimates from the International Diabetes Federation.

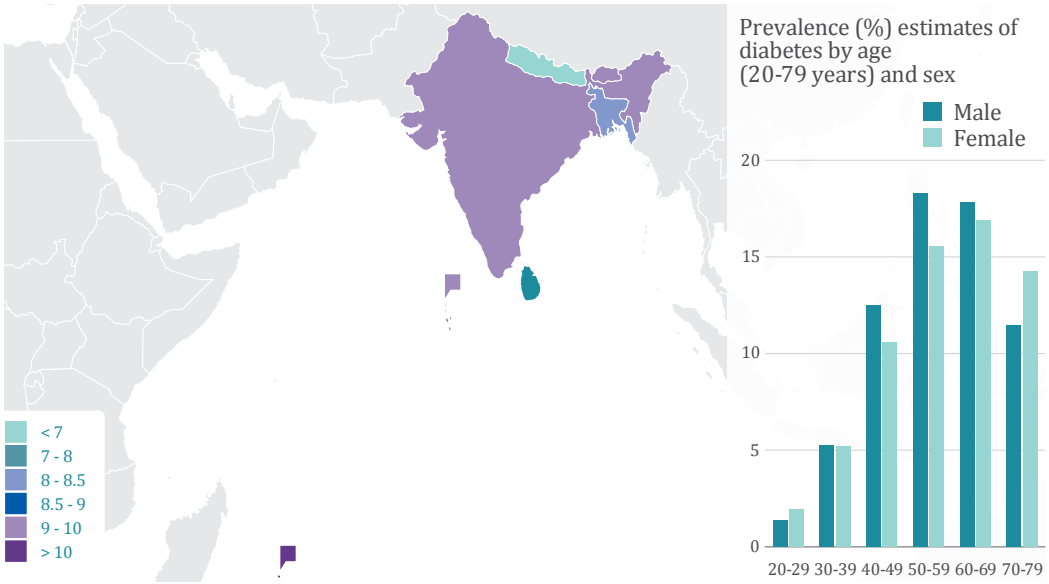


Figure: Prevalence of diabetes in south-east Asia.[8]

2 Functional Anatomy
The Pancreas

The pancreas (pan-whole, creas-flesh) is a soft lobulated gland; lies transversely across the posterior abdominal wall, behind the peritoneum.

Extension
This greyish-pink gland extends from the concavity of the duodenum (on the right) to the hilum of the spleen (on the left).

Situation
The pancreas lies posterior to the greater curvature of the stomach, at the epigastric and left hypochondriac regions.

(Vertebral level)

- Head lies opposite the L1 and L2 vertebrae.
- Tail lies opposite the lower border of T12 vertebra.

Size and shape
The pancreas is J-shaped or retort-shaped. Its length varies from 12 to 15 cm, thickness from 1.5 to 2 cm, and its breadth from 3 to 4 cm. Its weight is about 80 to 90 gm.

Type of gland
It is a mixed or double gland, because, it is partly exocrine and partly endocrine.

Its exocrine portion secretes pancreatic juice (containing enzymes capable of hydrolyzing carbohydrates, proteins, and fats) and the endocrine portion (islets of Langerhans) secretes hormones (such as insulin and glucagon).

Presenting parts
From right to left, the pancreas is divided into a head, neck, body, and tail.

Pancreatic ducts

1. Main duct (of Wirsung): It opens at the major duodenal papilla of duodenum after joining with the bile duct (in most people) forming the hepato-pancreatic ampulla or ampulla of Vater.
   – The main duct receives in its course a number of smaller ducts (from various lobules composing the gland), which join it at right angles, resembling Herring bone pattern.
2. Accessory duct (of Santorini): (when presents) It empties into the duodenum, about 2.5 cm above the main duct on the minor duodenal papilla.

These ducts convey the pancreatic secretion to the 2nd part of the duodenum.

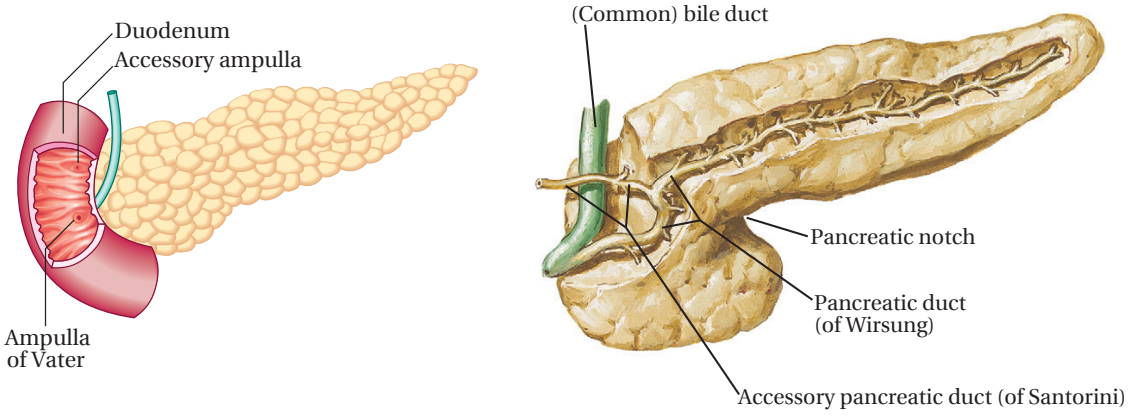


Figure: Pancreatic structure.[1, 21]

Histological structure

The pancreas resembles the salivary glands in structure. It is composed of two major types of tissues, (1) the acini, which secrete digestive juices into the duodenum, and (2) the islets of Langerhans, which secrete insulin and glucagon directly into the blood.[2]

Capsule

The pancreas is surrounded by a thin capsule of connective tissue that sends septa into its substances, which subdivide the gland into lobules.

Exocrine pancreas

The exocrine pancreas is classified as a compound tubuloacinous gland. The glandular epithelial cells that synthesize digestive enzymes are arranged in grape-like clusters called acini or alveoli. Each acinus is composed of several serous cells (columnar in shape) surrounding a lumen.

Endocrine pancreas

Composed of numerous islets of Langerhans (1–2 million). They appear as rounded cluster of cells which are embedded within the exocrine pancreatic tissue.
Islets contain several different endocrine cell types.

- beta cells (produce insulin and amylin[2]) 60%.
- alpha cells (produce glucagon) 25%.
- delta cell (secrete somatostatin) 10% and
- P cells (secrete pancreatic polypeptide).

The close interrelations among these cell types in the islets of Langerhans allow cell-to-cell communication and direct control of secretion of some of the hormones by the other hormones. For instance, insulin inhibits glucagon secretion, amylin inhibits insulin secretion, and somatostatin inhibits the secretion of both insulin and glucagon.[2]

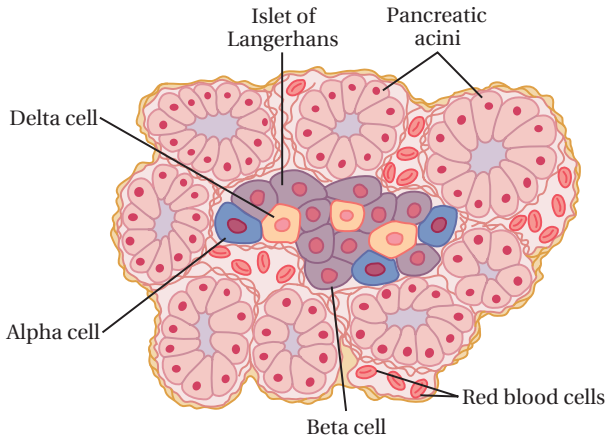


Figure: Physiological anatomy of an islet of Langerhans in the pancreas.[2]

Functions

Exocrine portion:

The pancreas produces 1200 – 1500 mL of pancreatic juice (pH 7.1 – 8.2) per day, consisting mostly of water, bicarbonate ions, and several digestive enzymes. Enzymes in pancreatic juice:

1. Proteolytic enzymes - Trypsinogen, chymotrypsinogen, procarboxypeptidase, and elastase.
2. Carbohydrate splitting enzymes - Pancreatic amylase.
3. Fat splitting enzymes - Lipase, phospholipase, cholesterol esterase.

Endocrine portion:

1. Insulin - Insulin is anabolic, increasing the storage of glucose (lowers blood glucose level), fatty acids, and amino acids.[3]
2. Glucagon - Glucagon is catabolic, mobilizing glucose (raises blood glucose level by accelerating breakdown of glycogen into glucose in the liver), fatty acids, and the amino acids from stores into the bloodstream.[3]
3. Somatostatin - inhibits secretion of both glucagon and insulin.
4. Pancreatic polypeptide - stimulates secretion of gastric and intestinal enzymes.

3 Blood glucose homeostasis

Blood glucose is tightly regulated and maintained within a narrow range. Despite the varying demands of food, fasting and exercise it is closely regulated in health and rarely stray outside the range of 3.5–8.0 mmol/L (63–144 mg/dL).[5] This is essential for ensuring a continuous supply of glucose to the central nervous system. The principal organ of glucose homeostasis is the liver, which absorbs and stores glucose (as glycogen) in the post-absorptive state and releases it into the circulation between meals to match the rate of glucose utilization by peripheral tissues.

Glucose homeostasis is achieved through the coordinated actions of multiple organs, but mainly reflects a balance between the entry of glucose into the circulation from the liver, supplemented by intestinal absorption of glucose after meals, and the uptake of glucose by peripheral tissues, particularly skeletal muscle and brain.[1,5]

Glucose production[5]

About 200 g of glucose is produced and utilized each day. More than 90% is derived from liver glycogen and hepatic gluconeogenesis, and the remainder from renal gluconeogenesis.

Glucose utilization[5]

The brain is the major consumer of glucose. Its requirement is 1 mg/kg body weight per minute, or 100 g daily in a 70 kg person. Glucose uptake by the brain is obligatory and is not dependent on insulin, and the glucose used is oxidized to carbon dioxide and water.

Tissues such as muscle and fat have insulin-responsive glucose transporters and absorb glucose in response to postprandial peaks in glucose and insulin. At other times, energy requirements are largely met by fatty-acid oxidation.

Glucose taken up by muscle is stored as glycogen or metabolized to lactate or carbon dioxide and water.

Fat uses glucose as a substrate for triglyceride synthesis; lipolysis releases fatty acids from triglyceride together with glycerol, a substrate for hepatic gluconeogenesis.

Hormonal regulation[1,5]

Insulin is the primary regulator of glucose metabolism and storage.[1] Its actions differ in the fasting and postprandial states.

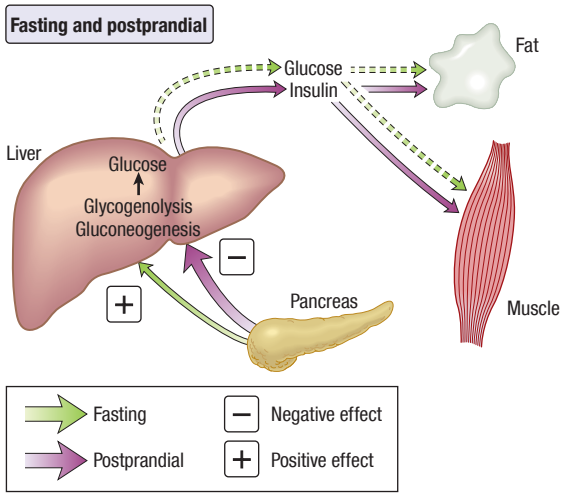


Figure: Fasting and postprandial effects of insulin. In the fasting state, insulin concentrations are low and it acts mainly as a hepatic hormone, modulating glucose production (via glycogenolysis and gluconeogenesis) from the liver. Hepatic glucose production rises as insulin levels fall. In the postprandial state, insulin concentrations are high and it then suppresses glucose production from the liver and promotes the entry of glucose into peripheral tissues (increased glucose utilization).[5]

In the fasting state, its main action is to regulate glucose release by the liver, and in the postprandial state it additionally promotes glucose uptake by fat and muscle.

Post-prandial state

The post-prandial rise in portal vein insulin and glucose, together with a fall in portal glucagon concentrations, suppresses hepatic glucose production and results in net hepatic glucose uptake. Depending on the size of the carbohydrate load, around one-quarter to one-third of ingested glucose is taken up in the liver. In addition, insulin stimulates glucose uptake in skeletal muscle and fat, mediated by the glucose transporter, GLUT 4.

That is after ingestion of a meal containing carbohydrate, normal blood glucose levels are maintained by:

1. suppression of hepatic glucose production
2. stimulation of hepatic glucose uptake
3. stimulation of glucose uptake by peripheral tissues.

Fasting state

When intestinal glucose absorption declines between meals, portal vein insulin and glucose concentrations fall while glucagon levels rise. This leads to increased hepatic glucose output via gluconeogenesis and glycogen breakdown. The liver now resumes net glucose production and glucose homeostasis is maintained.

The effect of counter-regulatory hormones (glucagon, adrenaline (epinephrine), cortisol and growth hormone) is to increase glucose production by the liver and reduce its utilization in fat and muscle for a given level of insulin. The main substrates for gluconeogenesis are glycerol and amino acids.

4 Insulin
Chemistry and secretion

Insulin was discovered in 1921 and isolated from the pancreas in 1922 by Banting and Best. It transformed the management of type 1 diabetes, until then a fatal disorder. Historically, insulin has been associated with "blood sugar,". However, insulin affects fat and protein metabolism almost as much as it affects carbohydrate metabolism. Insulin secretion is associated with energy abundance. When a person's diet includes a great abundance of foods that provide energy, especially excess amounts of carbohydrates, insulin secretion increases.[1,2]

Insulin chemistry and synthesis

Insulin is a small protein, coded for on chromosome 11 and synthesized in the β cells of the pancreatic islets.[2,5] Human insulin is composed of two amino acid chains, that are connected to each other by disulfide linkages. When the chains are split apart, the functional activity of the insulin molecule is lost.

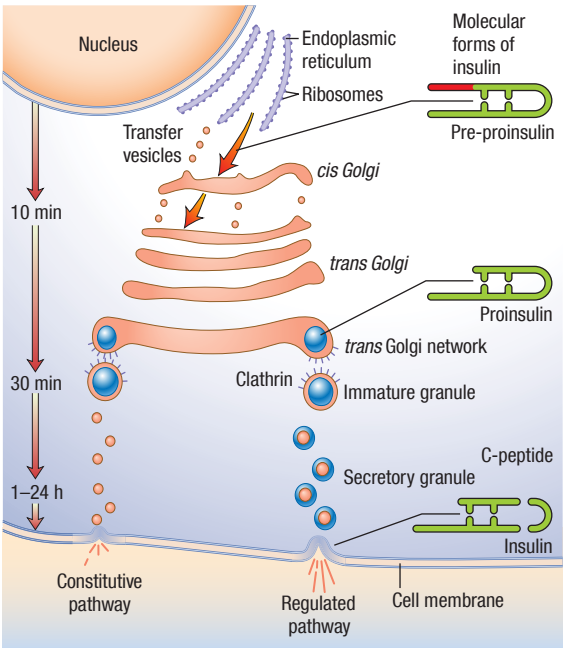


Figure: Insulin secretion in part of a beta cell.[5]

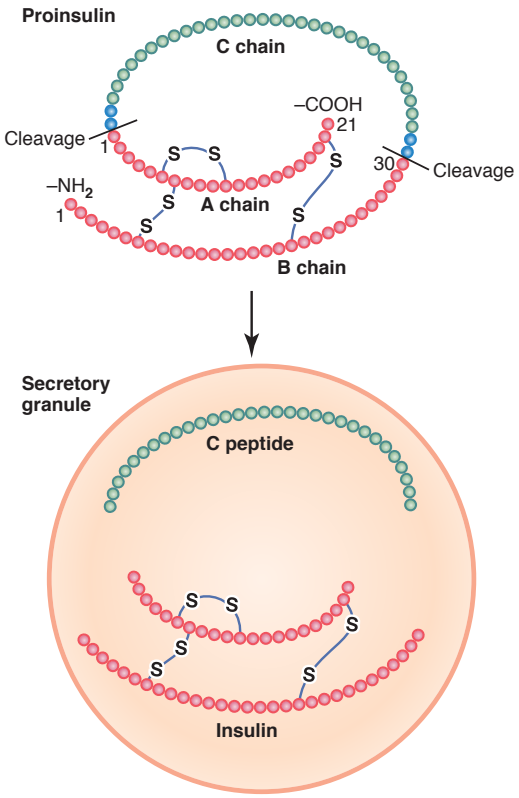


Figure: A schematic of the human proinsulin molecule, which is cleaved in the Golgi apparatus of the pancreatic beta cells to form connecting peptide (C peptide), and insulin, which is composed of the A and B chains connected by disulfide bonds. The C peptide and insulin are packaged in granules and secreted in equimolar amounts, along with a small amount of proinsulin.[2]

The synthesis, intracellular processing and secretion of insulin by the β cell is typical of the way that the body produces and manipulates many peptide hormones.[5]

1. The ribosomes attached to the endoplasmic reticulum manufacture **pre-proinsulin** from insulin messenger RNA (mRNA).
2. The hydrophobic 'pre' portion of pre-proinsulin allows it to transfer to the Golgi apparatus, and is subsequently enzymatically cleaved off.
3. Proinsulin is parceled into secretory granules in the Golgi apparatus.
4. These mature and pass towards the cell membrane, where they are stored before release.
5. The proinsulin molecule folds back on itself and is stabilized by disulphide bonds.
6. The biochemically inert peptide fragment known as connecting (C-)peptide splits off from proinsulin in the secretory process, leaving insulin as a complex of two linked peptide chains.
7. Equimolar quantities of insulin and C-peptide are released into the circulation via the 'regulated pathway'.
8. A small amount of insulin is secreted by the β cell directly via the 'constitutive pathway', which bypasses the secretory granules.

C peptide levels can be measured by radioimmunoassay in insulin-treated diabetic patients to determine how much of their own natural insulin they are still producing. Patients with type 1 diabetes who are unable to produce insulin will usually have greatly decreased levels of C peptide. [2]

Mechanism of insulin secretion[2,5]

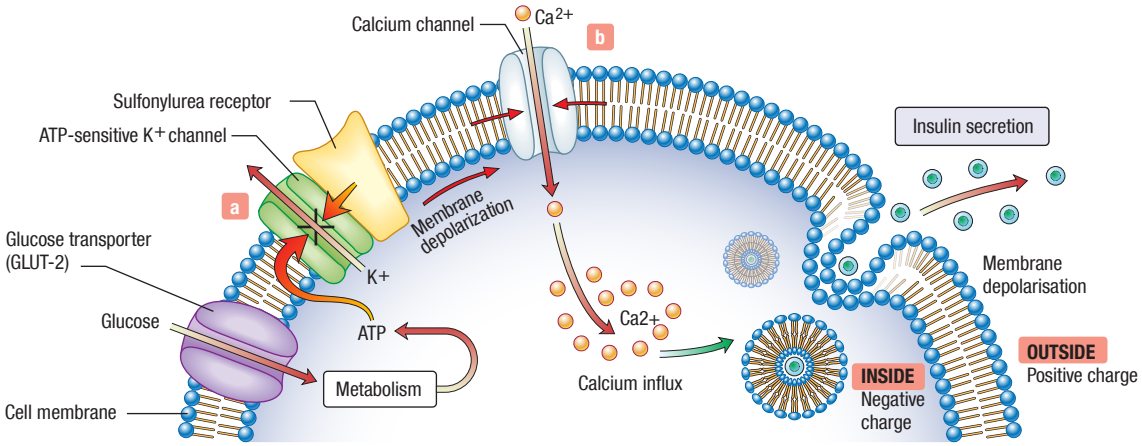
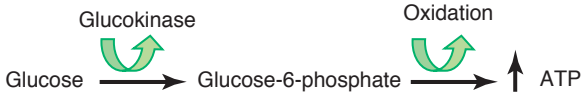


Figure: Mechanism of insulin secretion.[5]

1. The beta cells have a large number of glucose transporters that permit a rate of glucose influx that is proportional to the blood concentration in the physiological range.
2. Glucose (on the left) enters the β cell via the GLUT-2 transporter protein, which is closely associated with the glycolytic enzyme glucokinase.
3. Glucose is phosphorylated to glucose-6-phosphate by glucokinase. This is the rate limiting step for glucose metabolism.



4. Metabolism of glucose within the β cell generates adenosine triphosphate (ATP).
5. ATP closes potassium channels in the cell membrane (If a sulphonylurea binds to its receptor, this also closes potassium channels [a]).
6. Closure of the potassium channels depolarizes the cell membrane, thereby opening voltage-gated calcium channels, allowing calcium ions to enter the cell via calcium channels in the cell membrane [b].
7. The rise in intracellular calcium triggers activation of calcium-dependent phospholipid protein kinase which, via intermediary phosphorylation steps, leads to fusion of the docked insulin-containing granules with the cell membrane and exocytosis of the insulin-rich granule contents into the extracellular fluid.
8. Similar mechanisms produce hormone-granule secretion in many other endocrine cells.

A simplified figure of the secretion process:

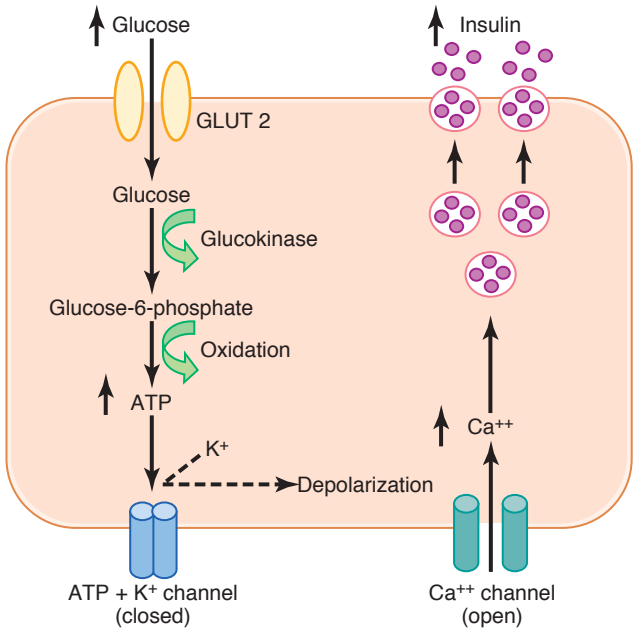


Figure: The basic mechanisms of glucose stimulation of insulin secretion by beta cells of the pancreas. GLUT, glucose transporter.[2]

Other nutrients, such as certain amino acids, can also be metabolized by the beta cells to increase intracellular ATP levels and stimulate insulin secretion.

Some hormones, such as glucagon, glucose-dependent insulinotropic peptide (gastric inhibitory peptide), and acetylcholine, increase intracellular calcium levels through other signaling pathways and enhance the effect of glucose, although they do not have major effects on insulin secretion in the absence of glucose.

Other hormones, including somatostatin and norepinephrine (by activating α- adrenergic receptors), inhibit exocytosis of insulin.

Control of insulin secretion[1,2]

At one time it was believed that insulin secretion was controlled almost entirely by the concentration of glucose in the blood. However, blood amino acids and other factors also play important roles in controlling the secretion of insulin.[2]

The incretin effect

The insulin response to oral glucose is greater than the response to intravenous glucose.[5] A number of factors released from the gut following food intake can augment insulin release.

- Two intestinal peptide hormones, glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1), have a potentiating effect on pancreatic secretion of insulin
- GIP causes 30%, and GLP-1 70%, of the incretin effect
- Both hormones have very short half-lives in the circulation, being degraded predominantly by the enzyme dipeptidyl peptidase-4 (DPP4)
- GIP is secreted from the K cells in the duodenum and GLP-1 from the L cells of the ileum in response to food

As a result, insulin release is greater when glucose is administered by mouth than when the same rise in plasma glucose is achieved by intravenous glucose infusion, a phenomenon termed the 'incretin' effect. [1]

The incretin effect is diminished in type 2 diabetes, and this has stimulated the development of two incretin-based therapeutic approaches.[1,5] Unlike sulphonylureas, both incretin-based therapies only promote insulin secretion when there is a glucose 'trigger' for insulin secretion. Thus, when the blood glucose is normal, the insulin secretion is not augmented and so these agents do not cause hypoglycaemia.[1]

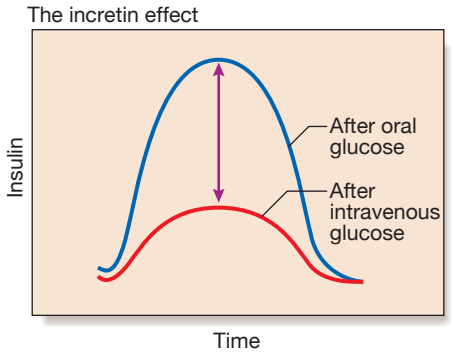


Figure: The incretin effect describes the observation that insulin secretion is greater when glucose is given by mouth than when glucose is administered intravenously to achieve the same rise in blood glucose concentrations. The additional stimulus to insulin secretion is mediated by release of peptides from the gut and these actions are exploited in incretin-based therapies.[1]

Increase Insulin Secretion	Decrease Insulin Secretion
Increased blood glucose	Decreased blood glucose
Increased blood free fatty acids	Fasting
Increased blood amino acids	Somatostatin
Gastrointestinal hormones (gastrin, cholecystokinin, secretin, gastric inhibitory peptide)	α-Adrenergic activity
	Leptin
Glucagon, growth hormone, cortisol	
Parasympathetic stimulation; acetylcholine	
β-Adrenergic stimulation Insulin resistance; obesity	
Sulfonylurea drugs (glyburide, tolbutamide)	

Increased blood glucose stimulates insulin secretion

At the normal fasting level of blood glucose of 80 to 90 mg/100 ml, the rate of insulin secretion is minimal— on the order of 25 ng/min/kg of body weight, a level that has only slight physiological activity. If the blood glucose concentration is suddenly increased to a level two to three times normal and is kept at this high level thereafter, insulin secretion increases markedly in two stages, The concentration of insulin in plasma increases almost 10-fold within 3 to 5 minutes. This results from immediate dumping of preformed insulin. Beginning at about 15 minutes, insulin secretion rises a second time and reaches a new plateau in 2 to 3 hours. This results both from the additional release of preformed insulin and from newly synthesized insulin from the cells.

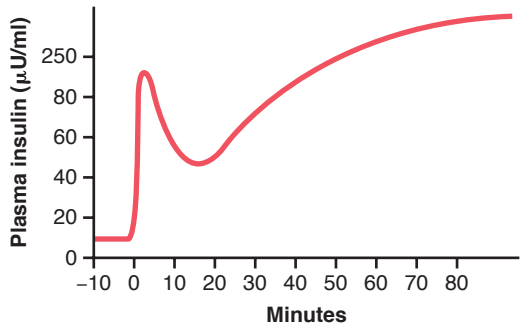


Figure: An increase in plasma insulin concentration after a sudden increase in blood glucose to two to three times the normal range. Note an initial rapid surge in insulin concentration and then a delayed but higher and continuing increase in concentration beginning 15 to 20 minutes later.[2]

Insulin secretion rate

As the blood glucose concentration rises above 100 mg/100 ml of blood, secretion of insulin rises rapidly, reaching a peak some 10 to 25 times the basal level at blood glucose concentrations between 400 and 600 mg/100 ml.

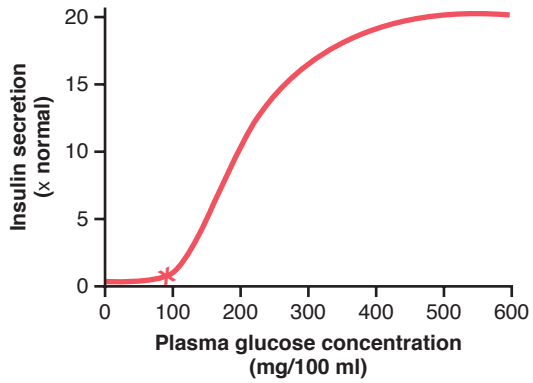


Figure: Approximate insulin secretion at different plasma glucose levels.[2]

The increase in insulin secretion during a glucose stimulus is dramatic both in its rapidity and in the high level of secretion that is achieved. Furthermore, the turnoff of insulin secretion is almost equally as rapid, occurring within 3 to 5 minutes after a reduction in blood glucose concentration back to the fasting level.

This response of insulin secretion to an elevated blood glucose concentration provides an extremely important feedback mechanism for regulating blood glucose concentration. That is, any rise in blood glucose increases insulin secretion, and the insulin in turn increases the rate of transport of glucose into liver, muscle, and other cells, thereby reducing blood glucose concentration back toward the normal value.

Circulation[2,5]

After secretion, insulin enters the portal circulation and is carried to the liver, its prime target organ.[5] When insulin is secreted into the blood, it circulates almost entirely in an unbound form. It has a plasma half-life that averages only about 6 minutes and cleared from the circulation within 10 to 15 minutes.

Except for the portion of the insulin that combines with receptors in the target cells, the insulin is degraded by the enzyme insulinase mainly in the liver (about 50% [5]), to a lesser extent in the kidneys and muscles, and slightly in most other tissues.

This rapid removal from the plasma is important because, at times, it is as important to rapidly turn off the control functions of insulin as it is to turn them on.

C-peptide is only partially extracted by the liver (and hence provides a useful index of the rate of insulin secretion) but is mainly degraded by the kidneys.

Glucose transport

Cell membranes are not inherently permeable to glucose. A family of specialized glucose transporter (GLUT-1, 2, 3, 4) proteins carry glucose through the membrane into cells.

GLUT-1 enables basal non-insulin-stimulated glucose uptake into many cells.

GLUT-2 transports glucose into the β cell, a prerequisite for glucose sensing, and is also present in the renal tubules and hepatocytes.

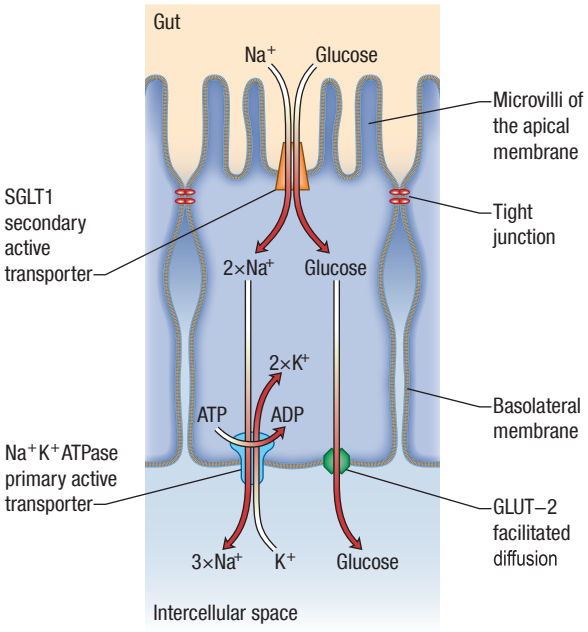
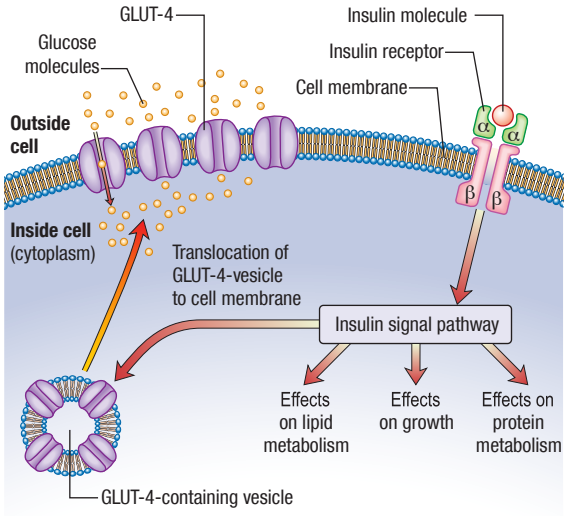


Figure: Transcellular uptake of glucose across the intestinal epithelia. Glucose is co-transported across the apical membrane with sodium ions by the sodium-dependent glucose transporter (SGLT). This is secondary active transport, as the sodium is travelling down its electrochemical gradient. The sodium gradient is maintained by the primary active transport of sodium across the basolateral membrane by the Na+/K+ ATPase (thus intracellular Na+ is kept low). Transcellular transport of glucose is achieved by facilitated diffusion across the basolateral membrane as glucose is moved down its concentration gradient by GLUT-2.[5]

GLUT-3 enables non-insulin-mediated glucose uptake into brain neurons and placenta.

GLUT-4 mediates much of the peripheral action of insulin. It is the channel through which glucose is taken up into muscle and adipose tissue cells following stimulation of the insulin receptor.

GLUT- 4 mediated peripheral action of insulin and the insulin receptor[2,5]



This is a glycoprotein (400 kDa), coded for on the short arm of chromosome 19, which straddles the cell membrane of many cells.

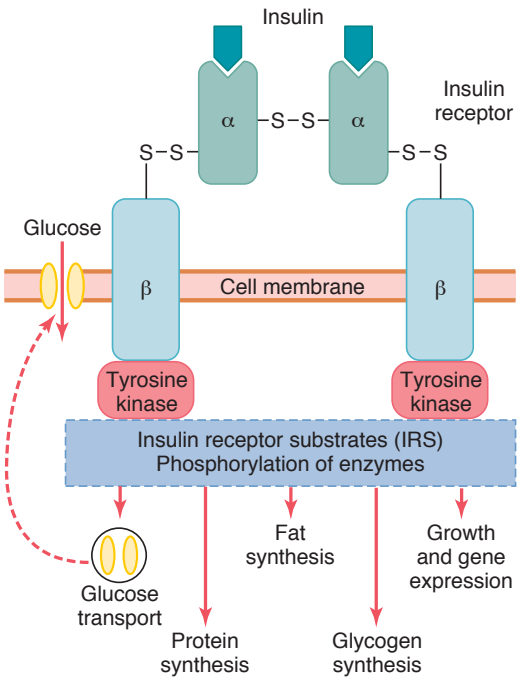
It consists of a dimer with two α- subunits, which include the binding sites for insulin, and two β-subunits, which traverse the cell membrane. α- and β-subunits are linked by disulphide bridges (top right). The β-subunits straddle the cell membrane. The transporter protein GLUT-4 (bottom left) is stored in intracellular vesicles.

When insulin binds to the α-subunits, it induces a conformational change in the β-subunits (autophosphorylation), resulting in activation of tyrosine kinase. The receptor tyrosine kinase activity begins a cascade of cell phosphorylation that increases or decreases the activity of enzymes, including insulin receptor substrates, that mediate the effects on glucose, fat, and protein metabolism.

One consequence of this is migration of the GLUT-4-containing intracellular vesicle to the cell surface and increased transport of glucose into the cell.

The insulin-receptor complex is then internalized by the cell, insulin is degraded, and the receptor is recycled to the cell surface.

Simplified figure of activation of target cell receptor by insulin[2]–



5 Metabolic effects of insulin

Insulin plays an important role in storing the excess energy. In the case of excess carbohydrates, it causes them to be stored as glycogen, mainly in the liver and muscles. Furthermore, all the excess carbohydrates that cannot be stored as glycogen are converted under the stimulus of insulin into fats and stored in adipose tissue. In the case of proteins, insulin has a direct effect in promoting amino acid uptake by cells and conversion of these amino acids into protein. In addition, it inhibits the breakdown of proteins that are already in the cells.

Metabolic actions of insulin[1]

Increase	Decrease
Carbohydrate metabolism	
Glucose transport (muscle, adipose tissue)	Gluconeogenesis
Glucose phosphorylation	Glycogenolysis
Glycogen synthesis	
Glycolysis	
Pyruvate dehydrogenase activity	
Pentose phosphate shunt	
Lipid metabolism	
Triglyceride synthesis	Lipolysis
Fatty acid synthesis (liver)	Lipoprotein lipase (muscle)
Lipoprotein lipase activity (adipose tissue)	Ketogenesis
	Fatty acid oxidation (liver)
Protein metabolism	
Amino acid transport	Protein degradation
Protein synthesis	

Effect in carbohydrate metabolism

Immediately after a high-carbohydrate meal is consumed, glucose that is absorbed into the blood causes rapid secretion of insulin, which in turn causes rapid uptake, storage, and use of glucose by almost all tissues of the body but especially by the muscles, adipose tissue, and liver.

Muscles

During much of the day, muscle tissue depends not on glucose but on fatty acids for its energy. Mainly because the normal resting muscle membrane is only slightly permeable to glucose, except when the muscle fiber is stimulated by insulin; between meals, the amount of insulin that is secreted is too small to promote significant amounts of glucose entry into the muscle cells.

However, under two conditions the muscles do use large amounts of glucose.

1. During moderate or heavy exercise. This usage of glucose does not require large amounts of insulin because muscle contraction increases translocation of glucose transporter 4 (GLUT 4) from intracellular storage depots to the cell membrane, which, in turn, facilitates diffusion of glucose into the cell.
2. During the few hours after a meal. At this time the blood glucose concentration is high and the pancreas is secreting large quantities of insulin.

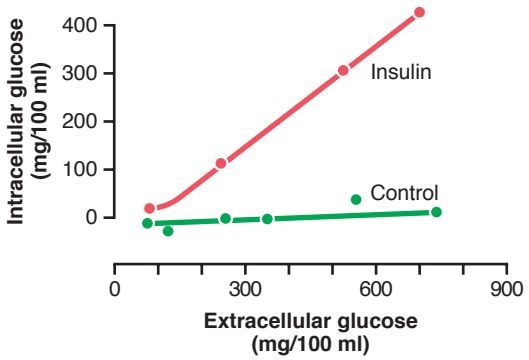


Figure: The effect of insulin in enhancing the concentration of glucose inside muscle cells. The lower curve labeled "control" shows the concentration of free glucose measured inside the cell, demonstrating that the glucose concentration remained almost zero despite increased extracellular glucose concentration up to as high as 750 mg/100 ml. In contrast, the curve labeled "insulin" demonstrates that the intracellular glucose concentration rose to as high as 400 mg/100 ml when insulin was added. Thus, it is clear that insulin can increase the rate of transport of glucose into the resting muscle cell by at least 15-fold.[2]

Liver

The liver removes glucose from the blood when it is present in excess after a meal and returns it to the blood when the blood glucose concentration falls between meals. Insulin causes most of the glucose absorbed after a meal to be rapidly stored in the liver in the form of glycogen.

Then, between meals, when food is not available and the blood glucose concentration begins to fall, insulin secretion decreases rapidly and the liver glycogen is split back into glucose, which is released back into the blood to keep the glucose concentration from falling too low.

Brain[1,2]

Most of the brain cells are permeable to glucose and can use glucose without the intermediation of insulin. The brain has little capacity to store energy in the form of glycogen or triglyceride and the blood–brain barrier is largely impermeable to fatty acids, so the brain depends on the liver for a constant supply of glucose for oxidation and hence generation of adenosine triphosphate (ATP).[1] The brain cells use only glucose for energy. Therefore, it is essential that the blood glucose level always be maintained above a critical level.

Effect in fat metabolism

Long-term effect of insulin deficiency causes extreme atherosclerosis, often leading to heart attacks, cerebral strokes, and other vascular accidents.

abnormalities of fat metabolism cause conditions such as acidosis and arteriosclerosis. In patients with prolonged, untreated diabetes, diminished ability to synthesize proteins leads to wasting of the tissues and many cellular functional disorders.

Insulin promotes fat synthesis and storage

Insulin increases utilization of glucose by most of the body's tissues, which automatically decreases the utilization of fat, thus functioning as a fat sparer.[2]

However, insulin also promotes fatty acid synthesis, especially when more carbohydrates are ingested than can be used for immediate energy, thus providing the substrate for fat synthesis.[2] Adipocytes (and the liver) synthesise triglyceride from non-esterified ('free') fatty acids (FFAs) and glycerol.[1] After the liver glycogen concentration reaches 5 to 6 percent, further glycogen synthesis is inhibited. Almost all this synthesis occurs in the liver cells, and the fatty acids are then transported from the liver by way of the blood lipoproteins to the adipose cells to be stored.[2] That is, high insulin levels after meals promote triglyceride accumulation.[1]

Insulin deficiency increases use of fat for energy

All aspects of fat breakdown are greatly enhanced in the absence of insulin. This occurs normally between meals when secretion of insulin is minimal, but it becomes extreme in persons with diabetes mellitus.[2]

In the absence of insulin, all the effects of insulin that cause storage of fat are reversed.[2]

The most important effect is that the enzyme hormone-sensitive lipase in the fat cells becomes strongly activated. This activation causes hydrolysis of the stored triglycerides, releasing large quantities of fatty acids and glycerol into the circulating blood. It begins to rise within minutes.[2]

These free fatty acids then become the main energy substrate used by essentially all tissues of the body except the brain.[2]

Occasionally the plasma lipoproteins increase as much as threefold in the absence of insulin (normal 0.6 percent). This high lipid concentration—especially the high concentration of cholesterol—promotes the development of atherosclerosis in people with severe diabetes.[2]

That is, in the fasting state, low insulin levels permit lipolysis and the release into the circulation of FFAs (and glycerol), which can be oxidised by many tissues. Their partial oxidation in the liver provides energy to drive gluconeogenesis and also produces ketone bodies (acetoacetate, which can be reduced to 3-hydroxybutyrate or decarboxylated to acetone), which are generated in hepatocyte mitochondria. Ketone bodies are organic acids which, when formed in small amounts, are oxidised and utilised as metabolic fuel.[1]

However, the rate of utilisation of ketone bodies by peripheral tissues is limited, and when the rate of production by the liver exceeds their removal, hyperketonaemia results. This occurs physiologically during starvation, when low insulin levels and high catecholamine levels increase lipolysis and delivery of FFAs to the liver.[1]

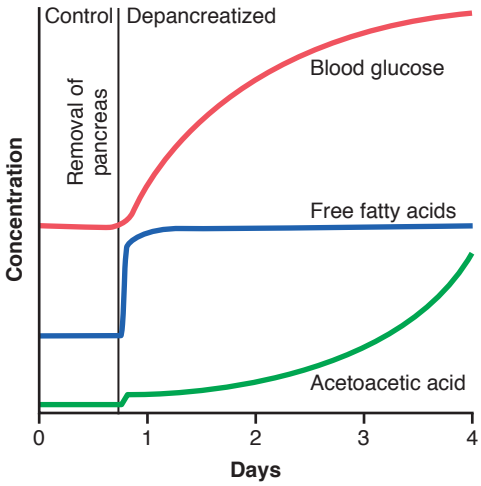


Figure: The effect of a lack of insulin on the plasma concentrations of free fatty acids, glucose, and acetoacetic acid. Note that almost immediately after removal of the pancreas, the free fatty acid concentration in the plasma begins to rise, more rapidly even than the concentration of glucose. Also excess usage of fats during insulin deficiency causes ketosis and acidosis. Some of the acetoacetic acid is also converted into β-hydroxybutyric acid and acetone. These two substances, along with the acetoacetic acid, are called ketone bodies, and their presence in large quantities in the body fluids is called ketosis.[2]

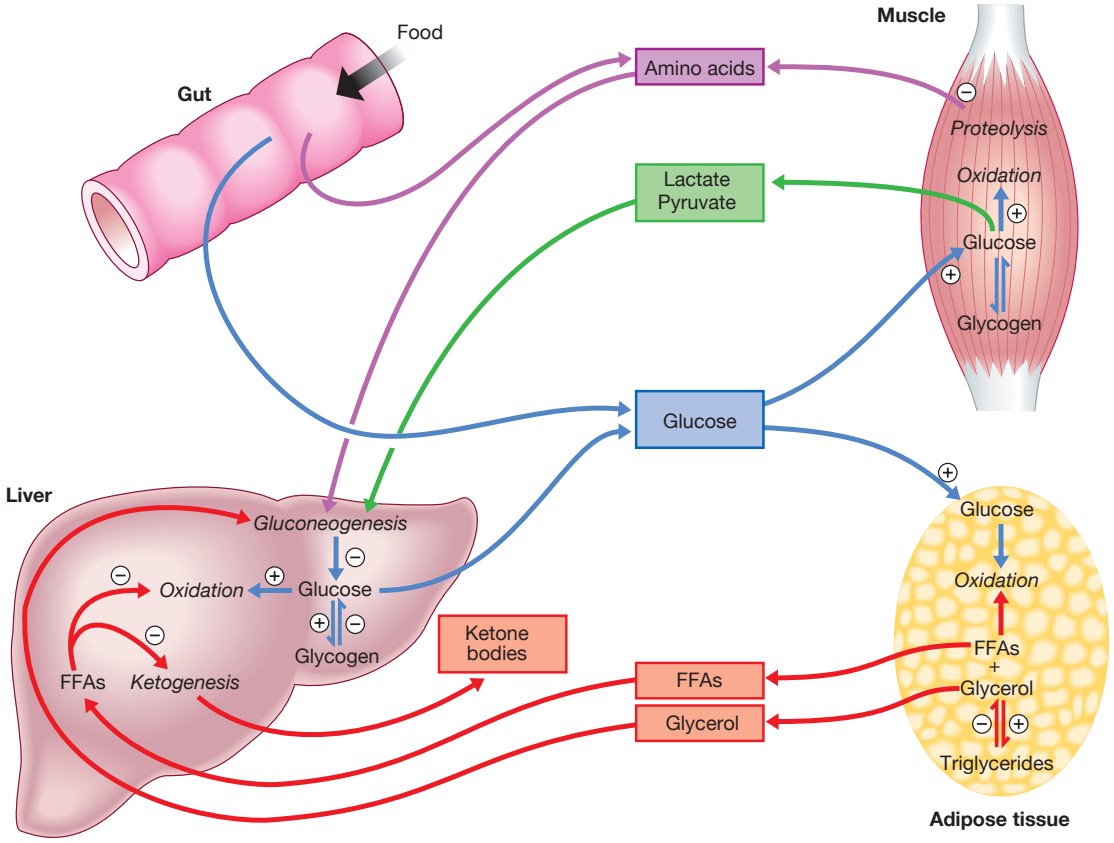


Figure: Major metabolic pathways of fuel metabolism and the actions of insulin.[1]
⊕ indicates stimulation and ⊖ indicates suppression by insulin. In response to a rise in blood glucose, e.g. after a meal, insulin is released, suppressing gluconeogenesis and promoting glycogen synthesis and storage. Insulin promotes the peripheral uptake of glucose, particularly in skeletal muscle, and encourages storage (as muscle glycogen). It also promotes protein synthesis and lipogenesis, and suppresses lipolysis. The release of intermediate metabolites, including amino acids (glutamine, alanine), 3-carbon intermediates in oxidation (lactate, pyruvate) and free fatty acids (FFAs), is controlled by insulin. In the absence of insulin, e.g. during fasting, these processes are reversed and favour gluconeogenesis in liver from glycogen, glycerol, amino acids and other 3-carbon precursors.

Effect in protein metabolism

Insulin promotes protein synthesis and storage by

1. Insulin stimulates transport of many of the amino acids into the cells
2. Insulin increases translation of messenger RNA
3. Insulin also increases the rate of transcription of selected DNA genetic sequences
4. Insulin inhibits catabolism of proteins
5. In the liver, insulin depresses the rate of gluconeogenesis

Insulin deficiency causes protein depletion and increased plasma amino acid. Catabolism of proteins increases, protein synthesis stops, and large quantities of amino acids are dumped into the plasma. This degradation of amino acids also leads to enhanced urea excretion in the urine. The resulting protein wasting is one of the most serious of all the effects of severe diabetes mellitus. It can lead to extreme weakness and many deranged functions of the organs.

Insulin and growth hormone interact synergistically to promote growth

Admission of either growth hormone or insulin one at a time causes almost no growth. The two hormones function synergistically as a combination of these hormones causes dramatic growth.

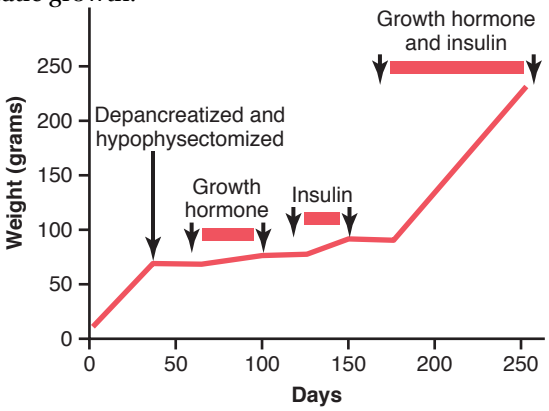


Figure: The effect of growth hormone, insulin, and growth hormone plus insulin on growth in a depancreatized and hypophysectomized rat.[2]

Classification of diabetes[5]

Diabetes may be primary (idiopathic) or secondary. Primary diabetes is classified into:

1. type 1 diabetes, which has an immune pathogenesis and is characterized by severe insulin deficiency
2. type 2 diabetes, which results from a combination of insulin resistance and less severe insulin deficiency.

Type 1 and type 2 diabetes represent two distinct diseases from the epidemiological point of view, but from a clinical point of view the two conditions should be seen as a spectrum, distinct at the two ends but overlapping in the middle.

Hybrid forms are increasingly recognized, and patients with immune-mediated diabetes (type 1) may, for example, also be overweight and insulinresistant. This is sometimes referred to as 'double diabetes'. It is more relevant to give patients the right treatment on clinical grounds than to worry about how to label their diabetes.

Although secondary diabetes accounts for barely 1–2% of all new cases at presentation, it should not be missed because the cause can sometimes be treated.

All forms of diabetes derive from inadequate insulin secretion relative to the needs of the body, and progressive insulin secretory failure is characteristic of both common forms of diabetes. Thus, some patients with immune-mediated diabetes type 1 may not at first require insulin, whereas many with type 2 diabetes will eventually do so.

Aetiological classification of diabetes mellitus, based on classification by the American Diabetes Association (ADA)[6]

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)

- A. Immune mediated
- B. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types

- A. Genetic defects of β -cell function
  1. Chromosome 12, HNF-1α (MODY3)
  2. Chromosome 7, glucokinase (MODY2)
  3. Chromosome 20, HNF-4α (MODY1)
  4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
  5. Chromosome 17, HNF-1β (MODY5)
  6. Chromosome 2, NeuroD1 (MODY6)
  7. Mitochondrial DNA
  8. Others
- B. Genetic defects in insulin action
  1. Type A insulin resistance
  2. Leprechaunism
  3. Rabson-Mendenhall syndrome
  4. Lipoatrophic diabetes
  5. Others
- C. Diseases of the exocrine pancreas
  1. Pancreatitis
  2. Trauma/pancreatectomy
  3. Neoplasia
  4. Cystic fibrosis
  5. Hemochromatosis
  6. Fibrocalculous pancreatopathy
  7. Others
- D. Endocrinopathies (Excess endogenous production of hormonal antagonists to insulin[1])
  1. Acromegaly (– Growth hormone)
  2. Cushing's syndrome (– Glucocorticoids)
  3. Glucagonoma (– Glucagon)
  4. Pheochromocytoma (– Catecholamines)
  5. Hyperthyroidism (– Thyroid hormone)
  6. Somatostatinoma
  7. Aldosteronoma
  8. Others
- E. Drug or chemical induced
  1. Vacor (pyrinuron[5])
  2. Pentamidine
  3. Nicotinic acid (niacin)
  4. Glucocorticoids
  5. Thyroid hormone
  6. Diazoxide
  7. β-adrenergic agonists
  8. Thiazides
  9. Dilantin
  10. γ-Interferon
  11. Immunosuppressive agents:[5] glucocorticoids, ciclosporin, tacrolimus, sirolimus
  12. Anti-psychotic agents:[5] clozapine, olanzapine
  13. Others (beta blocker[5], phenytoin[1,5], protease inhibitor[5])
- F. Infections
  1. Congenital rubella
  2. Cytomegalovirus
  3. Others
- G. Uncommon forms of immune-mediated diabetes
  1. "Stiff-man" syndrome
  2. Anti-insulin receptor antibodies
  3. Others (IPEX (immunodysregulation polyendocrinopathy X) syndrome)[1]
- H. Other genetic syndromes sometimes associated with diabetes
  1. Down syndrome
  2. Klinefelter syndrome
  3. Turner syndrome
  4. Wolfram syndrome (DIDMOAD – diabetes insipidus[1])
  5. Friedreich ataxia
  6. Huntington chorea
  7. Laurence-Moon-Biedl syndrome
  8. Myotonic dystrophy
  9. Porphyria
  10. Prader-Willi syndrome
  11. Others (optic atrophy, nerve deafness)[1]

IV. Gestational diabetes mellitus

Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient.

Adapted from: ADA Diabetes Care, Vol. 33, Suppl. 1 Jan. 2010

6 Etiology and Pathogenesis of diabetes

In both of the common types of diabetes, environmental factors interact with genetic susceptibility to determine which people develop the clinical syndrome, and the precipitating environmental factors and pathophysiology differ substantially between type 1 and type 2 diabetes.

Diabetes has many causes but is most commonly due to type 1 or type 2 diabetes.

Type 1 diabetes was previously termed 'insulin-dependent diabetes mellitus' (IDDM) and is invariably associated with profound insulin deficiency requiring replacement therapy. Type 2 diabetes was previously termed 'non-insulin-dependent diabetes mellitus' (NIDDM) because patients retain the capacity to secrete some insulin but exhibit impaired sensitivity to insulin (insulin resistance) and initially can usually be treated without insulin replacement therapy. However, 20% or more of patients with type 2 diabetes will ultimately develop profound insulin deficiency requiring replacement therapy, so that IDDM and NIDDM were misnomers.

Aetiology
Type 1 diabetes

Type 1 diabetes belongs to a family of human leucocyte antigen (HLA)-associated immune mediated organ-specific diseases.[5] Genetic factors account for about one-third of the susceptibility and the inheritance is polygenic.[1,5] Autoantibodies directed against pancreatic islet constituents appear in the circulation within the first few years of life, and often predate clinical onset by many years.[5]

Genetic susceptibility and inheritance[5]

Increased susceptibility to type 1 diabetes is inherited but the disease is not genetically predetermined. Because, the identical twin of a patient with type 1 diabetes has a 30–50% chance of developing the disease, which implies that non-genetic factors must also be involved.

The risk of developing diabetes by age 20, curiously, is greater with a diabetic father (3–7%) than with a diabetic mother (2–3%). Earlier onset in the parent is associated with increased risk in the child.

Since type 1 diabetes can present at any age, the lifetime risk for a sibling or child is at least double the risk by age 20.

Risk of type 1 diabetes among first-degree relatives of patients with type 1 diabetes[1]

Relative with type 1 diabetes	% overall risk
Identical twin	35
Non-identical twin	20
HLA-identical sibling	16
Non-HLA-identical sibling	3
Father	9
Mother	3
Both parents	Up to 30

HLA system

Human leucocyte antigen (HLA) region within the major histocompatibility complex on the short arm of chromosome 6 has the greatest contribution to type 1 diabetes. This locus is designated IDDM 1.[1] The HLA genes are highly polymorphic and modulate the immune defence system of the body.[3] Four genes are important: one (6q) determines islet sensitivity to damage (eg from viruses or cross-reactivity from cows' milk-induced antibodies).[4]

More than 90% of patients with type 1 diabetes carry HLA-DR3-DQ2, HLA-DR4-DQ8 or both, as compared with some 35% of the background population.[5]

HLA-DQ[5]

All DQB1 alleles with an aspartic acid at residue 57 confer neutral to protective effects, with the strongest effect from DQB1*0602 (DQ6), while DQB1 alleles with an alanine at the same position (i.e. DQ2 and DQ8) confer strong susceptibility.

The HLA haplotypes DR3 and/or DR4 are associated with increased susceptibility to type 1 diabetes in Caucasians and are in 'linkage disequilibrium', i.e. they tend to be transmitted together, with the neighbouring alleles of the HLA-DQA1 and DQB1 genes. (>90% carry HLA DR3 ± DR4 [4]) The latter may be the main determinants of genetic susceptibility, since these HLA class II genes code for proteins on the surface of cells which present foreign and self antigens to T lymphocytes.[1]

Genotypic combinations have a major influence on risk of disease. For example, HLA-DR3-DQ2/HLA-DR4-DQ8 heterozygotes have a considerably increased risk of disease, and some HLA class I alleles also modify the risk conferred by class II susceptibility genes.[5]

Other genes or gene regions

Candidate gene and genome-wide association studies have also implicated other genes in type 1 diabetes, e.g. CD25, which are involved in immune recognition of pancreatic islet antigens, T-cell development and immune regulation.[1]

The greatest genetic contribution still comes from the HLA region but this is modulated by a large number of genes with small effects (more than 50 non-HLA genes or gene regions that influence risk have been identified to date). These include[5]

- the gene encoding insulin (INS) on chromosome 11 and
- a number of genes involved in immune responses, including
    - the cytotoxic T-lymphocyte-associated protein-4 (CTLA4) gene,
    - the lymphoid-specific protein tyrosine phosphatase (PTPN22) gene and
    - the interleukin (IL)-2R α- subunit of the IL-2 receptor complex locus (IL2RA)

Autoimmunity and type 1 diabetes[1,5]

The genes associated with type 1 diabetes overlap with other organ-specific autoimmune disorders, consistent with clustering of these conditions in individuals or families. Associated other autoimmune disorders include

1. thyroid disease,
2. coeliac disease,
3. Addison's disease,
4. pernicious anaemia and
5. vitiligo

LADA

Latent autoimmune diabetes of adults (LADA) is a form of type 1 DM, with slower progression to insulin dependence in later life.[4]

Chicken or egg?[4]

Most type II diabetes-associated genes have a function in the vasculature, and stress in β-cells can result from vascular defects in the pancreas, so maybe vascular events trigger DM.

Environmental predisposition[1]

Although genetic susceptibility appears to be a prerequisite for type 1 diabetes, the concordance rate between monozygotic twins is less than 40%, and wide geographic and seasonal variations in incidence suggest that environmental factors have an important role in precipitating disease.[1] Islet autoantibodies (see above) appear in the first few years of life, indicating prenatal or early postnatal interactions with the environment.[5]

Although hypotheses abound, the nature of these environmental factors is uncertain. They may trigger type 1 diabetes through direct toxicity to β cells or by stimulating an autoimmune reaction directed against β cells. Potential candidates fall into three main categories:

1. viruses,
2. specific drugs or chemicals, and
3. dietary constituents.

Viruses

Viruses implicated in the aetiology of type 1 diabetes include mumps, Coxsackie B4, retroviruses, rubella (in utero), cytomegalovirus and Epstein–Barr virus.

Chemicals and dietary constituents

Various dietary nitrosamines (found in smoked and cured meats) and coffee have been proposed as potentially diabetogenic toxins.

Bovine serum albumin (BSA), a major constituent of cow's milk, has been implicated, since children who are given cow's milk early in infancy are more likely to develop type 1 diabetes than those who are breastfed. BSA may cross the neonatal gut and raise antibodies which cross-react with a heat-shock protein expressed by β cells.

It has also been proposed that a cleaner environment with reduced exposure to microorganisms in early childhood limits maturation of the immune system and increases susceptibility to type 1 diabetes, as for other autoimmune diseases such as atopic/allergic conditions (the 'hygiene hypothesis')[1,5] and more rapid weight gain in childhood and adolescence leading to increased insulin resistance might accelerate clinical onset (the 'accelerator hypothesis').[5]

Relative deficiency of vitamin D may also be possible candidates but the role in the causation of the disease has yet to be confirmed.[5]

Pre-type 1 diabetes and prevention of type 1 diabetes[5]

Children who test positive for two or more autoantibodies have a >80% risk of progression to diabetes, and the risk approaches 100% in those who additionally lose their first-phase insulin response to intravenous glucose and/or develop glucose intolerance. The ability to predict type 1 diabetes with this degree of precision has opened the way to trials of disease prevention, but intervention before clinical onset of diabetes has so far proved unsuccessful.

Aetiology
Type 2 diabetes

Type 2 diabetes is common in all populations enjoying an affluent lifestyle, and has increased in parallel with the adoption of a Western lifestyle and increasing obesity. The four major determinants are increasing age, obesity, ethnicity and family history. In poor countries, diabetes is a disease of the rich, but in rich countries, it is a disease of the poor; obesity is the common factor. Onset may be accelerated by the stress of pregnancy, drug treatment or intercurrent illness.[5]

Genetic susceptibility and inheritance

First, let's have a look at the risk of developing type 2 diabetes for siblings of an individual with type 2 diabetes.

Genetic factors are important in type 2 diabetes, as shown by marked differences in susceptibility in different ethnic groups and by studies in monozygotic twins where concordance rates for type 2 diabetes approach 100%.[1]

Identical twins of patients with type 2 diabetes have more than a 50% chance of developing diabetes; the risk to non-identical twins or siblings is of the order of 25%, confirming a strong inherited component to the disease.[5]

Risk of developing type 2 diabetes for siblings of and individuals with type 2 diabetes[1]

Age at onset of type 2 diabetes in proband	Age-corrected risk of type 2 diabetes for siblings (%)
25–44	53
45–54	37
55–64	38
65–80	31

Type 2 diabetes is a polygenic disorder and, as with type 1 diabetes.[5] Genome-wide association studies have identified over 65 genes or gene regions that are associated with type 2 diabetes, each exerting a small effect.[1]

Most of the genes known to contribute to risk of type 2 diabetes are involved in β-cell function or in regulation of cell cycling and turnover, suggesting that altered regulation of β-cell mass is a key factor.[1] Also, there is no overlap with the immune function genes identified for type 1 diabetes.[5]

There is no major gene susceptibility, involving the HLA region. However, transcription factor-7-like 2 (TCF7-L2) is the most common variant observed in type 2 diabetes in Europeans, and KCNQ1 (a potassium voltage-gated channel) in Asians. TCF7-L2 carries an increased risk of around 35%, while other common variants account for no more than 10–20%.[5] The population with two copies of the risk variant for this gene have a nearly twofold increase in risk of developing type 2 diabetes.[1] TCF7-L2 modulates pancreatic islet cell function.[5]

Paradoxically, the genes for type 2 diabetes account for a relatively small fraction of its observed heritability. They do not allow subtypes of the condition to be identified with any confidence; nor do they provide useful disease prediction.

However, the chance of developing diabetes is also influenced very powerfully by environmental factors.[1]

Environmental and other risk factors

Diet and obesity[1]

Epidemiological studies show that type 2 diabetes is associated with overeating, especially when combined with obesity and underactivity. Middle-aged people with diabetes eat significantly more and are fatter and less active than their non-diabetic siblings.

The risk of developing type 2 diabetes increases tenfold in people with a BMI of >30 kg/m^2.

Quantifying obesity with body mass index (weight/height^2)[1]

BMI (kg/m^2)	Classification*	Risk of obesity comorbidity
18.5–24.9	Reference range	Negligible
25.0–29.9	Overweight	Mildly increased
> 30.0	**Obese**	
30.0–34.9	Class I	Moderate
35.0–39.9	Class II	Severe
> 40.0	Class III	Very severe

*Classification of the WHO and International Obesity Task Force. The Western Pacific Region Office of WHO recommends that, amongst Asians, BMI > 23.0 is overweight and > 25.0 is obese.

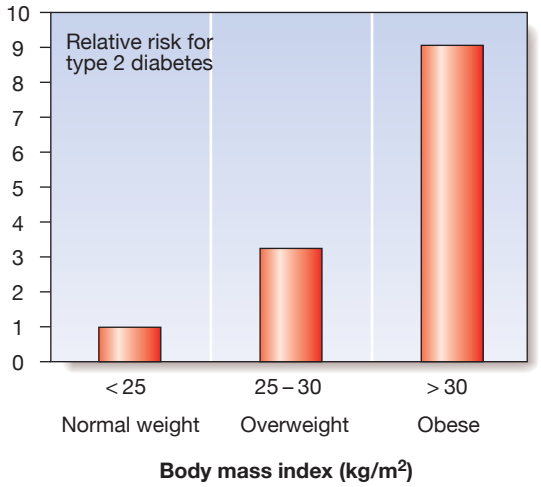


Figure: Risks of diabetes and in overweight and obese women.[1]

However, although the majority of patients with type 2 diabetes are obese, only a minority of obese people develop diabetes, as the majority of obese patients are able to increase insulin secretion to compensate for the increased demand resulting from obesity and insulin resistance.

Those who develop diabetes may have genetically impaired β-cell function, reduced β-cell mass, or a susceptibility of β cells to attack by toxic substances such as FFAs or inflammatory cytokines.

Low birth weight[5]

An association has been noted between low weight at birth

and at 12 months of age and glucose intolerance later in life, particularly in those who gain excess weight as adults.

The concept is that poor nutrition early in life impairs β-cell development and function, predisposing to diabetes in later life.

Low birth weight has also been shown to predispose to heart disease and hypertension.

Inflammation[5]

Subclinical inflammatory changes are characteristic of both type 2 diabetes and obesity; in diabetes, high-sensitivity C-reactive protein (CRP) levels are modestly elevated in association with raised fibrinogen and increased plasminogen activator inhibitor-1 (PAI-1), contributing to cardiovascular risk.

Circulating levels of the pro-inflammatory cytokines tumour necrosis factor alpha (TNF-α) and IL-6 are elevated in both diabetes and obesity.

Age[1]

Type 2 diabetes is more common in the middle-aged and elderly.

Diagnosis of diabetes mellitus in old age[1]

- **Prevalence**: increases with age, affecting ~10% of people over 65 years. Half of these people are undiagnosed. Impaired β-cell function and exaggerated insulin resistance with ageing both contribute.
- **Glycosuria**: the renal threshold for glucose rises with age, so glycosuria may not develop until the blood glucose concentration is markedly raised.
- **Pancreatic carcinoma**: may present in old age with the development of diabetes, in association with weight loss and diminished appetite.

In the UK, it affects 10% of the population over 65, and over 70% of all cases of diabetes occur after the age of 50 years.

Abnormalities of insulin secretion and action[5]

Even massively obese individuals with a fully functioning β-cell mass do not necessarily develop diabetes, which implies that some degree of β-cell dysfunction is necessary. So, the relative role of secretory failure versus insulin resistance in the pathogenesis of type 2 diabetes has been much debated.

Insulin resistance is, however, associated with central obesity and accumulation of intracellular triglyceride in muscle and liver in type 2 diabetes, and a high proportion of patients have nonalcoholic fatty liver disease (NAFLD).

It has long been stated that patients with type 2 diabetes retain up to 50% of their β-cell mass at the time of diagnosis, as compared with healthy controls, but the shortfall is greater than this when they are matched with healthy individuals who are equally obese.

In addition, patients with type 2 diabetes almost all show islet amyloid deposition at autopsy, derived from a peptide known as amylin or islet amyloid polypeptide (IAPP), which is co-secreted with insulin. It is not known if this is a cause or consequence of β-cell secretory failure.

Abnormalities of insulin secretion manifest early in the course of type 2 diabetes. An early sign is loss of the first phase of the normal biphasic response to intravenous insulin. Established diabetes is associated with hypersecretion of insulin by a depleted β-cell mass. Circulating insulin levels are therefore higher than in healthy controls, although still inadequate to restore glucose homeostasis. Relative insulin lack is associated with increased glucose production from the liver (owing to inadequate suppression of gluconeogenesis) and reduced glucose uptake by peripheral tissues. Hyperglycaemia and lipid excess are toxic to β cells, at least in vitro, a phenomenon known as glucotoxicity, and this is thought to result in further β- cell loss and further deterioration of glucose homeostasis. Circulating insulin levels are typically higher than in non-diabetics following diagnosis and tend to rise further, only to decline again after months or years due to secretory failure, an observation sometimes referred to as the 'Starling curve' of the pancreas. Type 2 diabetes is thus a condition in which insulin deficiency relative to increased demand leads to hypersecretion of insulin by a depleted β-cell mass and progression towards absolute insulin deficiency, requiring insulin therapy. Its time course varies widely between individuals.

Aetiology

Monogenic diabetes mellitus[1,5]

A number of unusual genetic diseases are associated with diabetes. Considerable progress has been made in understanding uncommon variants of diabetes. Infants who develop diabetes before 6 months of age are likely to have a monogenic defect and not true type 1 diabetes.

Rare genetic causes of type 2 diabetes[5]

Disorder	Features
Insulin receptor mutations	Obesity, marked insulin resistance, hyperandrogenism in women, acanthosis nigricans (areas of hyperpigmented skin)
Maternally inherited diabetes and deafness (MIDD)	Mutation in mitochondrial DNA. Diabetes onset before age 40. Variable deafness, neuromuscular and cardiac problems, pigmented retinopathy
Wolfram syndrome (diabetes insipidus, diabetes mellitus, optic atrophy and deafness, DIDMOAD)	Recessively inherited. Mutation in the transmembrane gene, WFS1. Insulin-requiring diabetes and optic atrophy in the first decade. Diabetes insipidus and sensorineural deafness in the second decade, progressing to multiple neurological problems. Few live beyond middle age
Severe obesity and diabetes	Alström, Bardet–Biedl and Prader–Willi syndromes. Retinitis pigmentosa, mental insufficiency and neurological disorders
Disorders of intracellular insulin signalling (all with severe insulin resistance)	Leprechaunism, Rabson–Mendenhall syndrome, pseudoacromegaly, partial lipodystrophy: lamin A/C gene mutation
Genetic defects of β-cell function	See box in the next page (*Genetic defects of beta cell function*)

In rare families, diabetes is caused by single gene defects of β-cell function with autosomal dominant inheritance. These subtypes constitute less than 5% of all cases of diabetes and typically present as 'maturity-onset diabetes of the young' (MODY), i.e. non-insulin-requiring diabetes presenting before the age of 25 years. Several variants have been described, each associated with different clinical phenotypes. These should be considered in people presenting with early onset diabetes in association with an affected parent and early-onset diabetes in approximately 50% of relatives.[1,5]

Monogenic diabetes mellitus: maturity-onset diabetes of the young (MODY)[1]

Functional defect	Main type*	Gene mutated*
β-cell glucose sensing	MODY2	GCK
The set point for basal insulin release is altered, causing a high fasting glucose, but sufficient insulin is released after meals. As a result, the HbA_{1c} is often normal and microvascular complications are rare. Treatment is rarely required		
β-cell transcriptional regulation	MODY3 MODY5 MODY1	HNF-1α HNF-1β HNF-4α
Diabetes develops during adolescence/early adulthood and can be managed with diet and tablets for many years, but ultimately, insulin treatment is required. The HNF-1α and 4α forms respond particularly well to sulphonylurea drugs. All types are associated with microvascular complications. HNF-1β mutations also cause renal cysts and renal failure		

*Other gene mutations have been found in rare cases. For further information, seehttp://diabetesgenes.org

Diabetes soon after birth

Very rarely, diabetes can develop at or soon after birth. This neonatal diabetes is usually genetic in origin, causing insulin deficiency and diabetic ketoacidosis.

1. Transient neonatal diabetes mellitus (TNDM) occurs soon after birth and resolves at a median of 12 weeks; some 50% of cases ultimately relapse later in life. Most have an abnormality of imprinting of the ZAC and HYMAI genes on chromosome 6q.
2. In permanent neonatal diabetes mellitus (PNDM) the most common cause (50%) is mutations in the KCNJ11 gene encoding the Kir6.2 subunit of the β-cell potassium–ATP (K_{ATP} channel) channel.

Neurological features are seen in 20% of patients. Diabetes is due to defective insulin release rather than β-cell destruction. However, sulphonylurea drugs overcome the defect in potassium channel signalling, so that insulin therapy is not necessary in these cases. Also, patients can be treated successfully with sulphonylureas, even after many years of insulin therapy.

Genetic defects of beta cell function[5]

Features	HNF-4a	Glucokinase	HNF-1a	IPF-1	HNF-1b
Chromosomal location	20q	7p	12q	13q	17q
Proportion of all cases	5%	15%	70%	<1%	2%
Onset	Teens/thirties	Present from birth	Teens/twenties	Teens/thirties	Teens/twenties
Progression	Progressive hyperglycaemia	Little deterioration with age	Progressive hyperglycaemia	Progression unclear	Progression unclear
Microvascular complications	Frequent	Rare	Frequent	Few data	Frequent
Other features	None	Reduced birth weight	Sensitivity to sulphonylureas	Pancreatic agenesis in homozygotes	Renal cysts, proteinuria, chronic kidney disease

The glucokinase gene is intimately involved in the glucose-sensing mechanism within the pancreatic β cell. The hepatic nuclear factor (HNF) genes and the insulin promoter factor-1 (IPF-1) gene control nuclear transcription in the β cell, where they regulate its development and function. Abnormal nuclear transcription genes may cause pancreatic agenesis or moresubtle progressive pancreatic damage. A handful of families with autosomal dominant diabetes have been described with mutations in neurogenic differentiation factor-1 (NeuroD1).

Pathology
Type 1 diabetes[1]

Type 1 diabetes is a T cell-mediated autoimmune disease involving destruction of the insulin-secreting β cells in the pancreatic islets.

Progressive loss of β cell function takes place over a prolonged period (months to years), but marked hyperglycaemia, accompanied by the classical symptoms of diabetes, occurs only when 80–90% of the functional capacity of β cells has been lost.

The pathology in the pre-diabetic pancreas is characterised by 'insulitis' (resembles that in other autoimmune diseases such as thyroiditis[5]), with infiltration of the islets by mononuclear cells containing

1. activated macrophages,
2. helper cytotoxic and suppressor T lymphocytes,
3. natural killer cells and
4. B lymphocytes.

Several islet antigens have been characterized and these include[5]

1. insulin itself,
2. the enzyme glutamic acid decarboxylase (GAD),
3. protein tyrosine phosphatase (IA-2) and
4. the cation transporter ZnT8.

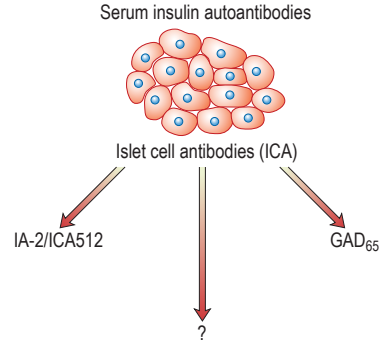


Figure: Islet autoantibodies. Islet cell antibodies (ICA) are detected by a fluorescent antibody technique that detects binding of autoantibodies to islet cells. Much of this staining reaction is due to antibodies specific for glutamic acid decarboxylase (GAD) and protein tyrosine phosphatase (IA-2, also known as ICA512). Not all the staining seen with ICA is due to these two autoantibodies, so it is assumed that other islet autoantibodies are also involved. Insulin autoantibodies also appear in the circulation but do not contribute to the ICA reaction.[5]

Initially, these lesions are patchy and, until a very late stage, lobules containing heavily infiltrated islets are seen adjacent to unaffected lobules.

The destructive process is β cell specific, the glucagon and other hormone-secreting cells in the islet remaining intact.

Islet cell antibodies are present before the clinical presentation of type 1 diabetes, and their detection can be useful in confirming a diagnosis of type 1 diabetes, but they are poorly predictive of disease progression and disappear over time

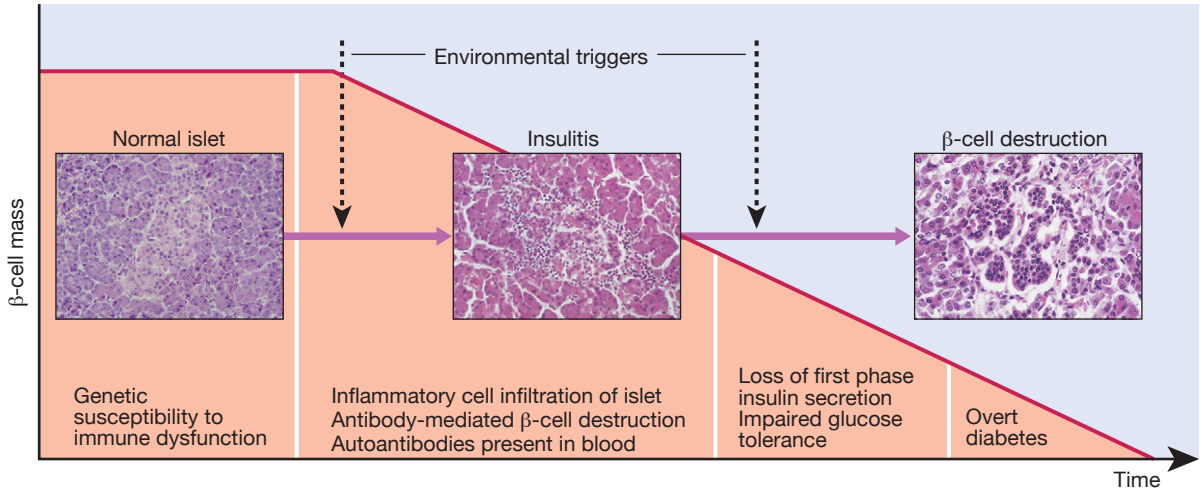


Figure: Pathogenesis of type 1 diabetes. Proposed sequence of events in the development of type 1 diabetes.[1]

Pathology
Type 2 diabetes

Type 2 diabetes is a diagnosis of exclusion, i.e. it is made when type 1 diabetes and other types of diabetes are ruled out, and is highly heterogeneous.

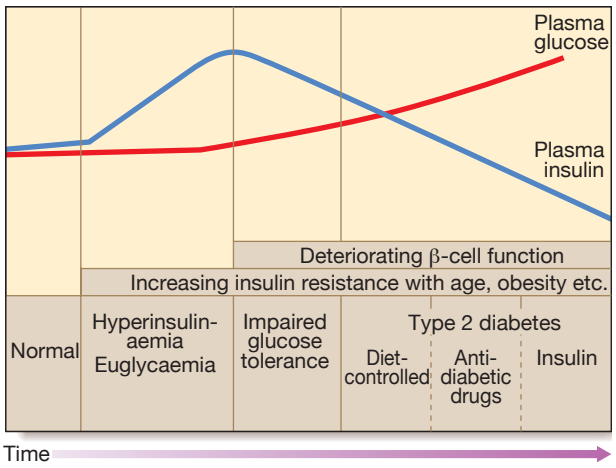


Figure: The natural history of typical type 2 diabetes. In the early stage of the disorder, the response to progressive insulin resistance is an increase in insulin secretion by the pancreatic cells, causing hyperinsulinaemia. Eventually, the β cells are unable to compensate adequately and blood glucose rises, producing hyperglycaemia. With further β-cell failure, glycaemic control deteriorates and treatment requirements escalate.[1]

Initially, insulin resistance leads to elevated insulin secretion in order to maintain normal blood glucose levels. However, in susceptible individuals, the pancreatic β cells are unable to sustain the increased demand for insulin and a slowly progressive insulin deficiency develops.

Some patients develop diabetes at a young age, usually driven by insulin resistance due to obesity and ethnicity; others, particularly the elderly, develop diabetes despite being non-obese and may have more pronounced β-cell failure.

The key feature is a 'relative' insulin deficiency, such that there is insufficient insulin production to overcome the resistance to insulin action. This contrasts with type 1 diabetes, in which there is rapid loss of insulin production and an absolute deficiency, resulting in ketoacidosis and death if the insulin is not replaced.

Pancreatic β-cell failure

In the early stages of type 2 diabetes, reduction in the total mass of pancreatic islet tissue is modest. At the time of diagnosis, around 50% of β-cell function has been lost and this declines progressively.

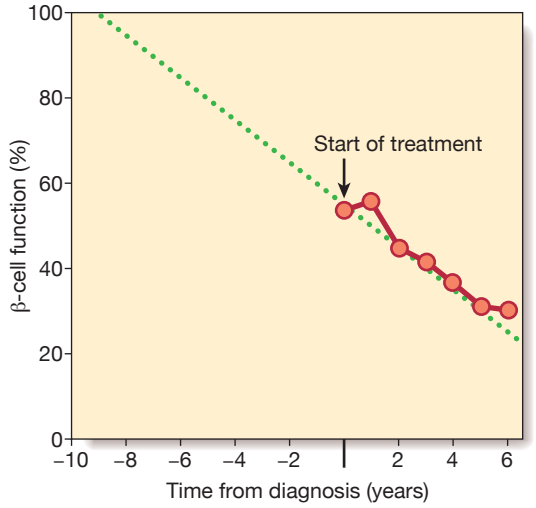


Figure: Progressive pancreatic β-cell failure in patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS). Beta-cell function was estimated using the homeostasis model assessment (HOMA) and was already below 50% at the time of diagnosis. Thereafter, long-term incremental increases in fasting plasma glucose were accompanied by progressive β-cell dysfunction. If the slope of this progression is extrapolated, it appears that pancreatic dysfunction may have been developing for many years before diagnosis of diabetes.[1]

Some pathological changes are typical of type 2 diabetes, the most consistent of which is deposition of amyloid in the islets. In addition, elevated plasma glucose and FFAs exert toxic effects on pancreatic β cells to impair insulin secretion.

However, while β-cell numbers are reduced, β-cell mass is unchanged and glucagon secretion is increased, which may contribute to hyperglycaemia.

Pathology
Other forms of diabetes[1]

In most cases, there is an obvious cause of destruction of pancreatic β cells. Some acquired disorders, notably other endocrine diseases such as acromegaly or Cushing's syndrome, can precipitate type 2 diabetes in susceptible individuals.

7 Insulin resistance and The metabolic syndrome

Type 2 diabetes, or its antecedent, impaired glucose tolerance, is one of a cluster of conditions thought to be caused by resistance to insulin action. Thus, patients with type 2 diabetes often have associated disorders including hypertension, dyslipidaemia, characterised by elevated levels of small dense low-density lipoprotein (LDL) cholesterol and triglycerides, and a low level of high-density lipoprotein (HDL) cholesterol, nonalcoholic fatty liver and, in women, polycystic ovarian syndrome. This cluster has been termed the 'insulin resistance syndrome' or 'metabolic syndrome', and is much more common in patients who are obese.[1]

Insulin resistance

Risk factors

Risk factors of insulin resistance[4]

Metabolic syndrome;	Acromegaly;
Obese;	Cushing's;
Asian;	Renal failure;
TB drugs;	Cystic fibrosis;
SSRI;	Polycystic ovary;
Pregnancy;	Werner's syndrome

Gujaratis, Punjabis, Sri Lankans, Pakistanis and Bangladeshis have a low threshold for diagnosing obesity (BMI >23) and for vigorous intervention.

Obesity increases the risk of type 2 diabetes 80–100-fold. On average, the inhabitants of affluent countries gain weight at the rate of 1 g/day or more between the ages of 25 and 55 years. This gain, due to a tiny excess in energy intake over expenditure (90 kcal or one chocolate-coated digestive biscuit per day), is often due to reduced exercise rather than increased food intake.[5]

Causes: [4]

1. Obesity: Possibly increased rate of release of non-esterified fatty acids causing post-receptor defects in insulin's action.
2. Genetics: mutations in genes encoding insulin receptors.
3. Circulating autoantibodies to the extra cellular domain of the insulin receptor.

The primary cause of insulin resistance remains unclear; it is likely that there are multiple defects in insulin signalling, affecting several tissues. [1]

Adipocyte[1]

One theory is centred around the adipocyte; this is particularly appealing, as obesity is a major cause of increased insulin resistance. Intra-abdominal 'central' adipose tissue is metabolically active, and releases large quantities of FFAs, which may induce insulin resistance because they compete with glucose as a fuel supply for oxidation in peripheral tissues such as muscle.

In addition, adipose tissue releases a number of hormones (including a variety of peptides, called 'adipokines' because they are structurally similar to immunological 'cytokines') which act on specific receptors to influence sensitivity to insulin in other tissues.

Because the venous drainage of visceral adipose tissue is into the portal vein, central obesity may have a particularly potent influence on insulin sensitivity in the liver, and thereby adversely affect gluconeogenesis and hepatic lipid metabolism.

Physical activity

Physical activity is another important determinant of insulin sensitivity. Inactivity is associated with downregulation of insulin-sensitive kinases and may promote accumulation of FFAs within skeletal muscle. Sedentary people are therefore more insulin-resistant than active people with the same degree of obesity. Moreover, physical activity allows non-insulin-dependent glucose uptake into muscle, reducing the 'demand' on the pancreatic β cells to produce insulin.

Fat deposition in the liver

Deposition of fat in the liver is a common association with central obesity and is exacerbated by insulin resistance and/or deficiency.

Many patients with type 2 diabetes have evidence of fatty infiltration of the liver (non-alcoholic fatty liver disease (NAFLD)). This condition may improve with effective treatment of the diabetes and dyslipidaemia, but despite this, a few patients progress to non-alcoholic steatohepatitis and cirrhosis.

The metabolic syndrome (syndrome X)

Definition

According to the IDF definition[7], for a person to be defined as having the metabolic syndrome they must have:

Central obesity (defined as waist circumference* with ethnicity specific values) plus any two of the following four factors:	
Raised triglycerides	≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
Reduced HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality
Raised blood pressure	systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension
Raised fasting plasma glucose	(FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.
* If BMI is >30kg/m², central obesity can be assumed and waist circumference does not need to be measured.	

Incidence

~20% are affected[4]; about one-third of the adult population has features of the syndrome, not necessarily associated with diabetes.[5]

Etiology[4]

weight, genetics, and insulin resistance important in aetiology.

Possible consequences[4]

1. Vascular events (MI)—but may not increase risk beyond individual risk factors;
2. DM;
3. Neuro degeneration;
4. Micro albuminuria;
5. Gallstones;
6. Cancers (eg pancreas);
7. Fertility problems (male & female)

Treatment[4]

- Exercise;
- Weight reduction ± Mediterranean (?ketogenic) diet,
- Antihypertensives,
- Hypoglycaemics (metformin ± glitazones),
- Statins.

Explain that benefits are more than simply chemical: there is an intriguing two-way inter action between depression and insulin resistance.

Criticism

Wise doctors and nurses will use this fact and work on many different levels to lead patients out of illness into health. Examples are motivational therapy and weekly phone interventions.[4]

Critics argue that the metabolic syndrome is not a distinct entity, but one end of a continuum in the relationship between lifestyle and body weight on the one hand, and genetic make-up on the other, and that diagnosis adds little to standard clinical practice in terms of diagnosis, prognosis or therapy.[5]

Waist circumference for central obesity[4,7]

Country/Ethnic group	Male	Female
Europeans	≥94cm	≥80 cm
South (S) Asians	≥90cm	≥80 cm
Chinese	≥90cm	≥80cm
Japanese	≥90cm	≥80cm
S & Central Americans use S Asian pro tem Africans + Middle East use European pro tem		
Originally different values were proposed for Japanese people but new data support the use of the values shown above.		

8 Clinical approach
To the patient with diabetes

Presentation[5]

Presentation may be acute, subacute or asymptomatic, or a patient may present with one of the complications of diabetes.

Acute presentation
Young people often present with a 2–6-week history and report the classic triad of symptoms:

- polyuria due to the osmotic diuresis that results when blood glucose levels exceed the renal threshold
- thirst due to the resulting loss of fluid and electrolytes
- weight loss due to fluid depletion and the accelerated breakdown of fat and muscle secondary to insulin deficiency.

Ketonuria is often present in young people and may progress to ketoacidosis if these early symptoms are not recognized and treated.

Subacute presentation
The clinical onset may be over several months or years, particularly in older patients.

Typical presentations –

- Thirst,
- polyuria and
- weight loss

patients may complain of such symptoms as

- lack of energy,
- visual blurring (owing to glucose-induced changes in refraction), or
- pruritus vulvae or balanitis that is due to Candida infection.

Complications as the presenting feature
These include:

- staphylococcal skin infections
- retinopathy noted during a visit to the optician
- a polyneuropathy causing tingling and numbness in the feet
- erectile dysfunction
- arterial disease, resulting in myocardial infarction or peripheral gangrene.

Asymptomatic diabetes
Glycosuria or a raised blood glucose may be detected on routine examination (e.g. for insurance purposes) in individuals who have no symptoms of ill-health. This is more common in older people, who have a raised renal threshold for glucose. When present, glycosuria is not diagnostic of diabetes but indicates the need for further investigations. Familial renal glycosuria is a monogenic disorder affecting function of the sodium–glucose co-transporter (SGLT2) and found in about 1:400 of the population.

Physical examination
At diagnosis[5]

Evidence of weight loss and dehydration may be present, and the breath may smell of ketones. Older patients may present with established complications, and the presence of the characteristic retinopathy is diagnostic of diabetes.

In occasional patients, there will be physical signs of an illness causing secondary diabetes (see the classification of diabetes).

Patients with severe insulin resistance may have acanthosis nigricans, which is characterized by blackish pigmentation at the nape of the neck and in the axillae.

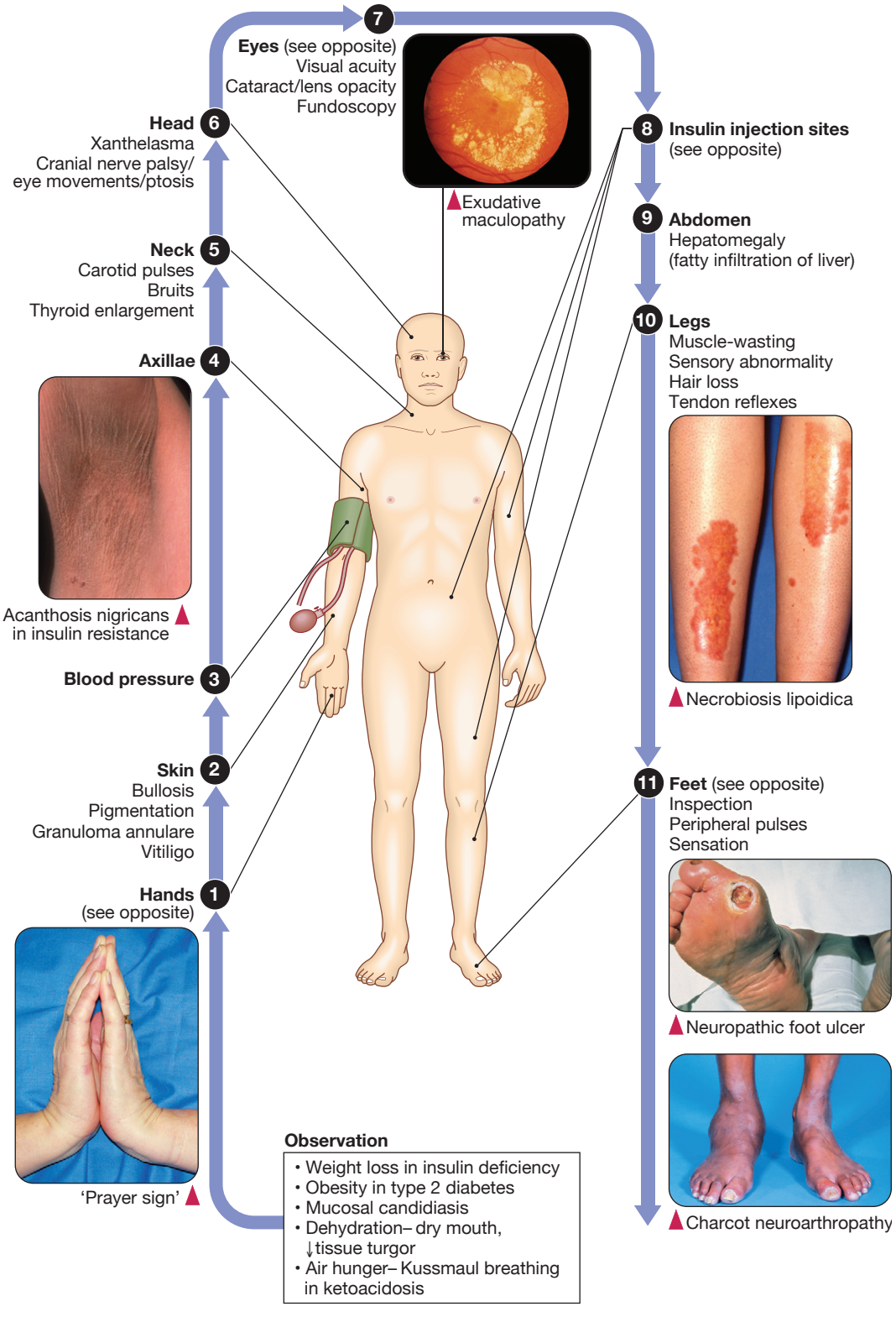


Figure: Clinical examination of the patient with diabetes.[1]

Diagnosis and Investigations

Diabetes is easy to diagnose when overt symptoms are present and a random blood glucose measurement of >11 mmol/L confirms the diagnosis.

In the absence of clear symptoms, diabetes can be diagnosed by any of three measures of glucose metabolism:

1. the oral glucose tolerance test (OGTT),
2. fasting plasma glucose and
3. haemoglobin A_{1C} (HbA_{1C}).

Unfortunately, there is limited overlap between these measures, especially in the 'grey zone' between diabetes and normality.[5]

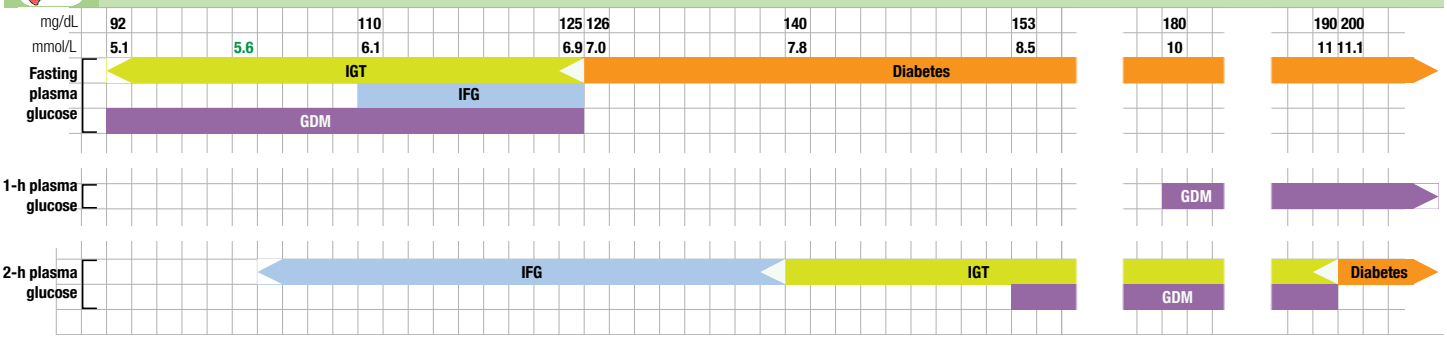
WHO diagnostic criteria for diabetes[9,10]

1.	HbA_{1c}	≥6.5%	The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*	Or,
2.	FPG	≥ 7.0 mmol/L (126 mg/dL)	Fasting is defined as no caloric intake for at least 8 h.*	Or,
3.	2-h plasma glucose during an OGTT.	≥ 11.1 mmol/L (200 mg/dL)	The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*	Or,
4.	Random plasma glucose	≥ 11.1 mmol/L (200 mg/dL)	+ classic symptoms of hyperglycemia or hyperglycemic crisis	

* In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

Random is defined as without regard to time since the last meal.
Hemoglobin A_{1c} test should be performed in a laboratory using a method approved by the National Glycohemoglobin Standardization Program and correlated to the reference assay of the Diabetes Control and Complications Trial. Point-of- care hemoglobin A_{1c} should not be used for diagnostic purposes.
OGTT is not recommended for routine clinical use.

Plasma glucose level spectrum in different forms of diabetes[10,11,12,13]



* Venous plasma glucose 1 and 2 hours after ingestion of 75 g oral glucose load

Pre-diabetes

Since any marker of abnormal glucose metabolism is associated with an increased risk of progression to diabetes and/or cardiovascular disease, it can be argued that a single abnormality is sufficient for admission into a risk category, which the American Diabetes Association (ADA) has labelled 'pre-diabetes'. On this basis, 86 million Americans suffer from pre-diabetes, in addition to the 25 million with known or undiagnosed diabetes. The World Health Organization (WHO) and other professional organizations avoid use of the term 'pre-diabetes', on the grounds that the majority will never, in fact, develop diabetes, and that the evidence to support screening and intervention is lacking.

Impaired glucose tolerance

Impaired glucose tolerance (IGT) is not a clinical entity but a risk factor for future diabetes and cardiovascular disease. The diagnosis can only be made with a glucose tolerance test, and is complicated by poor reproducibility of the key 2-hour value in this test. The group is heterogeneous; some patients are obese, some have liver disease and others are on medication that impairs glucose tolerance. Individuals with IGT have the same risk of cardiovascular disease as those with frank diabetes, but do not develop the specific microvascular complications.

Impaired fasting glucose

This diagnostic category (fasting plasma glucose between 6.1 and 6.9 mmol/L) has the practical advantage that it avoids the need for a glucose tolerance test. It is not a clinical entity but indicates future risk of frank diabetes and cardiovascular disease. Impaired fasting glucose (IFG) only overlaps with IGT to a limited extent, and the associated risks of cardiovascular disease and future diabetes are not directly comparable. A lower cut-off of 5.6 mmol/L (rather than 6.1 mmol/L) has been recommended by the ADA and would, if implemented, greatly increase the number of those in this category.

Haemoglobin A_{1C}

Haemoglobin A_{1C} (HbA_{1C}; also referred to as A_{1C} in the USA) is an integrated measure of an individual's prevailing blood glucose concentration over several weeks. Standardization of this measure has enabled it to be proposed as an alternative diagnostic test for diabetes by the ADA. As currently proposed, an HbA_{1c} of >6.5% (48 mmol/mol) would be considered diagnostic of diabetes, whereas a level of 5.7–6.4% (39–46 mmol/mol) would denote increased risk of diabetes. A WHO consultation also concluded that HbA_{1c} 'can be used as a diagnostic test for diabetes'. The ADA has recommended that HbA_{1c} should be used together with IGT and IFG as a marker of 'pre-diabetes', with a range of 5.6–6.4% (38–46 mmol/mol).

Other investigations

No further tests are needed to diagnose diabetes. Other routine investigations include urine testing for protein, a full blood count, urea and electrolytes, liver biochemistry and random lipids. The latter test is useful to exclude associated hyperlipidaemia and, if elevated, should be repeated as a fasting measurement after diabetes has been brought under control. Diabetes may be secondary to other conditions, precipitated by underlying illness, and associated with autoimmune disease or hyperlipidaemia. Hypertension is present in 50% of patients with type 2 diabetes and a higher proportion of African and Caribbean patients.

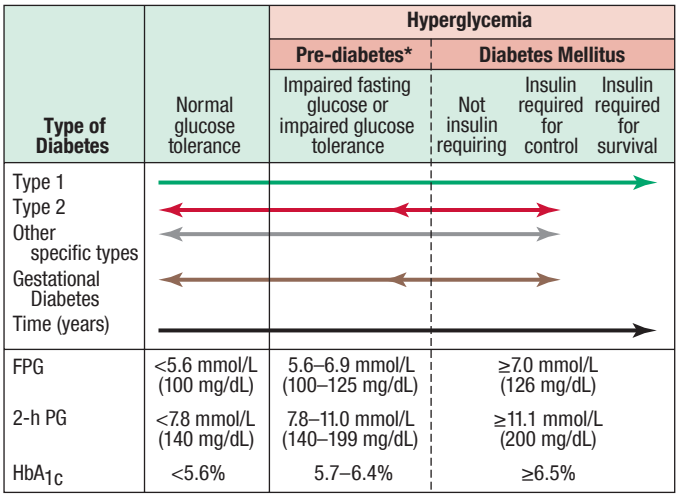


Figure: Spectrum of glucose homeostasis and diabetes mellitus.[9] (These traverses should be viewed not as abrupt categories but as a spectrum).

Arrows indicate that changes in glucose tolerance may be bidirectional in some types of diabetes. For example, individuals with type 2 DM may return to the impaired glucose tolerance category with weight loss; in gestational DM, diabetes may revert to impaired glucose tolerance or even normal glucose tolerance after delivery.

***The fasting plasma glucose** (FPG), the **2-h plasma glucose** (PG) after a glucose challenge, and the **HbA_{1c}** for the different categories of glucose tolerance are shown at the lower part of the figure. These values do not apply to the diagnosis of gestational DM.*

***Some use the term increased risk for diabetes or intermediate hyperglycemia (World Health Organization) rather than prediabetes.*

9 Investigations and screening

Urine testing

Glucose

Testing the urine for glucose with dipsticks is a common screening procedure for detecting diabetes. If possible, testing should be performed on urine passed 1–2 hours after a meal to maximise sensitivity. Glycosuria always warrants further assessment by blood testing.

Disadvantages:
The greatest disadvantage of urinary glucose measurement is the individual variation in renal threshold for glucose. The most frequent cause of glycosuria is a low renal threshold, which is common during pregnancy and in young people; the resulting 'renal glycosuria' is a benign condition unrelated to diabetes.

Another disadvantage is that some drugs (such as β-lactam antibiotics, levodopa and salicylates) may interfere with urine glucose tests.

Ketones

Ketone bodies can be identified by the nitroprusside reaction, which measures acetoacetate, using either tablets or dipsticks.

Ketonuria may be found in normal people -

1. who have been fasting or exercising strenuously for long periods,
2. who have been vomiting repeatedly, or
3. who have been eating a diet high in fat and low in carbohydrate.

Ketonuria is therefore not pathognomonic of diabetes but, if associated with glycosuria, the diagnosis of diabetes is highly likely. In diabetic ketoacidosis, ketones can also be detected in plasma using test sticks (see below).

Protein

Standard dipstick testing for albumin detects urinary albumin at concentrations above 300 mg/L, but smaller amounts (microalbuminuria) can only be measured using specific albumin dipsticks or by quantitative biochemical laboratory measurement.

Microalbuminuria or proteinuria, in the absence of urinary tract infection, is an important indicator of diabetic nephropathy and/or increased risk of macrovascular disease.

Quantifying proteinuria in random urine samples [1]

ACR[1]	PCR[2]	Typical dipstick results[3]	Significance
< 3.5 (female) < 2.5 (male)		–	Normal
~3.5–15		–	Microalbuminuria
~15–50	~15–50	+ to ++	Dipsticks positive; equivalent to 24-hr protein excretion < 0.5 g
50–200	> 250	++ to +++	Glomerular disease more likely
> 200	> 300	+++ to ++++	Nephrotic range: always glomerular disease, equivalent to 24-hr protein excretion > 3 g

[1]Urinary albumin (mg/L)/urine creatinine (mmol/L). [2]Urine protein (mg/L)/urine creatinine (mmol/L). (If urine creatinine is measured in mg/dL, reference values for PCR and ACR can be derived by dividing by 11.31.)
[3]Dipstick results are affected by urine concentration and are occasionally weakly positive on normal samples.

Blood testing

Glucose

Laboratory glucose testing in blood relies upon an enzymatic reaction (glucose oxidase) and is cheap, usually automated and highly reliable. However, blood glucose levels depend on whether the patient has eaten recently, so it is important to consider the circumstances in which the blood sample was taken. Blood glucose can also be measured with colorimetric or other testing sticks, which are often read with a portable electronic meter. These are used for capillary (fingerprick) testing to monitor diabetes treatment.

To make the diagnosis of diabetes, the blood glucose concentration should be estimated using an accurate laboratory method rather than a portable technique.

Glucose concentrations are lower in venous than arterial or capillary (fingerprick) blood. Whole blood glucose concentrations are lower than plasma concentrations because red blood cells contain relatively little glucose. Venous plasma values are usually the most reliable for diagnostic purposes.

Ketones

Blood ketone monitoring is increasingly available. Urinary ketone measurements described above are semi-quantitative, difficult to perform and retrospective (i.e. the urine has accumulated over several hours), and do not measure the major ketone in blood during diabetic ketoacidosis (DKA), beta-hydroxybutyrate (β- OHB).

Whole blood ketone monitoring detects β-OHB and is useful in assisting with insulin adjustment during intercurrent illness or sustained hyperglycaemia to prevent or detect DKA. Blood ketone monitoring is also useful in monitoring resolution of DKA in hospitalised patients.

Interpretation of capillary blood ketone measurements[1]

Measurement*	Interpretation
< 0.6 mmol/L	Normal; no action required
0.6–1.5 mmol/L	Suggests metabolic control may be deteriorating; continue to monitor and seek medical advice if sustained/ progressive
1.5–3.0 mmol/L	With high blood glucose (> 10 mmol/L), there is a high risk of diabetic ketoacidosis; seek medical advice
> 3.0 mmol/L	Severe ketosis; in the presence of high glucose (> 10 mmol/L) suggests presence of diabetic ketoacidosis; seek urgent medical help

*To convert to mg/dL, divide values by 0.098.

Glycated haemoglobin

Glycated haemoglobin provides an accurate and objective measure of glycaemic control integrated over a period of weeks to months.

In diabetes, the slow non-enzymatic covalent attachment of glucose to haemoglobin (glycation) increases the amount in the HbA_1 (HbA_{1c}) fraction relative to nonglycated adult haemoglobin (HbA_0). These fractions can be separated by chromatography; laboratories may report glycated haemoglobin as total glycated haemoglobin (GHb), HbA_1 or HbA_{1c}.

In most countries, HbA_{1c} is the preferred measurement. The rate of formation of HbA_{1c} is directly proportional to the ambient blood glucose concentration; a rise of 1% in HbA_{1c} corresponds to an approximate average increase of 2 mmol/L (36 mg/dL) in blood glucose. Although HbA_{1c} concentration reflects the integrated blood glucose control over the lifespan of erythrocytes (120 days), HbA_{1c} is most sensitive to changes in glycaemic control occurring in the month before measurement.[1] Glycated haemoglobin (HbA1c) relates to mean glucose level over previous 8 weeks (RBC ½-life).[4]

Various assay methods are used to measure HbA_{1c}, but most laboratories have been reporting HbA_{1c} values (as %) aligned with the reference range that was used in the Diabetes Control and Complications Trial (DCCT).

To allow worldwide comparisons of HbA_{1c} values, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has developed a standard method; IFCC-standardised HbA_{1c} values are reported in mmol/mol.

In 2011, many countries adopted the IFCC reference method.

Conversion between DCCT and IFCC units for HbA_{1c}[1]

DCCT units (%)	IFCC units (mmol/mol)
4	20
5	31
6	42
7	53
8	64
9	75
10	86

IFCC HbA_{1c} (mmol/mol) = [DCCT HbA_{1c}(%)–2.15] × 10.929

(DCCT = Diabetes Control and Complications Trial; IFCC = International Federation of Clinical Chemistry and Laboratory Medicine

HbA_{1c} estimates may be erroneously diminished in anaemia or during pregnancy, and may be difficult to interpret with some assay methods in patients who have uraemia or a haemoglobinopathy.

10 Presenting problems of Hyperglycaemia

Hyperglycaemia is a very common biochemical abnormality. It is frequently detected on routine biochemical analysis of asymptomatic patients, following routine dipstick testing of urine showing glycosuria, or during severe illness ('stress hyperglycaemia'). Alternatively, hyperglycaemia may present with the symptoms.

Occasionally, patients present as an emergency with acute metabolic decompensation. The key goals are to establish whether the patient has diabetes, and if so, what type of diabetes it is and how it should be treated.

Establishing the diagnosis of diabetes

Glycaemia can be classified into three categories:

1. normal,
2. impaired (pre-diabetes) and
3. diabetes.

The glucose cut-off that defines diabetes is based upon the level above which there is a significant risk of microvascular complications (retinopathy, nephropathy, neuropathy).

People categorised as having pre-diabetes have blood glucose levels that carry a negligible risk of microvascular complications but are at increased risk of developing diabetes. Also, because there is a continuous risk of macrovascular disease (atheroma of large conduit blood vessels) with increasing glycaemia in the population, people with pre-diabetes have increased risk of cardiovascular disease (myocardial infarction, stroke and peripheral vascular disease).

When a person has symptoms of diabetes, the diagnosis can be confirmed with

1. either a fasting glucose ≥ 7.0 mmol/L (126 mg/dL) or
2. a random glucose ≥ 11.1 mmol/L (200 mg/dL)

Asymptomatic individuals should have a second confirmatory test. Diabetes should not be diagnosed by capillary blood glucose results.

The World Health Organization (WHO) guidelines (2011) introduced the use of HbA_{1c} for diagnosis of diabetes, with an IFCC HbA_{1c} of more than 48 mmol/mol also being diagnostic.

Pre-diabetes can be diagnosed either as 'impaired fasting glucose' (IFG), based upon a fasting plasma glucose result, or 'impaired glucose tolerance' (IGT), based upon the fasting and 2-hour oral glucose tolerance test results (OGTT). This is not associated with a substantial risk of microvascular disease, but is connected with an increased risk of large vessel disease (e.g. atheroma leading to myocardial infarction) and with a greater risk of developing diabetes in future. Patients with prediabetes should be advised of their risk of progression to diabetes, given advice about lifestyle modification to reduce this risk (as for type 2 diabetes), and be ensured of aggressive management of cardiovascular risk factors such as hypertension and dyslipidaemia.

Diagnosis of diabetes and pre-diabetes[1]

Diabetes is confirmed by either:

- Plasma glucose in random sample or 2 hrs after a 75 g glucose load ≥ 11.1 (200 mg/dL) or
- Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL)

In asymptomatic patients, two diagnostic tests are required to confirm diabetes.

'Pre-diabetes' is classified as:

- Impaired fasting glucose = fasting plasma glucose ≥ 6.0 (108 mg/dL) and < 7.0 mmol/L (126 mg/dL)
- Impaired glucose tolerance = fasting plasma glucose < 7.0 mmol/L (126 mg/dL) and 2-hr glucose after 75 g oral glucose drink 7.8–11.1 mmol/L (140–200 mg/dL)

In some people, an abnormal blood glucose result is observed under conditions which impose a burden on the pancreatic β cells, e.g. during pregnancy, infection, myocardial infarction or other severe stress, or during treatment with diabetogenic drugs such as corticosteroids. This 'stress hyperglycaemia' usually disappears after the acute illness has resolved. However, blood glucose should be remeasured and an OGTT will often show persistence of impaired glucose tolerance.

The diagnostic criteria recommended for diabetes in pregnancy are more stringent than those for nonpregnant subjects. Pregnant women with abnormal glucose tolerance should be referred urgently to a specialist unit for

full evaluation. When a diagnosis of diabetes is confirmed, other investigations should include plasma urea, creatinine and electrolytes, lipids, liver and thyroid function tests, and urine testing for ketones, protein or microalbuminuria.

Clinical assessment

Hyperglycaemia causes a wide variety of symptoms.

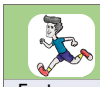
Symptoms of hyperglycaemia[1]

- Thirst, dry mouth
- Polyuria
- Nocturia
- Tiredness, fatigue, lethargy
- Change in weight (usually weight loss)
- Blurring of vision
- Pruritus vulvae, balanitis (genital candidiasis)
- Nausea
- Headache
- Hyperphagia; predilection for sweet foods
- Mood change, irritability, difficulty in concentrating, apathy

The classical clinical features of the two main types of diabetes are compared below.

Occasionally it may be difficult to differentiate whether a patient has type 1 or 2 DM. Features that suggest type 1 DM include [4] –

- weight loss;
- persistent hyperglycaemia despite diet and medications;
- presence of autoantibodies: islet cell antibodies (ICA) and anti-glutamic acid decarboxylase (GAD) antibodies;
- ketonuria on urine dipstick.



Classical features of type 1 and type 2 diabetes

Features	Type 1	Type 2
Typical age of onset	<40 years, often starts before puberty	>50 years
Duration of symptoms	Weeks	Months to years
Body weight	Normal or low	Obese
Ketonuria	Yes	No
Higher-risk ethnicity[5]	Northern European	Asian, African, Polynesian and Native American
Rapid death without treatment with insulin	Yes	No
Seasonal onset[5]	Yes	No
Genetics[4,5]	HLA DR3 and DR4 linked in >90%	No HLA association
Pathogenesis[5]	Autoimmune disease	No immune disturbance
Autoantibodies	Positive in 80-90%	Negative
Presentation	Polydipsia, polyuria, weight loss, ketosis	Asymptomatic/ complications, eg. MI
Diabetic complications at diagnosis	No	25%
Family history of diagnosis	Uncommon	Common
Other autoimmune diseases	Common	Uncommon
Biochemical[5]	C-peptide disappears	C-peptide persists

HLA, human leucocyte antigen.

Symptoms of thirst, polyuria, nocturia and rapid weight loss are prominent in type 1 diabetes, but are often absent in patients with type 2 diabetes, many of whom are asymptomatic or have non-specific complaints such as chronic fatigue and malaise. Uncontrolled diabetes is associated with an increased susceptibility to infection and patients may present with skin sepsis (boils) or genital candidiasis, and complain of pruritus vulvae or balanitis.

While the distinction between type 1 and type 2 diabetes is usually obvious, overlap occurs, particularly in age at onset, duration of symptoms and family history. There are many patients in whom the type of diabetes is not immediately apparent. For example, patients with type 2 diabetes may present with marked and rapid weight loss and even diabetic ketoacidosis, and type 2 diabetes is increasingly diagnosed in children and young adults.

Type 1 diabetes can occur at any age, not just in younger people, and may develop more insidiously; the presence of pancreatic autoantibodies confirms the diagnosis of slow-onset type 1 diabetes, termed latent autoimmune diabetes of adults (LADA).[1] If ketotic ± a poor response to oral hypoglycaemics (and patient is slim or has a family or personal history of autoimmunity), think of latent autoimmune diabetes in adults (LADA) and measure islet cell antibodies.[4]

Pancreatic autoantibodies are detectable at high titre in 80–90% of patients with type 1 diabetes, so a negative result should prompt consideration of other aetiologies.

Other causes of diabetes, such as MODY, should not be forgotten, particularly in those presenting in childhood or as young adults.

A history of pancreatic disease, particularly in patients with a history of alcohol excess, makes insulin deficiency more likely. Sometimes the definitive classification of the type of diabetes is only made later, once the natural history or responsiveness to different therapies becomes apparent.

Physical signs in patients with type 2 diabetes at diagnosis depend on the mode of presentation. In Western populations, more than 80% are overweight, and the obesity is often central (truncal or abdominal). Obesity is much less evident in Asians. Hypertension is present in at least 50% of patients with type 2 diabetes. Although dyslipidaemia is also common, skin lesions such as xanthelasma and eruptive xanthomas are rare.

An increasing number of patients now present with NAFLD, usually identified by their elevated blood transaminase values, but they may also have non-tender hepatomegaly.

11 Management and therapies

The goals of therapy for type 1 or type 2 diabetes mellitus (DM) are to[1,9]

1. eliminate symptoms related to hyperglycemia,
2. reduce or eliminate the long-term microvascular and macrovascular complications of DM and
3. allow the patient to achieve as normal a lifestyle as possible.

To reach these goals, the physician should identify a target level of glycemic control for each patient, provide the patient with the educational and pharmacologic resources necessary to reach this level, and monitor/treat DM-related complications. Symptoms of diabetes usually resolve when the plasma glucose is <11.1 mmol/L (200 mg/dL), and thus most DM treatment focuses on achieving the second and third goals. The care requires a multidisciplinary team. Central to the success of this team are the patient's participation, input, and enthusiasm, all of which are essential for optimal diabetes management.[9]

The role of patient education and community care[5]

The care of diabetes is based on self-management by the patient, who is helped and advised by those with specialized knowledge. The quest for improved glycaemic control has made it clear that whatever the technical expertise applied, the outcome depends on willing cooperation by the patient. This, in turn, depends on an understanding of the risks of diabetes and the potential benefits of glycaemic control and other measures such as maintaining a lean weight, stopping smoking and taking care of the feet. If accurate information is not supplied, misinformation from friends and other patients will take its place. For this reason, the best time to educate the patient is soon after diagnosis. Organized education programmes involve all healthcare workers, including nurse specialists, dieticians and podiatrists, and should include ongoing support and updates wherever possible.

Treatment methods[1]

Treatment methods for diabetes include -

1. dietary/lifestyle modification,
2. oral anti-diabetic drugs and
3. injected therapies.

In new cases of diabetes, adequate glycaemic control can be obtained by diet and lifestyle advice alone in approximately 50%, 20–30% will need oral anti-diabetic medication, and 20–30% will require insulin.

In patients with suspected type 1 diabetes, urgent treatment with insulin is required and prompt referral to a specialist is usually needed. In patients with suspected type 2 diabetes, first-line therapy involves advice about dietary and lifestyle modification.[1] Diet and lifestyle changes are the key to successful treatment of type 2 diabetes, and no amount of medication will succeed where these have failed.[5] Oral anti-diabetic drugs are usually added in those who do not achieve glycaemic targets as a result of dietary and lifestyle modification (within 4–6 weeks[5]), or who have severe symptomatic hyperglycaemia at diagnosis and a high HbA_{1c}. However, the guidelines in some countries are to introduce medication immediately upon diagnosis of diabetes without waiting to assess the impact of diet and lifestyle changes.[1]

In each individual, the regimen adopted is effectively a therapeutic trial and should be reviewed regularly. In parallel with treatment of hyperglycaemia, other risk factors for complications of diabetes need to be addressed, including treatment of hypertension and dyslipidaemia, and advice on smoking cessation.

The importance of lifestyle changes such as undertaking regular physical activity, observing a healthy diet and reducing alcohol consumption should not be underestimated in improving glycaemic control, but many people, particularly the middle-aged and elderly, find them difficult to sustain. Patients should also be encouraged to stop smoking.

Choice of treatment[1]

Regardless of aetiology, the choice of treatment is determined by the adequacy of residual β-cell function. However, this cannot be determined easily by measurement of plasma insulin concentration because a level which is adequate in one patient may be inadequate in another, depending upon sensitivity to insulin.

12 Diet and lifestyle management

The diet for people with diabetes is no different from that considered healthy for everyone.[5] That is, foods made just for diabetics are not needed.[4]
To achieve the recommended composition of diet, food for people with diabetes should be:[4,5]

- low in sugar (though not sugar-free)
- high in starchy carbohydrate (especially foods with a low glycaemic index), i.e. slower absorption
- high in fibre
- low in fat (especially saturated fat)
- moderate protein[4]

Aims of dietary management[1]

- Achieve good glycaemic control
- Reduce hyperglycaemia and avoid hypoglycaemia
- Assist with weight management:
    - Weight maintenance for type 1 diabetes and non-obese type 2 diabetes
    - Weight loss for overweight and obese type 2 diabetes
- Reduce the risk of micro- and macrovascular complications
- Ensure adequate nutritional intake
- Avoid 'atherogenic' diets or those that aggravate complications, e.g. high protein intake in nephropaty.

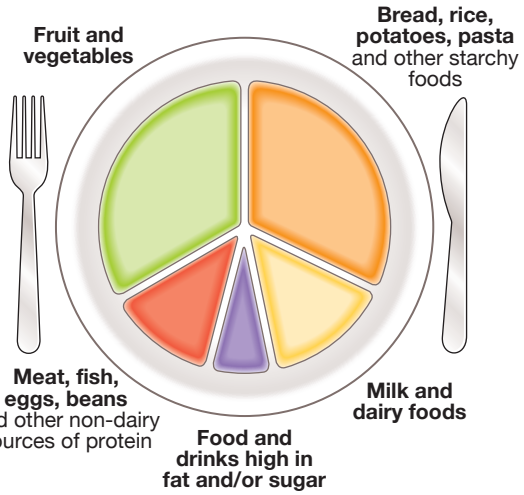


Figure: Proportion of key food groups recommended for a healthy, well-balanced diet.[1]

They should have access to a dietitian at diagnosis, at review and at times of treatment change. Nutritional advice should be tailored to individuals and take account of their age and lifestyle. Many people with type 2 diabetes require dietary advice for achieving weight loss, to include caloric restriction and, in particular, reduced fat intake. Structured education programmes are available for both common types of diabetes.[1]

Carbohydrate

Both the amount and source of carbohydrate determine post-prandial glucose.[1] The glucose peak seen in the blood after eating pasta is much flatter than that seen after eating the same amount of carbohydrate as white potato. Pasta has a lower 'glycaemic index'. Foods with a low glycaemic index prevent rapid swings in circulating glucose, and are thus preferred to those with a higher glycaemic index.[5]

Therefore, the best diet for obese patients with type 2 diabetes is low-carbohydrate diets.[4]

How do low carbohydrate, ketogenic diets (<20g of carbohydrate daily; LCKD) compare with low-glycaemic index, reduced-calorie diet (eg 500kcal/day deficit from weight maintenance diet)?[4]

In one randomized study over 24 weeks, LCKD had greater improvements in HbA_{1c} (–15 vs –5mmol/L), weight (–11kg vs –7kg), and HDL. Diabetes drugs were reduced or eliminated in 95% of LCKD vs 62% of LGID participants.

NB: effects on renal function and mortality are unknown so these diets remain controversial.

Fat

The intake of total fat should be restricted to less than 35% of energy intake, with less than 10% as saturated fat, and 10–20% from monounsaturated fat through consumption of oils and spreads made from olive, rapeseed or groundnut oils.[1]

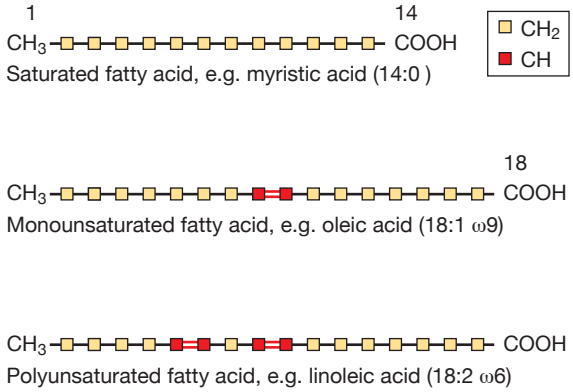


Figure: Schematic representation of fatty acids.[1] Standard nomenclature specifies the number of carbon atoms and indicates the number and position of the double bond(s) relative to the methyl (–CH3, ω) end of the molecule after a colon.

Salt

People with diabetes should follow the advice given to the general population: namely, to limit sodium intake to no more than 6 g daily.[1]

Alcohol

Alcohol is recognised as having both beneficial and harmful effects on cardiovascular disease and this also appears to apply in patients with diabetes. Alcohol can therefore be taken in moderation in diabetes with the aim of keeping within national guidelines relating to recommendations for people without diabetes.

In the UK, the weekly recommended maximum is

- 14 U for women and
- 21 U for men.

Risks

Alcohol can reduce hypoglycaemia awareness and, by suppressing gluconeogenesis, increase hypoglycaemia risk.

Exercise

All patients with diabetes should be made aware of the high calorie content of alcohol and the implications for body weight management, which are often overlooked.

No treatment for diabetes is complete without exercise. All patients with diabetes should be advised to achieve a significant level of physical activity and to maintain this in the long term. Any increase in activity levels is to be encouraged but participation in more formal exercise programmes is best.[1,5]

Supervised and structured exercise programmes may be of particular benefit to people with type 2 diabetes. Several trials have shown that regular exercise reduces the risk of progression to type 2 diabetes by 30–60%, and the lowest long-term morbidity and mortality rates are seen in those with established disease who have the highest levels of cardiorespiratory fitness.[5]

Both aerobic and resistance training improve insulin sensitivity and metabolic control in type 1 and type 2 diabetes, although reported effects on metabolic control are inconsistent.[5]

Patients on insulin or sulphonylureas should be warned that there is an increased risk of hypoglycaemia for up to 6–12 hours following heavy exertion.[5]

Guidelines

Various guidelines exist for physical activity in the general population.

US Department of Health and Human services (2008):

For adults (18–64 years):

1. a weekly minimum of 2.5 hours of moderate-intensity exercise or
2. 75 minutes of vigorous-intensity exercise, or
3. a combination thereof.

The aerobic (moderate-intensity) activity should be performed for at least 10 minutes each time and spread throughout the week, with at least 30 minutes on at least 5 days of the week.

Older adults:

They should also follow these guidelines as far as their abilities allow.

Recently, it has also been suggested that a combination of both aerobic and resistance exercise may lead to greater improvements in glycaemic control.

In type 1 diabetes:

Exercise can increase the risk of hypoglycaemia, so patients should seek specialist advice on taking extra carbohydrate, reducing insulin doses and choosing an injection site.

Glycaemic index[1]

Definition

The glycaemic index (GI) of a carbohydrate-containing food is a measure of the change in blood glucose following its ingestion relative to the rise in blood glucose observed following a liquid oral glucose tolerance test.

Different foods can be ranked by their effect on post-prandial glycaemia.

Consumption of foods with a low GI is encouraged because they produce a slow, gradual rise in blood glucose. Examples include starchy foods such as basmati rice, spaghetti, porridge, noodles, granary bread, and beans and lentils.

However, different methods of food processing and preparation can influence the GI of foods, as can the ripeness of some foods and differences in strains of rice. In addition, while consideration of GI is useful in choosing between types of carbohydrate, it does not address the total amount consumed.

Recent studies suggest short-term (6 months), very low carbohydrate diets (containing as little as 50 g carbohydrate per day – 13% of daily energy) are safe and effective means

of reducing weight and improving glycaemic control. However, high dropout rates and poor adherence suggest that this type of diet is not widely applicable.

Prescribing a diet[5]

Most people find it extremely difficult to modify their eating habits, and repeated advice and encouragement are needed if this is to be achieved.

A diet history is taken, and the diet prescribed should involve the least possible interference with the person's lifestyle. Advice from dieticians is more likely to affect medium-term outcome than advice from doctors.

People taking insulin or oral agents have traditionally been advised to eat roughly the same amount of food (particularly carbohydrate) at roughly the same time each day, so that treatment can be balanced against food intake and exercise.[5] In type 1 diabetes, the development of modern insulin regimens, particularly using insulin analogues or continuous subcutaneous insulin infusion (CSII), has allowed increased flexibility in the timing and choice of carbohydrate intake.[1]

It is now possible to match the amount of carbohydrate in a meal with a dose of short-acting insulin using methods such as Dose Adjustment for Normal Eating (DAFNE), although this is demanding and requires extensive patient education.[1] Knowledgeable and motivated patients with type 1 diabetes, who have feedback from regular blood glucose monitoring, can vary the amount of carbohydrate consumed, or mealtimes, by learning to adjust their exercise pattern and treatment. This is the basis of the DAFNE regimen.[5] This approach enables motivated individuals with type 1 diabetes to achieve and maintain good glycaemic control, while avoiding post-prandial hyper- and hypoglycaemia.[1]

Weight management[1]

In patients with diabetes, weight management is important, as a high percentage of people with type 2 diabetes are overweight or obese, and many anti-diabetic drugs, including insulin, encourage weight gain. Obesity, particularly central obesity with increased waist circumference, also predicts insulin resistance and cardiovascular risk.

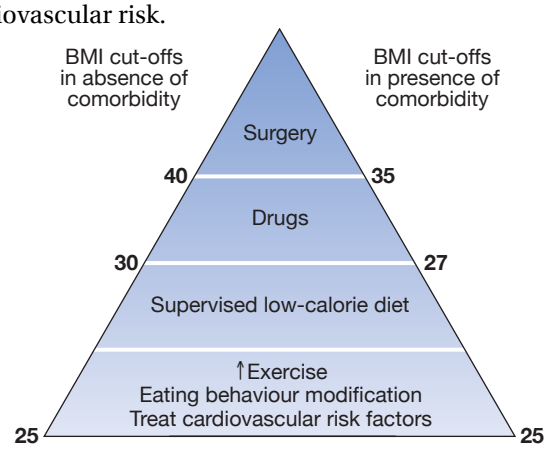


Figure: Therapeutic options for obesity. Relevant comorbidities include type 2 diabetes, hypertension, cardiovascular disease, sleep apnoea, and waist circumference > 102 cm in men or 88 cm in women. This is an approximate consensus of the numerous national guidelines, which vary slightly in their recommendations and are revised every few years.[1]

- Weight loss can be achieved through a reduction in energy intake and an increase in energy expenditure through physical activity.
- Lifestyle interventions or pharmacotherapy for obesity when associated with weight reduction have beneficial effects on HbA_{1c}, but long-term benefits in terms of glycaemic control and microvascular disease have not been adequately assessed.
- More recently, bariatric surgery has been shown to induce marked weight loss in obese individuals with type 2 diabetes and this is often associated with significant improvements in HbA_{1c} and withdrawal of or reduction in diabetes medications.

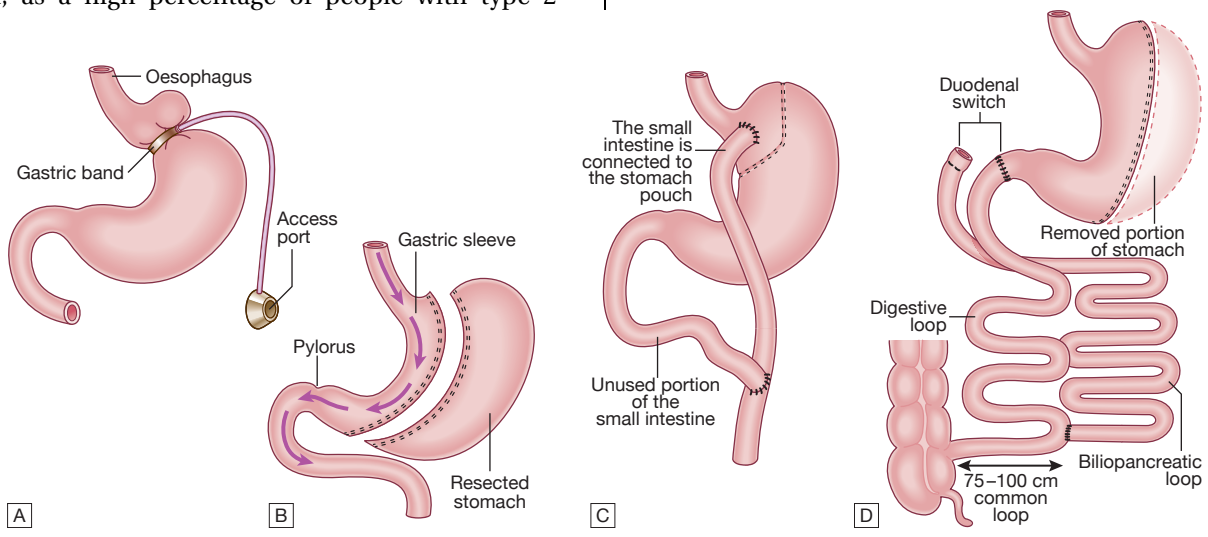


Figure: Bariatric surgical procedures. [A] Laparoscopic banding, with the option of a reservoir band and subcutaneous access to restrict the stomach further after compensatory expansion has occurred. [B] Sleeve gastrectomy. [C] Roux-en-Y gastric bypass. [D] Biliopancreatic diversion with duodenal switch.

Diabetes may improve rapidly after surgery, particularly after gastric bypass, and although this may be attributed to severe energy restriction in the perioperative period, it is possible that increased release of incretin hormones such as glucagonlike peptide (GLP)-1 may contribute to the improvement in glucose control.[1]

Recommended composition of the diet for people with diabetes[1,5]

Component of diet	Recommended % (of energy intake)	How the recommended diet may be achieved
Protein	10-15%	Do not exceed ~1 g/kg ideal body weight/day
Total fat	<35%	Limit: fat/oil in cooking, fried foods, processed meats (burgers, salami, sausages), high-fat snacks (crisps, cake, nuts, chocolate, biscuits, pastry). Encourage: lower-fat dairy products (skimmed milk, reduced-fat cheese, low-fat yoghurt), lean meat
Saturated and transunsaturated fat	<10%	
n-6 polyunsaturated fat	<10%	
n-3 polyunsaturated fat	No absolute quantity recommended.	Encourage: fish, especially oily fish, once or twice weekly. Not recommended: fish oil supplements
Cis-monounsaturated fat	10–20%	(olive oil, avocado)
Total carbohydrate	45-60%	40–60% of total energy intake Encourage: artificial (intense) sweeteners instead of sugar (sugar-free fizzy drinks, squashes and cordials). Limit: fruit juices, confectionery, cake, biscuits
Sucrose	Up to 10%	provided this is eaten in the context of a healthy diet (e.g. fibre-rich breakfast cereals, baked beans)
Fibre		No absolute quantity recommended. Soluble fibre has beneficial effects on glycaemic and lipid metabolism. Insoluble fibre has no direct effects on glycaemic metabolism, but benefits satiety and gastrointestinal health
Vitamins and antioxidants	5 portions per day	Best taken as fruit and vegetables in a mixed diet. There is no evidence for the use of supplements
Alcohol		Not forbidden. Its energy content should be taken into account, as should its tendency to cause delayed hypoglycaemia in those treated with insulin
Salt	<6 g/day	lower in hypertension
The overweight or obese should be encouraged to lose weight by a combination of changes in food intake and physical activity.		

Dietary carbohydrates[1]

Class	Components	Examples	Source
Free sugars	Monosaccharides Disaccharides	Glucose, fructose Sucrose, lactose, maltose	Intrinsic: fruits, milks, vegetables Extrinsic (extracted, refined): beet or cane sucrose, high-fructose corn syrup
Short-chain carbohydrates	Oligosaccharides	Maltodextrins, fructo-oligosaccharides	
Starch polysaccharides	Rapidly digestible Slowly digestible Resistant		Cereals (wheat, rice), root vegetables (potato), legumes (lentils, beans, peas)
Non-starch polysaccharides (NSP, dietary fibre)	Fibrous Viscous	Cellulose Hemicellulose Pectins Gums	Plants
Sugar alcohols		Sorbitol, xylitol	Sorbitol: stone fruits (apples, peaches, prunes) Xylitol: maize, berry fruits Both used as low-calorie sugar alternatives

13 Non-insulin glucose lowering agents

Controlling diabetes is not just a matter of swallowing tablets, and these should never, in general, be prescribed until lifestyle changes have been implemented.[5]

For many years, there were only a few choices of drugs available for type 2 diabetes – the biguanide metformin, the sulphonylureas and insulin. Acarbose was also available but little used in most countries. Since the late 1990s, however, several new classes of agents have been approved for use in type 2 diabetes, with more in development.[1]

Classification of noninsulin glucose-lowering agents[1,9,10,14,15]

Glucose lowering agent		Duration of action (hours)	Max. approved daily dose
Biguanides			
Metformin (IR 500, 850, 1000mg, ER 500, 750, 1000mg)		12	~2g
Insulin secretagogues			
Sulfonylureas	1st generation: Tolbutamide 2nd generation • Glipizide (10mg IR, 10mg XL) • Glimepiride (4mg) • Gliclazide (common in UK, not available in US), • Glibenclamide (common in USA, as glyburide outside USA) (5mg and micronized 6mg)	 16-24 >24 18-24 18-24	 40mg IR, 20mg XL 8mg 40-320mg 20mg, micronized 12mg
Meglitinides (glinides)	Repaglinide (2mg) Nateglinide (120mg)		16mg 360mg
Thiazolidinediones (glitazones)			
Pioglitazone (45mg) Rosiglitazone (4mg) §		24 24	45mg 8mg
α-Glucosidase inhibitors			
Acarbose (100mg) Miglitol (100mg)		3	300mg 300mg
Incretin-based therapies			
DPP-IV (Dipeptidyl peptidase-4) inhibitors (gliptins)	Sitagliptin (100mg) Saxagliptin (5mg) Linagliptin (5mg) Alogliptin (25mg)	>24	100mg 5mg 5mg 25mg
GLP-1 receptor agonists	Exenatide (10 μg pen) Liraglutide (18mg/3mL pen) Albiglutide (50mg pen) Dulaglutide (1.5/0.5mL pen)		20μg 1.8mg 50mg* 1.5mg*
Bile acid sequestrant			
Colesevelam (625mg tab., 1.875g suspension)			3.75g
Dopamine-2 agonists			
Bromocriptine (0.8mg)			4.8mg
SGLT2 (Sodium-glucose cotransporter 2) inhibitors			
Canagliflozin (300mg) Dapagliflozin (10mg) Empagliflozin (25mg)		24 24	300mg 10mg 25mg
Amylin mimetics/agonists			
Pramlintide (120μg pen)			120μg

ER and XL, extended release; IR, immediate release.
*Administered once weekly. §Not licensed in Europe for type 2 diabetes.

Biguanides

Metformin is the only biguanide currently in use and remains the best validated primary treatment for type 2 diabetes.[1,5]

Mechanism of action

A full explanation of the mechanism of action of the biguanides remains elusive, but their primary effect is to activate the enzyme AMP-activated protein kinase (AMPK) and reduce hepatic glucose production.[14]

Metformin acts as a weak inhibitor of mitochondrial respiration, which increases intracellular AMP and reduces ATP. This has direct effects on the flux through gluconeogenesis, and activates the intracellular energy sensor AMP-activated protein kinase (AMPK), leading to multiple beneficial metabolic effects.[1]

The biguanide blood glucose-lowering action does not depend on functioning pancreatic beta cells (insulin independent[1]).

Primary physiological action

Its effect is to reduce the rate of gluconeogenesis, and hence hepatic glucose output, and to increase insulin sensitivity that is insulin-mediated glucose uptake.[1,5] It also has effects on gut glucose uptake and utilisation.[1]

Metformin reduces fasting plasma glucose (FPG) and insulin levels, improves the lipid profile, and promotes modest weight loss.[9]

Advantages

It does not affect insulin secretion, does not induce hypoglycaemia and does not predispose to weight gain. It is thus particularly helpful in the overweight, although normal-weight individuals also benefit, and may be given in combination with sulphonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP4) inhibitors or insulin.

Metformin was as effective as sulphonylurea or insulin in glucose control and the UKPDS (UK Prospective Diabetic Study) reported that metformin therapy decreases the risk of macrovascular (proved unexpectedly beneficial in reducing cardiovascular risk) as well as microvascular disease; this is in contrast to the other therapies, which only modified microvascular morbidity.[5,14] This effect has recently been questioned.[5]

Disadvantages

1. Approximately 25% of patients develop mild gastrointestinal side-effects
    a. diarrhoea,
    b. abdominal cramps,
    c. bloating and
    d. nausea
2. Only 5% are unable to tolerate it even at low dose.[1]

Diarrhoea should never be investigated in a diabetic patient without testing the effect of stopping metformin or changing to a slow-release preparation.[5]

Lactic acidosis has occurred in patients with severe hepatic or renal disease.[5] Lactic acidosis can sometimes occur with metformin therapy. It is more likely to occur in conditions of tissue hypoxia when there is increased production of lactic acid and in renal failure when there is decreased clearance of metformin.[14] A Cochrane review showed little risk of lactic acidosis with standard clinical use, but most clinicians withdraw the drug when serum creatinine exceeds 150 μmol/L.[5]

Metformin interferes with the calcium-dependent absorption of vitamin B_{12}-intrinsic factor complex in the terminal ileum, and vitamin B_{12} deficiency can occur after many years of metformin use. Vitamin B_{12} levels are ~30% lower during metformin treatment.[9] Periodic screening for vitamin B_{12} deficiency should be considered, especially in patients with peripheral neuropathy or macrocytic anemia. Increased intake of calcium may prevent the metformin-induced B_{12} malabsorption.[14]

Clinical use

Metformin works mostly on fasting glucose.[4] It is employed as first-line therapy in all patients who tolerate it, and its use is maintained when additional agents are added as glycaemia deteriorates. It is now widely used as first-line therapy for type 2 diabetes, irrespective of body weight. Metformin is also given increasingly as an adjunct to insulin therapy in obese patients with type 1 diabetes.[1]

Dose

Metformin is usually introduced at low dose (500 mg twice daily[1] after food[4]) to minimise the risk of gastrointestinal side effects.

The usual maintenance dose is 1 g twice daily.[1] An extended-release form is available and may have fewer gastrointestinal side effects.[9]

Although the recommended maximal dosage is 2.55 g daily, little benefit is seen above a total dosage of 2000 mg daily. Common schedules would be 500 mg once or twice daily increased to 1000 mg twice daily. The maximal dosage is 850 mg three times a day.[14]

Contraindications

Kidney, liver, or cardio-respiratory insufficiency; alcoholism.[5,14]

As metformin is cleared by the kidneys, it can accumulate in renal impairment, so the dose should be halved when estimated glomerular filtration rate (eGFR) is 30–45 mL/min, and it should not be used below an eGFR of 30 mL/min.[1]

Its use is also contraindicated in patients with impaired hepatic function and in those who drink alcohol in excess, in whom the risk of lactic acidosis is significantly increased.[1]

Cautions

It should be discontinued, at least temporarily, if any other serious medical condition develops, especially one causing severe shock or hypoxia (eg. MI, sepsis). In such circumstances, treatment with insulin should be substituted if required.[1]

Also discontinue morning before GA, in patients who can take nothing orally and prior to intravascular administration of iodinated contrast agent because of the risk of renal failure and subsequent lactic acidosis. Restart no earlier than 48 hours after test of renal function has shown no deterioration.[4,5,9]

Sulphonylureas

Sulphonylureas are 'insulin secretagogues', i.e. they promote pancreatic β-cell insulin secretion[1] in response to glucose and other secretagogues.[5]

Similar to metformin, the long-term benefits of sulphonylureas in lowering microvascular complications of diabetes were established in the UKPDS.[1]

Mechanism of action

The major action of sulfonylureas is to increase insulin release from the pancreas. They bind to a 140-kDa high-affinity sulfonylurea receptor that causes closure of the pancreatic β-cell ATP-sensitive potassium (K_{ATP}) channel. It inhibits the efflux of K^+ through the channel and results in depolarization. Depolarization opens a voltage-gated calcium channel and results in calcium influx and the release of preformed insulin.[1,14]

Adverse effect

The main adverse effects of sulphonylureas are –

1. weight gain and
2. hypoglycaemia.

The weight gain is not ideal in patients with diabetes who are already overweight or obese, and are best avoided although sulphonylureas are effective treatments in this group.[1,5]

Hypoglycaemia occurs because the closure of K_{ATP} channels brings about unregulated insulin secretion, even with normal or low blood glucose levels.[1] Episodes are generally mild, but fatal hypoglycaemia may occur especially in the elderly. Severe cases should always be admitted to hospital, monitored carefully, and treated with a continuous glucose infusion since some sulphonylureas have long half-lives.[5]

A related isoform of ATP-sensitive potassium channels is present in the myocardium and the brain. All of these agents except glyburide have a low affinity for this isoform. Despite concerns that this agent might affect the myocardial response to ischemia and observational studies suggesting that sulfonylureas increase cardiovascular risk, studies have not shown an increased cardiac mortality with glyburide or other agents in this class.[9,14]

Clinical use

Sulphonylureas are an effective therapy for lowering blood glucose and are often used as an add-on to metformin, if glycaemia is inadequately controlled on metformin alone.[1]

These drugs are cheap and more effective than many other oral agents in achieving short-term (1–3 years) glucose control. They are most effective in individuals with type 2 DM of relatively recent onset (<5 years) who have residual endogenous insulin production and their effect wears off as the β-cell mass declines. First-generation sulfonylureas (chlorpropamide, tolazamide, tolbutamide) have a longer half-life, a greater incidence of hypoglycemia, and more frequent drug interactions, and are no longer used. Second-generation sulfonylureas have a more rapid onset of action and better coverage of the postprandial glucose rise, but the shorter half-life of some agents may require more than once-a-day dosing.[5,9]

They are ineffective in patients without a functional β-cell mass, and are usually avoided in pregnancy.[5]

Dose

The dose–response of all sulphonylureas is steepest at low doses; little additional benefit is obtained when the dose is increased to maximal levels.[1]

Sulfonylureas increase insulin acutely and thus should be taken shortly before a meal; with chronic therapy, though, the insulin release is more sustained.[9]

Glimepiride and glipizide can be given in a single daily dose and are preferred over glyburide, especially in the elderly.[9]

Caution

Most sulfonylureas are metabolized in the liver and are cleared by the kidney. Thus, their use in individuals with significant hepatic or renal dysfunction is not advisable.[5,9]

Some sulfonylureas have significant drug interactions with alcohol and some medications including warfarin, aspirin, ketoconazole, α-glucosidase inhibitors, and fluconazole.[9]

Meglitinides

Meglitinides[1,4,5,9], e.g. repaglinide and nateglinide, are insulin secretagogues. Meglitinides are the non-sulphonylurea moiety of glibenclamide. They are essentially sulphonylurea-like drugs.

Mechanism of action

As with the sulphonylureas, they act via closure of the K^+-ATP channel in the β cells. They are short-acting agents that promote insulin secretion in response to meals.

Their effects are similar to those of the short-acting sulphonylurea tolbutamide but they are much more costly.

Clinical use

Because of their short half-life, these agents are given with each meal or immediately before to reduce meal-related glucose excursions. As they target post-prandial hyperglycaemia, they have a role in those with irregular mealtimes if glycaemic control is poor.

α-glucosidase inhibitors

Postprandial hyperglycemia, secondary to impaired hepatic and peripheral glucose disposal, contributes significantly to the hyperglycemic state in type 2 DM. These drugs, taken just before each meal, reduce postprandial hyperglycemia by delaying glucose absorption; they do not affect glucose utilization or insulin secretion.[9]

Mechanism of action

α-Glucosidase inhibitors reduce glucose absorption by inhibiting the enzyme (disaccharidases[1]) that cleaves oligosaccharides into simple sugars in the intestinal lumen.[4,9]

Acarbose and miglitol are potent inhibitors of glucoamylase, α-amylase, and sucrase but have less effect on isomaltase and hardly any on trehalase and lactase.[14]

Side effects

The main side-effects are flatulence (less if slow dose build-up[4]), abdominal bloating (distension and pain[4]) and diarrhoea.[1] These result from the appearance of undigested carbohydrate in the colon that is then fermented into short-chain fatty acids, releasing gas.[14] They can be reduced somewhat by gradual upward dose titration.[9]

These adverse effects tend to diminish with ongoing use because chronic exposure to carbohydrate induces the expression of α-glucosidase in the jejunum and ileum, increasing distal small intestine glucose absorption and minimizing the passage of carbohydrate into the colon.[14]

Although not a problem with monotherapy or combination therapy with a biguanide, hypoglycemia may occur with concurrent sulfonylurea treatment.[14] If hypoglycemia from other diabetes treatments occurs while taking these agents, the patient should consume glucose (dextrose and not sucrose, whose breakdown may be blocked[14]) because the degradation and absorption of complex carbohydrates will be retarded.[9]

Contraindications

These agents should not be used in individuals with inflammatory bowel disease, gastroparesis, or a serum creatinine >177 µmol/L (2 mg/dL).[9]

Clinical use

This class of agents is not as potent as other oral agents in lowering the HbA_{1c} and modestly improve overall glycaemic control but is unique because it reduces the postprandial glucose rise even in individuals with type 1 DM.[1,9]

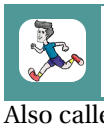
They can be combined with a sulphonylurea.[1] It is an add-on drug, often disappointing![4]

They are used widely in the Far East but infrequently in the UK.[1]

Dose

50mg chewed at start of each meal. Maximum 200mg/8hours.[4]

Therapy should be initiated at a low dose with the evening meal and increased to a maximal dose over weeks to months.[9]



Thiazolidinediones

Also called TZDs, 'glitazones' or PPAR γ agonists.[1]

Mechanism of action[1,9,14]

Thiazolidinediones reduce insulin resistance. They are ligands of PPAR-γ (peroxisome proliferator-activated receptor-gamma), part of the steroid and thyroid superfamily of nuclear receptors (which forms a heterodimer with the retinoid X receptor). These PPAR receptors are found in muscle, fat, and liver (present mainly in adipose tissue). The PPAR- γ receptor is found at highest levels in adipocytes but is expressed at lower levels in many other tissues. PPAR- γ receptors modulate the expression of the genes involved in lipid and glucose metabolism, insulin signal transduction, and adipocyte and other tissue differentiation. Causing reduced hepatic fat accumulation, and promoting fatty acid storage.

Thiazolidinediones increase pre-adipocyte differentiation, resulting in an increase in fat mass and in body weight that is TZDs promote a redistribution of fat from central to peripheral locations.

Observed effects of the thiazolidinediones include –

- increased glucose transporter expression (GLUT 1 and GLUT 4),
- decreased free fatty acid levels,
- decreased hepatic glucose output,
- increased adiponectin and decreased release of resistin from adipocytes, and
- increased differentiation of preadipocytes to adipocytes.
- Thiazolidinediones have also been shown to decrease levels of plasminogen activator inhibitor type 1, matrix metalloproteinase-9, C-reactive protein, and interleukin-6.

TZDs enhance the actions of endogenous insulin, in part directly (in the adipose cells) and in part indirectly (by altering release of 'adipokines', such as adiponectin, which alter insulin sensitivity in the liver). Circulating insulin levels decrease with use of the thiazolidinediones, indicating a reduction in insulin resistance.

Health concerns

TZDs have been prescribed widely since the late 1990s, but recently a number of adverse effects have become apparent and their use has declined.[1]

The prototype of this class of drugs, troglitazone, was withdrawn from the U.S. market after reports of hepatotoxicity and an association with an idiosyncratic liver reaction that sometimes led to hepatic failure.[9]

Rosiglitazone was reported to increase the risk of myocardial infarction and was withdrawn in 2010.[1] Subsequent study failed to confirm these findings, so US restrictions have been lifted while still unavailable in Europe.[14]

Adverse effects

Thiazolidinediones are associated with[9,14] –

- Weight gain (2–3 kg). Weight gain occurs, especially when used in combination with a sulfonylurea or insulin. Some of the weight gain is fluid retention but there is also an increase in total fat mass.
- A small reduction in the hematocrit, and a mild increase in plasma volume.
- Anemia, which might be due to a dilutional effect of increased plasma volume rather than a reduction in red cell mass.
- Peripheral edema and CHF are more common in individuals treated with these agents.
- Loss of bone mineral density and increased atypical extremity bone fractures in women are described for both compounds, which is postulated to be due to decreased osteoblast formation.
- Macular edema is a rare side effect that improves when the drug is discontinued.

Pioglitazone (the only remaining agent in this class in Europe) does not appear to increase the risk of myocardial infarction but it does exacerbate[1]

- cardiac failure by causing fluid retention,
- increases the risk of bone fracture and
- possibly increased risk of bladder cancer.

Clinical use and advantages

TZDs don't increase plasma insulin concentrations so, hypoglycaemia does not occur. The combination of a thiazolidinedione and metformin has the advantage of not causing hypoglycemia.[1,14]

These drugs also have some additional effects apart from glucose lowering.[9,14]

- Pioglitazone lowers triglycerides and increases HDL cholesterol without affecting total cholesterol and low-density lipoprotein (LDL) cholesterol.
- Rosiglitazone increases total cholesterol, HDL cholesterol, and LDL cholesterol but does not have significant effect on triglycerides.
- These drugs have been shown to improve the biochemical and histologic features of nonalcoholic fatty liver disease.
- They seem to have a positive effect on endothelial function: pioglitazone reduces neointimal proliferation after coronary stent placement, and rosiglitazone has been shown to reduce microalbuminuria.

Pioglitazone can be very effective at lowering blood glucose in some patients and appears more effective in insulin-resistant patients. In addition, it has a beneficial effect in reducing fatty liver and NASH. Pioglitazone is usually added to metformin with or without sulphonylurea therapy. It may be given with insulin therapy, when it can be very effective, but the combination of insulin and TZDs markedly increases fluid retention and risk of cardiac failure, so should be used with caution.[1]

Contraindication[4,9,14]

1. Past or present CCF and with NYHA class III or IV cardiac status
2. Active liver disease or, pretreatment elevation of alanine aminotransferase (ALT) 2.5 times greater than normal
3. Osteoporosis

Caution[4,9]

- FDA recommends measurement of liver function tests prior to initiating therapy and do LFT every 8 weeks for 1 year, stop if ALT up >3 fold.
- Monitor weight, and stop if weight gain or oedema

Thiazolidinediones have been shown to induce ovulation in premenopausal women with polycystic ovary syndrome. Women should be warned about the risk of pregnancy because the safety of thiazolidinediones in pregnancy is not established.

DPP-4 inhibitors

Mechanism of action

The 'gliptins', or DPP-4 inhibitors, inhibit degradation of native GLP-1 and thus enhance the incretin effect and therefore enhance concentrations of endogenous GLP-1 and GIP.[1] These enhance the incretin effect.[1,9]

The enzyme dipeptidyl peptidase-4 (DPP4), which is widely expressed on the cell surface of endothelial cells and some lymphocytes, degrades a wide range of peptides (not GLP-1 specific). It rapidly inactivates glucagon-like peptide-1 (GLP-1) as this is released into the circulation.

Dipeptidyl peptidase-4 inhibitors increase insulin secretion and lower glucagon secretions, and inhibition of this enzyme thus potentiates the effect of endogenous GLP-1 secretion.[5] The levels of GLP-1 action in the patient are greater with the GLP-1 receptor agonists than with DPP-4 inhibitors.[9]

DPP-4 inhibitors promote insulin secretion in the absence of hypoglycemia or weight gain and appear to have a preferential effect on postprandial blood glucose.[9]

Adverse effects

The main side-effect is nausea, and there have been occasional reports of acute pancreatitis.[5]

Although, initial concerns about the pancreatic side effects of GLP-1 receptor agonists and DPP-IV inhibitors (pancreatitis, possible premalignant lesions) appear to be unfounded.[9]

Clinical use

These drugs are very well tolerated and are weight-neutral.[1] They have a moderate effect in lowering blood glucose and do not cause hypoglycaemia.[5]

They are most effective in the early stages of type 2 diabetes, when insulin secretion is relatively preserved, and are currently recommended for second-line use in combination with metformin or a sulphonylurea.[5]

They may be an alternative to insulin (if eGFR >50), eg if obese (they decrease appetite)[4]

Their place in the management of type 2 diabetes has yet to be fully established and cost remains a constraint. Although the short-term safety record is good, DPP4 is widely distributed in the body, and the long-term consequences of inhibition of this enzyme in other tissues are unknown.[5]

Caution

Reduced doses should be given to patients with renal insufficiency.[9]

GLP-1 receptor agonists

The GLP-1 receptor agonists have a similar structure to GLP-1 but have been modified to resist breakdown by DPP-4.[1]

Mechanism of action

They enhance the incretin effect.

Exenatide, a synthetic version of a peptide initially identified in the saliva of the Gila monster (exendin- 4), is an analogue of GLP-1. Unlike native GLP-1, which has a half-life of >5 min, differences in the exenatide amino acid sequence render it resistant to the enzyme that degrades GLP-1 (dipeptidyl peptidase IV [DPP-IV]). Thus, exenatide has prolonged GLP-1-like action and binds to GLP-1 receptors found in islets, the gastrointestinal tract, and the brain.[9]

Liraglutide, another GLP-1 receptor agonist, is almost identical to native GLP-1 except for an amino acid substitution and addition of a fatty acyl group (coupled with a γ-glutamic acid spacer) that promote binding to albumin and plasma proteins and prolong its half-life.[9]

GLP-1 receptor agonists increase glucose-stimulated insulin secretion, suppress glucagon, and slow gastric emptying, thus blunting the postprandial rise in plasma glucose. These agents do not promote weight gain; in fact, most patients experience modest weight loss and appetite suppression.[5,9]

Advantage

The key advantage over the DPP-4 inhibitors: because the GLP-1 activity achieved is supra-physiological, it delays gastric emptying and, at the level of the hypothalamus, decreases appetite. Thus, injectable GLP-1 analogues lower blood glucose and result in weight loss – an appealing therapy, as the majority of patients with type 2 diabetes are obese.[1] They work well in 70% but have limited benefit in 30% of those treated.[5]

Agents in this class do not cause hypoglycaemia.

Whether GLP-1 receptor agonists enhance beta cell survival, promote beta cell proliferation (does promote in rodents), or alter the natural history of type 2 DM in human is not known.[5,9]

Disadvantage

These agents are not orally active and have to be given by subcutaneous injection[1] and their main clinical disadvantage is the need for subcutaneous injection.[5]

Because GLP-1 receptor agonists slow gastric emptying, they may influence the absorption of other drugs.[9]

Adverse effects

Unwanted effects include nausea, acute pancreatitis and acute kidney injury.[5]

Clinical use

At present, they are used as an alternative to insulin, particularly in the overweight. A once-weekly version of exenatide has been developed.[5]

Doses

Currently available GLP-1 receptor agonists include[1]

- Exenatide (5μg subcutaneously bd ¼h before meal, (>6h apart; avoid if eGFR <30; increase after >4 weeks to 10μg bd[4]),
- Exenatide MR (once weekly) and
- Liraglutide (once daily).

SGLT2 inhibitors

The sodium/glucose transporter 2 (SGLT2) is a sodium-dependent glucose transport protein, which is expressed almost exclusively in the proximal, convoluted tubule in the kidney. Whose function is to reabsorb glucose from the renal filtrate and restore it to the circulation. Its activity thus determines the renal threshold for glucose, which normally averages around 10 mmol/L.[5,9]

Mechanism of action

Normally glucose is filtered freely in the renal glomeruli and reabsorbed in the proximal tubules. These agents lower the blood glucose by selectively inhibiting this co-transporter. This inhibits glucose reabsorption, lowers the renal threshold for glucose, and leads to increased urinary glucose excretion. It results in approximately 25% of the filtered glucose not being reabsorbed. Thus, the glucose-lowering effect is insulin independent and not related to changes in insulin sensitivity or secretion.[1,9]

This has the effect of removing both glucose and calories from the circulation, thus lowering blood glucose and facilitating weight loss. Small reductions in systolic blood pressure have also been reported.[5]

Adverse effects

Due to the increased urinary glucose, urinary or vaginal infections are more common, including an increase in genital candidiasis and a small increase in urinary tract infections.[5,9] Also the diuretic effect can lead to reduced intravascular volume.[9]

Advantages

This approach to therapy has the potential advantage of lowering glucose by a mechanism not mediated by insulin. One recent study showed a decrease in cardiovascular mortality when empagliflozin was added to standard care.[9]

Clinical use

Because these agents are the newest class to treat type 2 DM, clinical experience is limited and he most appropriate position for SGLT2 inhibitors in the therapy of type 2 diabetes has yet to be established.[1,9]

Other agents

Bile acidbinding resins[9]

Bile acids, by signaling through nuclear receptors, may have a role in metabolism. Bile acid metabolism is abnormal in type 2 DM.

They are bile acid sequestrant and cholesterol-lowering drug, that is approved as an antihyperglycemic therapy for persons with type 2 diabetes who are taking other medications or have not achieved adequate control with diet and exercise.[14]

The most common side effects are gastrointestinal (constipation, abdominal pain, and nausea).

Bile acid–binding resins can increase plasma triglycerides and should be used cautiously in patients with a tendency for hypertriglyceridemia.

The role of this class of drugs in the treatment of type 2 DM is not yet defined.

Bromocriptine[9]

A formulation of the dopamine receptor agonist bromocriptine (Cycloset) has been approved by the FDA for the treatment of type 2 DM. However, its role in the treatment of type 2 DM is uncertain.

Pramlintide[14]

Pramlintide is an islet amyloid polypeptide (IAPP, amylin) analog. IAPP is a 37-amino-acid peptide present in insulin secretory granules and secreted with insulin. It has approximately 46% homology with the calcitonin gene-related peptide and physiologically acts as a negative feedback on insulin secretion.

At pharmacologic doses, IAPP reduces glucagon secretion, slows gastric emptying by a vagally medicated mechanism, and centrally decreases appetite.

Pramlintide is approved for use in insulin-treated type 1 and type 2 patients who are unable to achieve their target postprandial blood glucose levels.

Pramlintide is injected immediately before eating; dosages range from 15 to 60 μg subcutaneously for type 1 patients and from 60 to 120 μg for type 2 patients. Therapy with this agent should be initiated at the lowest dosage and titrated upward.

Because of the risk of hypoglycemia, concurrent rapid- or short-acting mealtime insulin dosages should be decreased by 50% or more. Pramlintide should always be injected by itself using a separate syringe; it cannot be mixed with insulin.

The major adverse effects of pramlintide are hypoglycemia and gastrointestinal symptoms, including nausea, vomiting, and anorexia.

Since the drug slows gastric emptying, recovery from hypoglycemia can be problematic because of the delay in absorption of fast-acting carbohydrates.

Selected patients with type 1 diabetes who have problems with postprandial hyperglycemia can use pramlintide effectively to control the glucose rise especially in the setting of a high-carbohydrate meal.

The drug is not that useful in type 2 patients who can instead use the GLP-1 receptor agonists.

Intestinal enzyme inhibitors[5]

Intestinal enzyme inhibitors include acarbose, a sham sugar that competitively inhibits α- glucosidase enzymes situated in the brush border of the intestine, reducing absorption of dietary carbohydrate. Undigested starch may then enter the large intestine, where it will be broken down by fermentation. Abdominal discomfort, flatulence and diarrhoea can result, and dosage needs careful adjustment to avoid these side-effects.

Orlistat[5]

Orlistat is a lipase inhibitor that reduces the absorption of fat from the diet. It benefits diabetes indirectly by promoting weight loss in patients under careful dietary supervision on a low-fat diet. This is necessary to avoid unpleasant steatorrhoea.

Effects of drugs used in the treatment of type 2 diabetes[1]

	Insulin	Sulphonylureas and meglitinides	Metformin	Acarbose	Thiazolidinediones (glitazones)	DPP-4 inhibitors (gliptins)	GLP-1 receptor agonists	SGLT2 inhibitors
Fasting blood glucose	↓	↓	↓	↘	↓	↓	↓	↓
Post-prandial blood glucose	↓	↓	↓	↓	↓	↓	↓	↓
Plasma insulin	↑	↑	↓	↓	↓	↑	↑	↓
Body weight	↑	↑	→	→	↑	→	↓	↓
Risk of hypoglycaemia	++	+	–	–	–	–	–	–
Tolerability	Good	Good	Moderate	Moderate	Moderate	Good	Moderate	Limited experience

(DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1; SGLT2 = sodium and glucose transporter 2)

Properties of available glucose-lowering agents that may guide individualized treatment choices in patients with type 2 diabetes[9,10]

Class	Compound (s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Contraindications
Oral						
Biguanides*	• Metformin	Activates AMP-kinase (? other)	↓ Hepatic glucose production	• Extensive experience • Rare hypoglycemia • ↓ CVD events[a] • Relatively higher A_{1C} efficacy	• Gastrointestinal side effects (diarrhea, abdominal cramping, nausea) • Vitamin B12 deficiency • Lactic acidosis risk (rare)	eGFR 30 mL/min/1.73 m^2, acidosis, hypoxia, dehydration, CHF, radiographic contrast studies, hospitalized patients etc.
Sulfonylureas*	2nd generation • Glyburide • Glipizide • Glimepiride	Closes K_{ATP} channels on β-cell plasma membranes	↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk[a] • Relatively higher A_{1C} efficacy • Short onset of action[9] • ↓ postprandial glucose[9]	• Hypoglycemia • ↑ Weight	Renal/liver disease
Meglitinides (glinides) ***	• Repaglinide • Nateglinide	Closes K_{ATP} channels on β -cell plasma membranes	↑ Insulin secretion	• ↓ Postprandial glucose excursions • Dosing flexibility	• Hypoglycemia • ↑ Weight • Frequent dosing schedule	Renal/liver disease
TZDs***	• Pioglitazone‡ • Rosiglitazone§	Activates the nuclear transcription factor PPAR-γ	• ↑ Insulin sensitivity • ↑ glucose utilization[9]	• Rare hypoglycemia • Relatively higher A_{1C} efficacy • Durability • ↓ Triglycerides (pioglitazone) • ? ↓ CVD events (PROactive[d], pioglitazone) • ↓ Risk of stroke and MI in patients without diabetes and with insulin resistance and history of recent stroke or TIA (pioglitazone)	• ↑ Weight • Peripheral edema/heart failure • Bone fractures • ↑ LDL-C (rosiglitazone) • Macular edema[9]	CHF, liver disease
α-Glucosidase inhibitors**	• Acarbose • Miglitol	Inhibits intestinal α-glucosidase	Slows intestinal carbohydrate digestion/absorption	• Rare hypoglycemia • ↓ Postprandial glucose excursions • ? ↓ CVD events in prediabetes[b] • Nonsystemic	• Generally modest A_{1C} efficacy • GI side effects (flatulence, diarrhea) • Frequent dosing schedule	Renal/liver disease
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)	Reduced dose with renal disease; one associated with increase heart failure risk; possible association with ACE inhibitor–induced angioedema
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 A_{1C} efficacy • Constipation • ↑ Triglycerides • May ↓ absorption of other medications	
Dopamine-2 agonists***	• Bromocriptine (quick release)§	Activates dopaminergic receptors	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• Rare hypoglycemia • ? ↓ CVD events (Cycloset Safety Trial)	• Modest A_{1C} efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis	

...cont.

Class	Compound (s)	Cellular mechanism(s)	Primary physiological action(s	Advantages	Disadvantages	Contraindications
Oral (cont.)						
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[c]) • Insulin secretion and action independent[9]	• Genitourinary infections • Polyuria • Volume depletion/dehydration/ hypotension/dizziness • ↑ LDL-C • ↑ Creatinine (transient) • DKA, urinary tract infections leading to urosepsis, pyelonephritis	Limited clinical experience; moderate renal insufficiency
Parenteral						
GLP-1 receptor agonists***	• Exenatide • Exenatide extended release • 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 • ↑risk of hypoglycemia with insulin secretagogues[9]	Renal disease, agents that also slow GI motility; medullary carcinoma of thyroid
Amylin mimetics***	• Pramlintide§	Activates amylin receptors	• ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety	• ↓ Postprandial glucose excursions • ↓ Weight	• Modest A_{1C} efficacy • GI side effects (nausea/vomiting) • Hypoglycemia unless insulin dose is simultaneously reduced • Injectable • Frequent dosing schedule • Training requirements	Agents that also slow GI motility
Insulins****	• Rapid-acting analogs – Lispro, Aspart, Glulisine, Inhaled insulin • Short-acting - Human Regular • Intermediate-acting - Human NPH • Basal insulin analogs	Activates insulin receptors	• ↑ Glucose disposal • ↓ Hepatic glucose production • Suppresses ketogenesis	• Nearly universal response • Theoretically unlimited efficacy • ↓ Microvascular risk[a]	• Hypoglycemia • Weight gain • Training requirements • Patient and provider reluctance • Injectable (except inhaled insulin) • Pulmonary toxicity (inhaled insulin)	

Cost of agents: *Low, **Moderate, ***High. ****Variable

[a] UKPDS, UK Prospective Diabetes Study. Cycloset trial of quick-release bromocriptine
[b] STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus
[c] EMPA-REG OUTCOME, (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
[d] PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events

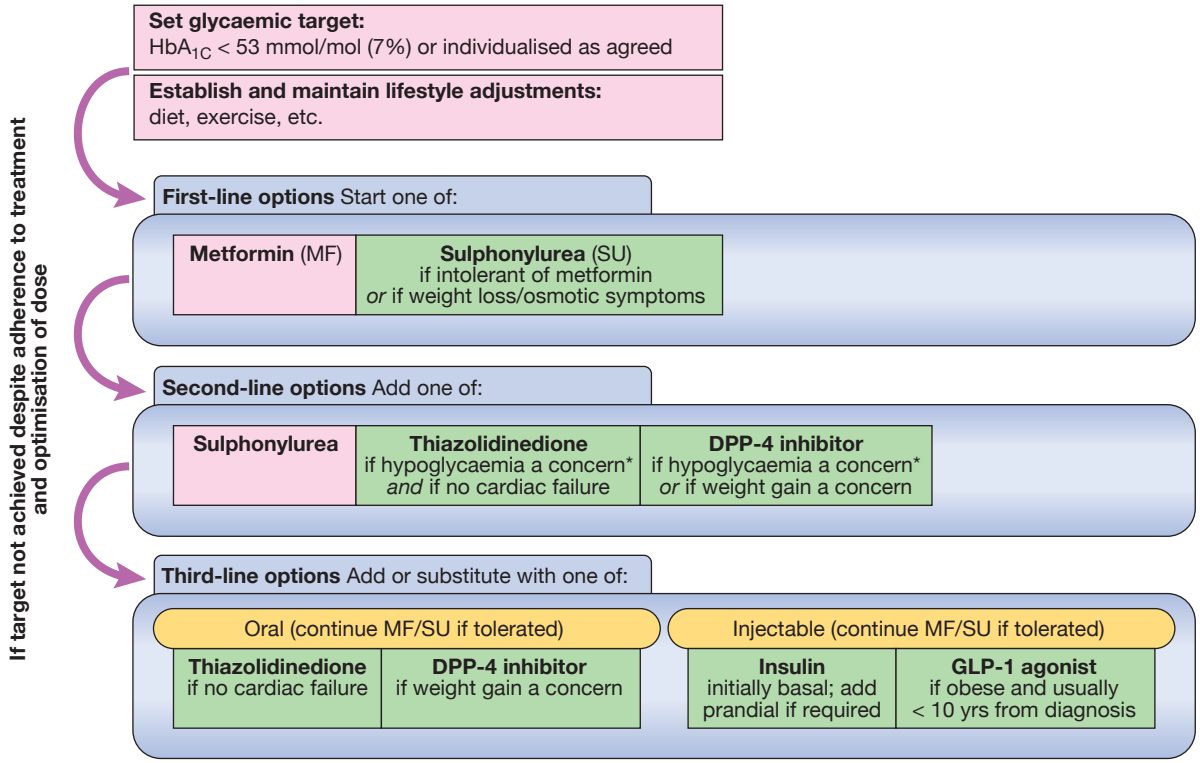
GIP, glucose-dependent insulinotropic peptide; HDL-C, HDL cholesterol; IRIS, Insulin Resistance Intervention After Stroke Trial; PPAR-g, peroxisome proliferator–activated receptor g;

‡Initial concerns regarding bladder cancer risk are decreasing after subsequent study.
§Not licensed in Europe for type 2 diabetes.

14 Principles of therapy
Guidelines

This makes for an exciting time in diabetes pharmacotherapy, but exactly how, when and in what order these agents should be used remains uncertain. The older drugs are cheaper and have established benefits for reducing microvascular disease; they are therefore usually recommended as first-line therapy. Use of the newer drugs is not supported by evidence for reduction in microvascular disease (because the trials have not yet been done) and they are much more expensive, so are often reserved for later therapy after failure of metformin and sulphonylureas.[1]

One guideline which follows these principles is shown below[1] –



*Management of hyperglycaemia in type 2 diabetes. Purple boxes indicate the usual approach, and green boxes show alternatives which are selected according to individual circumstances. *Hypoglycaemia risk includes driving, occupational hazards and risk of falls. Note that SGLT2 inhibitors were not available when this guideline was produced. (DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide 1). Adapted from SIGN 116*

However, this does not necessarily reflect the optimum positioning of these newer drugs. As large trials, which aim to establish their cardiovascular benefit, report in the next few years, these recommendations may change dramatically.

Another recommended pharmacological therapy adapted by ADA is shown below[10] –

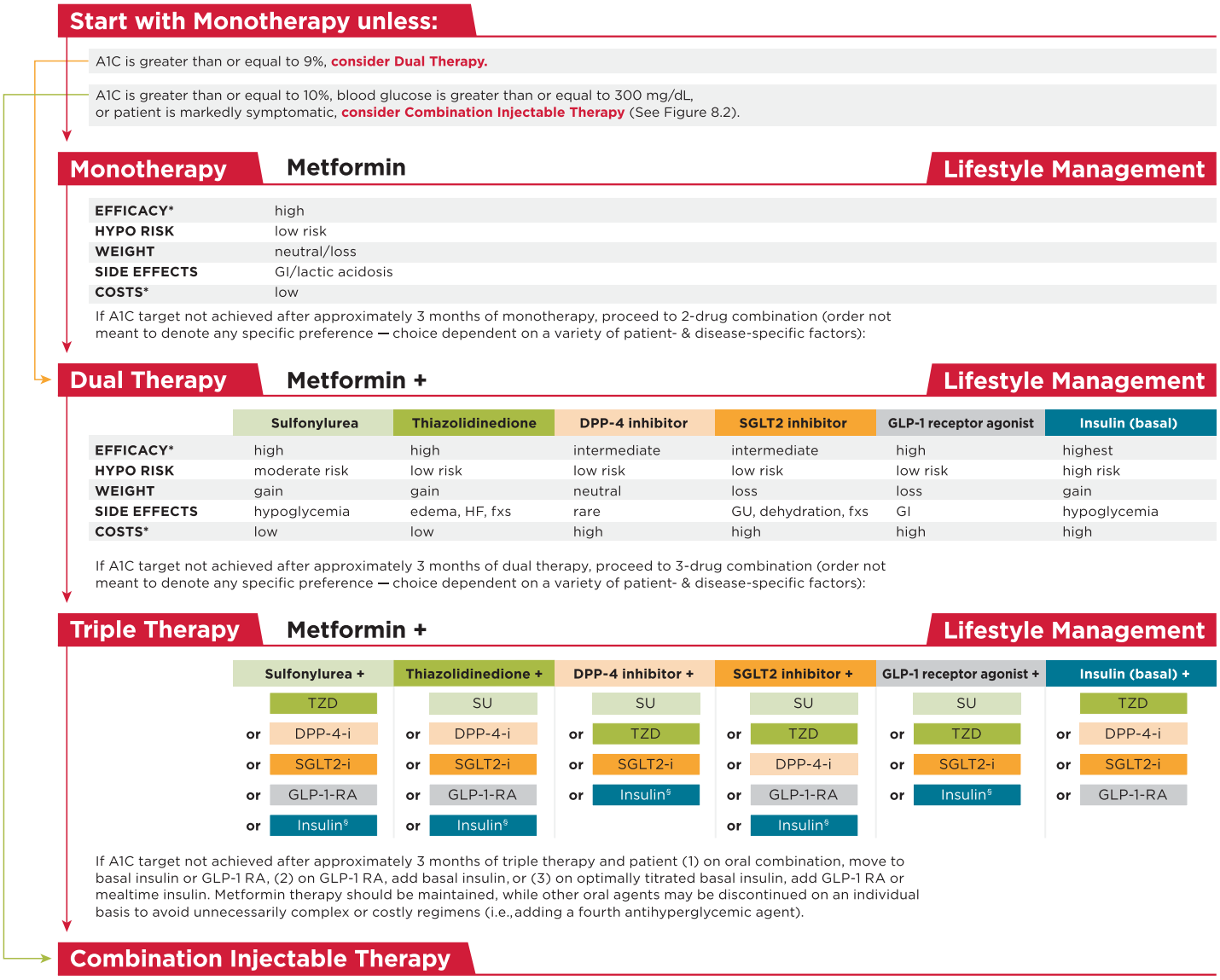


Figure: Antihyperglycemic therapy in type 2 diabetes: general recommendations. The order in the chartwas determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic therapy 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.

15 Insulin Characteristics and treatment

Insulin is found in every vertebrate and the key parts of the molecule show few species differences. Small differences in the amino acid sequence may alter the antigenicity of the molecule. Until the 1980s, insulin was obtained by extraction and purification from pancreata of cows (bovine insulin) and pigs (porcine insulin), and some patients still prefer to use animal insulins. Recombinant DNA technology enabled large-scale production of human insulin. This is produced by adding a DNA sequence coding for insulin or proinsulin into cultured yeast or bacterial cells. More recently, the amino acid sequence of insulin has been altered to produce analogues of insulin, which differ in their rate of absorption from the site of injection.[1,5]

The pharmacokinetics and dose forms of these various insulin preparations[1,9,10,14]

Preparations		Onset (h)	Peak (h)	Effective duration (h)	Dose form/ product
Rapid-acting insulin analogs					
	Lispro	<0.25	0.5–1.5	2–4	U-100 vial, U-100 3 mL cartridges, U-100 prefilled pen, U-200 prefilled pen
	Aspart	<0.25	0.5–1.5	2–4	U-100 vial, U-100 3 mL cartridges, U-100 prefilled pen
	Glulisine	<0.25	0.5–1.5	2–4	U-100 vial, U-100 prefilled pen
	Inhaled insulin				Inhalation cartridges
Short-acting					
	Human Regular (Soluble)	0.5-1.0	2–3	3–6	U-100 vial
Intermediate-acting					
	Human NPH	2–4	4–10	10–16	U-100 vial, U-100 prefilled pen
Concentrated Human Regular insulin					
	U-500 Human Regular insulin				U-500 vial, U-500 prefilled pen
Basal insulin analogs (Long acting)					
	Glargine	2–4	–[a]	20–24	U-100 vial, U-100 prefilled pen, U-300 prefilled pen
	Detemir	1–4	–[a]	12–24[b]	U-100 vial, U-100 prefilled pen
	Degludec				U-100 prefilled pen, U-200 prefilled pen
Premixed products					
	NPH/Regular 70/30	0.5–1	Duel[c]	10-16	U-100 vial, U-100 prefilled pen
	Protimine/Lispro 50/50	<0.25	Duel[c]	10-16	U-100 vial, U-100 prefilled pen
	Protimine/Lispro 75/25	<0.25	Duel[c]	10-26	U-100 vial, U-100 prefilled pen
	Protimine/Aspart 70/30	<0.25	Duel[c]	15-18	U-100 vial, U-100 prefilled pen

[a]Glargine and Detemir have minimal peak activity
[b]Duration is dose dependent (shorter at lower dose)
[c]Duel: two peak – one at 2–3 h and second one several hours later

Commercial insulin preparations differ in a number of ways, such as differences in the recombinant DNA production techniques, amino acid sequence, concentration, solubility, and the time of onset and duration of their biologic action.[14]

Principal types[14]

Four principal types of injected insulins are available:

1. rapid-acting, with very fast onset and short duration;
2. short-acting, with rapid onset of action;
3. intermediate-acting; and
4. long-acting, with slow onset of action.

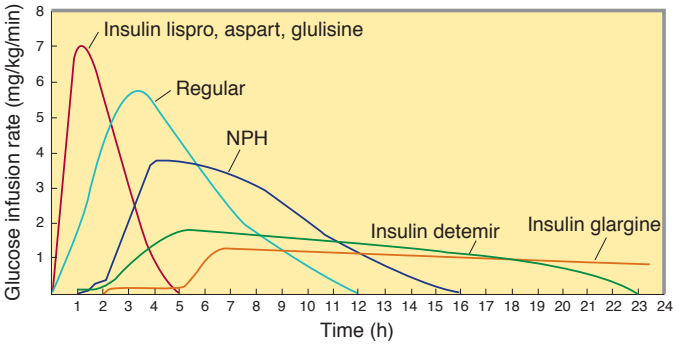


Figure: Extent and duration of action of various types of insulin as indicated by the glucose infusion rates (mg/kg/min) required to maintain a constant glucose concentration. The durations of action shown are typical of an average dose of 0.2–0.3 U/kg. The durations of regular and NPH insulin increase considerably when dosage is increased.[14]

Injected rapid-acting and short-acting insulins are dispensed as clear solutions at neutral pH and contain small amounts of zinc to improve their stability and shelf life.

Injected intermediate-acting NPH insulins have been modified to provide prolonged action and are dispensed as a turbid suspension at neutral pH with protamine in phosphate buffer (neutral protamine Hagedorn [NPH] insulin).

Insulin glargine and insulin detemir are clear, soluble long-acting insulins.

Rapid-acting insulin[14]

The rapid-acting insulins permit more physiologic prandial insulin replacement because their rapid onset and early peak action more closely mimic normal endogenous prandial insulin secretion than regular insulin, and they have the additional benefit of allowing insulin to be taken immediately before the meal without sacrificing glucose control.[14]

Insulin analogues such as the rapid-acting insulins (insulin lispro, insulin aspart and insulin glulisine) enter the circulation more rapidly than human soluble insulin, and also disappear more rapidly.[5]

Advantage

Their duration of action is rarely more than 4–5 hours, which decreases the risk of late postmeal hypoglycemia.

Short acting insulin analogues have been engineered to dissociate more rapidly following injection without altering the biological effect.[5]

The injected rapid-acting insulins have the lowest variability of absorption (approximately 5%) of all available commercial insulins (compared with 25% for regular insulin and 25% to over 50% for long-acting analog formulations and intermediate insulin, respectively).

They are the preferred insulins for use in continuous subcutaneous insulin infusion devices.

For the most part, insulin analogues have replaced soluble and isophane insulins, especially for people with type 1 diabetes, because they allow more flexibility and convenience. Unlike soluble insulin, which should be injected 30 minutes before eating, rapid-acting insulin analogues can be administered immediately before, during or even after meals. Long acting insulin analogues are better able than isophane insulin to maintain 'basal' insulin levels for up to 24 hours, so need only be injected once daily. Despite these pharmacokinetic benefits, the impact of insulin analogues on glycaemic control and adverse events appears to be minor.[1]

Insulin lispro

Insulin lispro, the first monomeric insulin analog to be marketed, is produced by recombinant technology wherein two amino acids near the carboxyl terminal of the B chain have been reversed in position: Proline at position B28 has been moved to B29, and lysine at position B29 has been moved to B28.

Reversing these two amino acids does not interfere in any way with insulin lispro's binding to the insulin receptor, its circulating half-life, or its immunogenicity, which are similar to those of human regular insulin. However, the advantage of this analog is its very low propensity—in contrast to human insulin—to self-associate in antiparallel fashion and form dimers.

To enhance the shelf life of insulin in vials, insulin lispro is stabilized into hexamers by a cresol preservative.

When injected subcutaneously, the drug quickly dissociates into monomers and is rapidly absorbed with onset of action within 5–15 minutes and peak activity as early as 1 hour. The time to peak action is relatively constant, regardless of the dose.

Insulin aspart

Insulin aspart is created by the substitution of the B28 proline with a negatively charged aspartic acid. This modification reduces the normal ProB28 and GlyB23 monomer-monomer interaction, thereby inhibiting insulin self-aggregation.

Its absorption and activity profile are similar to those of insulin lispro, and it is more reproducible than regular insulin, but it has binding properties, activity, and mitogenicity characteristics similar to those of regular insulin in addition to equivalent immunogenicity.

Insulin glulisine

Insulin glulisine is formulated by substituting a lysine for asparagine at B3 and glutamic acid for lysine at B29. Its absorption, action, and immunologic characteristics are similar to those of other injected rapid-acting insulins.

After high-dose insulin glulisine interaction with the insulin receptor, there may be downstream differences in IRS-2 pathway activation relative to native insulin. The clinical significance of such differences is unclear.

Short-acting insulin

Human insulin is absorbed slowly, reaching a peak 60–90 minutes after subcutaneous injection, and its action tends to persist after meals, predisposing to hypoglycaemia.[5]

Regular insulin is a short-acting soluble crystalline zinc insulin that is now made by recombinant DNA techniques to produce a molecule identical to human insulin.

Pharmacokinetics

In high concentrations, eg, in the vial, regular insulin molecules self-aggregate in antiparallel fashion to form dimers that stabilize around zinc ions to create insulin hexamers. The hexameric nature of regular insulin causes a delayed onset and prolongs the time to peak action.[14] Absorption is delayed because soluble insulin is in the form of stable hexamers (six insulin molecules around a zinc core) and needs to dissociate to monomers or dimers before it can enter the circulation.[5]

After subcutaneous injection, the insulin hexamers are too large and bulky to be transported across the vascular endothelium into the bloodstream. As the insulin depot is diluted by interstitial fluid and the concentration begins to fall, the hexamers break down into dimers and finally monomers.

This results in three rates of absorption of the injected insulin, with the final monomeric phase having the fastest uptake out of the injection site.

Disadvantage

The clinical consequence is that when regular insulin is administered at mealtime, the blood glucose rises faster than the insulin with resultant early postprandial hyperglycemia and an increased risk of late postprandial hypoglycemia. Therefore, regular insulin should be injected 30–45 or more minutes before the meal to minimize the mismatching.

Clinical use

Short-acting, regular soluble insulin is the only type that should be administered intravenously because the dilution causes the hexameric insulin to immediately dissociate into monomers.

It is particularly useful for – [5,14]

- intravenous therapy in the management of diabetic ketoacidosis,
- when the insulin requirement is changing rapidly, such as after surgery, in labour, during acute infections or during medical emergencies.

It can also be used for pre-meal injection in multiple-dose regimens and in patients using insulin pumps.[5]

Disadvantage

As with all older insulin formulations, the duration of action as well as the time of onset and the intensity of peak action increase with the size of the dose. Clinically, this is a critical issue because the pharmacokinetics and pharmacodynamics of small doses of regular and NPH insulins differ greatly from those of large doses.

The delayed absorption, dose-dependent duration of action, and variability of absorption (~ 25%) of regular human insulin frequently results in a mismatching of insulin availability with need, and its use is declining.

Also, the short-acting analogues have little effect on overall glucose control in most patients, mainly because improved postprandial glucose is balanced by higher levels before the next meal. A Cochrane review has concluded that there is little evidence of their benefit in type 2 diabetes.[5]

Intermediate-acting and long-acting insulins

The action of human insulin can be prolonged by the addition of zinc or protamine derived from fish sperm. The most widely used form is NPH (isophane insulin), which has the advantage that it can be premixed with soluble insulin to form stable mixtures (biphasic insulins); the combination of 30% soluble with 70% NPH is most widely used. Long-acting analogues have their structure modified to delay absorption or to prolong their duration of action.[5]

Although popular and widely used, these insulins are much more expensive than, and have little demonstrated advantage over, human NPH, especially in the management of type 2 diabetes, although they are useful in those on intensified therapy or with troublesome hypoglycaemia. NICE advises that insulin analogues should be reserved for those who fail to respond well to human NPH insulin.[5]

NPH insulin

The duration of action of short-acting, unmodified insulin ('soluble' or 'regular' insulin), which is a clear solution, can be extended by the addition of [1]–

1. protamine and zinc at neutral pH (isophane or NPH insulin) or
2. excess zinc ions (lente insulins).

– These modified 'depot' insulins are cloudy preparations.

NPH (neutral protamine Hagedorn, or isophane) insulin is an intermediate-acting insulin whose absorption and onset of action are delayed by combining appropriate amounts of insulin and protamine so that neither is present in an uncomplexed form ("isophane").

After subcutaneous injection, proteolytic tissue enzymes degrade the protamine to permit absorption of insulin.

NPH insulin is usually mixed with regular, lispro, aspart, or glulisine insulin and given two to four times daily for insulin replacement.

The dose regulates the action profile; specifically, small doses have lower, earlier peaks and a short duration of action with the converse true for large doses.

The action of NPH is highly unpredictable, and its variability of absorption is over 50%. The clinical use of NPH is waning because of its adverse pharmacokinetics combined with the availability of long-acting insulin analogs that have a more predictable and physiologic action.

Insulin glargine

Insulin glargine is a soluble, "peakless" (ie, having a broad plasma concentration plateau), long-acting insulin analog.

This product was designed to provide reproducible, convenient, background insulin replacement.

The attachment of two arginine molecules to the B-chain carboxyl terminal and substitution of a glycine for asparagine at the A21 position created an analog that is soluble in an acidic solution but precipitates in the more neutral body pH after subcutaneous injection.[14] Insulin glargine is soluble in the vial as a slightly acidic (pH 4) solution but precipitates at subcutaneous pH, thus prolonging its duration of action.[5]

Individual insulin molecules slowly dissolve away from the crystalline depot and provide a low, continuous level of circulating insulin.

Insulin glargine has a slow onset of action (1–1.5 hours) and achieves a maximum effect after 4–6 hours. This maximum activity is maintained for 11–24 hours or longer.

Glargine is usually given once daily, although some very insulin-sensitive or insulin-resistant individuals benefit from split (twice a day) dosing.

To maintain solubility, the formulation is unusually acidic (pH 4.0), and insulin glargine should not be mixed with other insulins. Separate syringes must be used to minimize the risk of contamination and subsequent loss of efficacy.

The absorption pattern of insulin glargine appears to be independent of the anatomic site of injection, and this drug is associated with less immunogenicity than human insulin in animal studies.

Insulin detemir

This insulin is the most recently developed long-acting insulin analog.

fatty acid 'tail' that allows it to bind reversibly to serum albumin, and its slow dissociation from the bound state prolongs its duration of action.

Insulin detemir has the most reproducible effect of the intermediate- and long-acting insulins, and its use is associated with less hypoglycemia than NPH insulin.

Insulin detemir has a dose-dependent onset of action of 1–2 hours and duration of action of more than 12 hours.

It is given twice daily to obtain a smooth background insulin level.

Insulin degludec[5]

Insulin degludec is a newer, long-term insulin that has proved non-inferior to insulin glargine, with a small reduction in nocturnal hypoglycaemia.

Inhaled insulin[5]

The first inhaled insulin was withdrawn from the market in 2007 on the grounds of limited clinical demand, although lung cancer was also observed. A new formulation (Afrezza®) received FDA approval in July 2014.

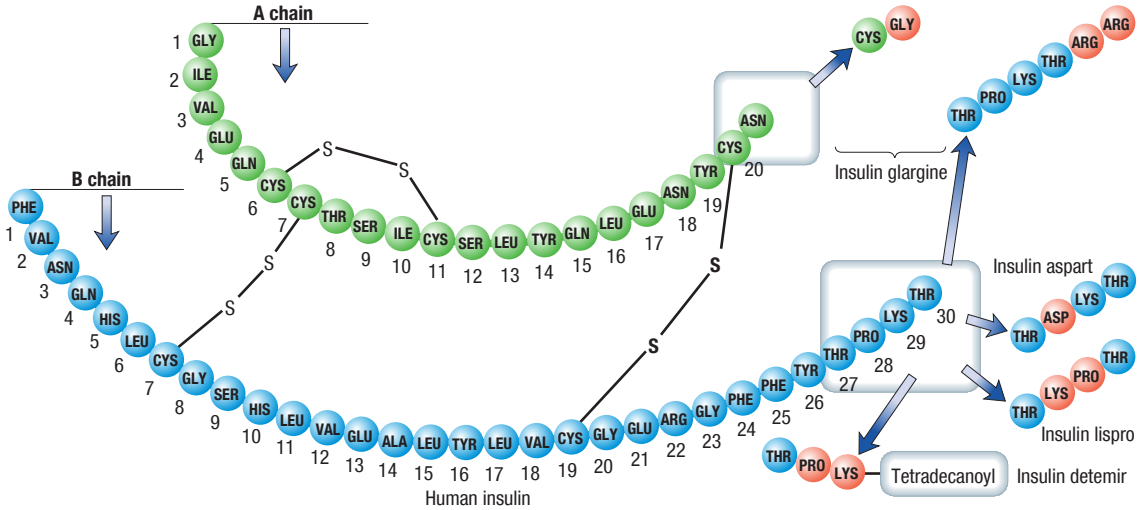


Figure: Amino acid structure of human insulin.[5] Modification of human insulin produces rapid-acting insulins, of which two examples (lispro and aspart) are shown, and long-acting insulins (glargine and detemir).

- ***Lispro** is created by reversing the order of the amino acids proline and lysine in positions 28 and 29 of the B chain.*
- ***Aspart** is a similar analogue created by replacing proline at position 28 of the B chain with an aspartic acid residue.*
- ***Glargine** is created by replacing asparagine in position 21 of the A chain with a glycine residue and adding two arginines to the end of the B chain.*
- ***Detemir** discards threonine in position 30 of the B chain and adds a fatty acyl chain to lysine in position B29.*

Mixtures of insulins

Because intermediate-acting NPH insulins require several hours to reach adequate therapeutic levels, their use in diabetic patients usually requires supplements of rapid-or short-acting insulin before meals.

For convenience, these are often mixed together in the same syringe before injection. Insulin lispro, aspart, and glulisine can be acutely mixed (ie, just before injection) with NPH insulin without affecting their rapid absorption.[14] These are useful for patients who have difficulty mixing insulins, but are inflexible as the individual components cannot be adjusted independently. They need to be resuspended by shaking the vial several times before administration.[1]

However, premixed preparations have thus far been unstable. To remedy this, intermediate insulins composed of isophane complexes of protamine with insulin lispro and insulin aspart have been developed. These intermediate insulins have the same duration of action as NPH insulin and have been designated as –

- "NPL" (neutral protamine lispro) and
- "NPA" (neutral protamine aspart)

The FDA has approved premixed formulations are –

- 75%/25% NPL/insulin lispro and
- 70%/30% NPA/insulin aspart.

Additional ratios are available abroad.

Fixed-mixture insulins also have altered pharmacodynamic profiles, such that the peak insulin action and time to peak effect are significantly reduced compared with injecting the same insulins separately.[1]

Insulin glargine and detemir must be given as separate injections. They are not miscible acutely or in a premixed preparation with any other insulin formulation.

Premixed formulations of 70%/30% NPH/regular continue to be available. These preparations have all the limitations of regular insulin, namely, highly dose-dependent pharmacokinetic and pharmacodynamic profiles, and variability in absorption.

Concentration of insulins

All insulins in the USA, Canada and in most countries, the concentration in available formulations has been standardised at 100 U/mL (U100).[1,4,14]

A limited supply of U500 regular human insulin is available for use in rare cases of severe insulin resistance in which larger doses of insulin are required.[14]

Insulin delivery systems

Insulin delivery systems are[14] –

1. Standard delivery by subcutaneous injection
2. Portable pen injectors
3. Continuous subcutaneous insulin infusion devices (CSII, Insulin pumps) and
4. Inhaled insulin

In most patients, insulin is injected subcutaneously several times a day. Other routes of administration (intravenous and intraperitoneal) are reserved for specific circumstances. Clinical trials with intrapulmonary (inhalation), transdermal and oral insulins are ongoing but as yet none has proven commercially viable.[1]

Subcutaneous multiple dose insulin therapy[1]

Even though most injections are virtually painless, patients are understandably apprehensive and treatment begins with a lesson in injection technique. Slim adults and children usually use a 31-gauge 6- mm needle and fatter adults a 30-gauge 8-mm needle.[5]

Sites

In most patients, insulin is injected subcutaneously several times a day into the –

- anterior abdominal wall,
- upper arms,
- outer thighs and
- buttocks.

Rate of absorption

The rate of absorption of insulin may be influenced by –

- insulin formulation,
- site, depth and volume of injection (absorption is more rapid from the abdomen than from the arm, and is slowest from the thigh[5]),
- skin temperature (warming)[1], subcutaneous blood flow[5],
- local massage and
- exercise.

Side effects and caution

- Accidental intramuscular injection often occurs in children and thin adults.
- The injection site should be changed regularly to prevent areas of lipohypertrophy (fatty lumps).[5]
- Absorption is delayed from areas of lipohypertrophy at injection sites, which results from the local trophic action of insulin.
- Once absorbed into the blood, insulin has a half-life of just a few minutes. It is removed mainly by the liver and also the kidneys, so plasma insulin concentrations are elevated in patients with liver disease or renal failure. Rarely, the rate of clearance can be affected by binding to insulin antibodies (induced by use of animal insulins).

Procedure of subcutaneous insulin administration

- Needle sited at right angle to the skin
- Subcutaneous (not intramuscular) injection
- Delivery devices: glass syringe (requires re-sterilisation), plastic syringe (disposable), pen device (reusable, some disposable), infusion pump

CSII, Open loop system[1,5,14]

Continuous subcutaneous insulin infusion (CSII) devices are external open-loop pumps for insulin delivery.

'Open-loop' systems are battery-powered portable pumps providing continuous subcutaneous (CSII), intraperitoneal or intravenous infusion of insulin without reference to the blood glucose concentration. Usually a small pump is strapped around the waist that infuses a constant trickle of insulin via a needle in the subcutaneous tissues.

The rate of insulin infusion is variable; it can be programmed to match the patient's diurnal variation in requirements and then manually boosted at mealtimes.

This approach is particularly useful in the overnight period, since the basal overnight infusion rate can be programmed to fit each patient's needs.

In practice, the 'loop' is closed by the patient performing blood glucose estimations, and the use of these devices requires a high degree of patient motivation. These increasingly sophisticated systems can achieve excellent glycaemic control but widespread therapeutic use is limited by cost.

Disadvantages include the nuisance of being attached to a gadget, skin infections, the risk of ketoacidosis if the flow of insulin is broken (since these patients have no protective reservoir of injected depot insulin), and cost.

Infusion pumps should only be used by specialized centres able to offer a round-the-clock service to their patients. This form of treatment has revolutionized the lives of some people with type 1 diabetes.

The 'Artificial Pancreas' project aims to close the loop by using miniaturised glucose sensors to communicate wirelessly with the insulin pump, which would automatically adjust its rate, but this has not yet reached widespread clinical practice.

Treatment with insulin

Type 1 diabetes

ADA recommendations[10] –

- Most people with type 1 diabetes should be treated with multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion.
- Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk.

Type 2 diabetes

ADA recommendations[10] –

- Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes who are symptomatic and/or have A_{1C} ≥10% (86 mmol/mol) and/or blood glucose levels ≥300 mg/dL (16.7 mmol/L).
- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A_{1C} target after 3 months, add a second oral agent, a glucagon-like peptide 1 receptor agonist, or basal insulin.
- For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed.

The great majority of patients presenting over the age of 40 will have type 2 diabetes but clinicians should be alert for the occasional type 1 patient presenting late. Most patients on tablets will eventually require insulin and it is helpful to explain this from the outset.[5]

NICE recommends NPH as the initial insulin to use in type 2 diabetes, and metformin is a useful adjunct in those able to tolerate it. NPH insulin at night, together with metformin during the day, is initially as effective as multidose insulin regimens in controlling glucose levels and is less likely to promote weight gain. Addition of a morning dose of insulin may become necessary to control postprandial hyperglycaemia. Twice-daily injections of pre-mixed soluble and NPH (biphasic isophane) insulin are widely used and effective. More aggressive treatment, with multiple injections or continuous infusion pumps, is increasingly used in younger patients with type 2 diabetes.[5]

Insulin treatment in special circumstances

- Diabetic ketoacidosis
- Hyperosmolar hyperglycemic syndrome

Insulin dosing regimens

In healthy individuals, a sharp increase in insulin occurs after meals; this is superimposed on a constant background of secretion.[5]

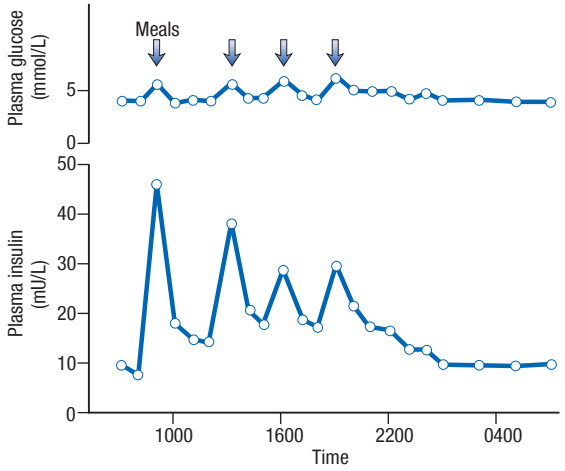


Figure: Glucose and insulin profiles in normal subjects.[5]

Insulin therapy attempts to reproduce this pattern but ideal control is difficult to achieve for four reasons[5]:

1. In normal subjects, insulin is secreted directly into the portal circulation and reaches the liver in high concentration; about 50% of the insulin produced by the pancreas is cleared on first passage through the liver. By contrast, insulin injected subcutaneously passes into the systemic circulation before reaching the liver. Insulin-treated patients therefore have lower portal levels of insulin and higher systemic levels relative to the physiological situation.
2. Subcutaneous soluble insulin takes 60–90 min to achieve peak plasma levels, so it is slower to reach its peak, and slower to leave the circulation.
3. The absorption of subcutaneous insulin into the circulation is variable.
4. Basal insulin levels are constant in healthy people but injected insulin invariably peaks and declines, with resulting swings in metabolic control in those with diabetes.

No insulin regimen reproduces the precise insulin secretory pattern of the pancreatic islet. However, the most physiologic regimens entail more frequent insulin injections, greater reliance on short-acting insulin, and more frequent capillary plasma glucose measurements.[9]

The choice of regimen depends on[5] –

1. the desired degree of glycaemic control,
2. the severity of underlying insulin deficiency,
3. the patient's lifestyle, and
4. his or her ability to adjust the insulin dose.

Twice-daily administration

Twice-daily administration of a short-acting and intermediate-acting insulin (usually soluble and isophane insulins), given in combination before breakfast and the evening meal, is the simplest regimen and is still used commonly in many countries.[1]

- Morning: 2/3rd of the total daily requirement. (short-acting to intermediate-acting = 1 : 2)
- Before evening meal: Remaining 1/3rd (~ 1: 1)[1,9]

Disadvantage[9]

- The drawback to such a regimen is that it forces a rigid schedule on the patient, in terms of daily activity and the content and timing of meals.
- Although it is simple and effective at avoiding severe hyperglycemia, it does not generate near-normal glycemic control in individuals with type 1 DM.
- If the patient's meal pattern or content varies or if physical activity is increased, hyperglycemia or hypoglycemia may result.
- Moving the long-acting insulin from before the evening meal to bedtime may avoid nocturnal hypoglycemia and provide more insulin as glucose levels rise in the early morning (so-called dawn phenomenon).

Adjustments[9]

The insulin dose in such regimens should be adjusted based on SMBG (self-monitoring of blood glucose) results with the following general assumptions:

1. the fasting glucose is primarily determined by the prior evening long-acting insulin;
2. the pre-lunch glucose is a function of the morning short-acting insulin;
3. the pre-supper glucose is a function of the morning long-acting insulin; and
4. the bedtime glucose is a function of the pre-supper, short-acting insulin.

Clinical use[9]

This is not an optimal regimen for the patient with type 1 DM, but is sometimes used for patients with type 2 DM.

Multiple injection regimens

Multiple-component insulin regimens refer to the combination of basal insulin and bolus insulin (preprandial short-acting insulin).[9] Multiple injection regimens (intensive insulin therapy) are popular, with short-acting insulin being taken before each meal, and intermediate- or long-acting insulin being injected once or twice daily (basal-bolus regimen).[1]

A multiple-injection regimen with short-acting insulin and a longer-acting insulin at night is appropriate for most younger patients.[5]

Examples[9]

One such regimen, consists of

- basal insulin with glargine or detemir and
- preprandial lispro, glulisine, or insulin aspart.

The insulin aspart, glulisine, or lispro dose is based on individualized algorithms that integrate the preprandial glucose and the anticipated carbohydrate intake.

Meal component of the preprandial insulin dose[9]

To determine the meal component of the preprandial insulin dose, the patient uses an insulin-to-carbohydrate ratio. A common ratio for type 1 DM is –

- 1–1.5 units/10 g of carbohydrate (but this must be determined for each individual).

To this insulin dose is added the supplemental or correcting insulin based on the preprandial blood glucose. To calculate that –

- one formula uses 1 unit of insulin for every 2.7 mmol/L [50 mg/dL] over the preprandial glucose target;
- another formula uses [body weight in kg] × [blood glucose – desired glucose in mg/dL]/1500).

An alternative multiple-component insulin regimen consists of

- bedtime NPH insulin,
- a small dose of NPH insulin at breakfast (20–30% of bedtime dose), and
- preprandial short-acting insulin.

Other variations of this regimen are in use.

Disadvantages[9]

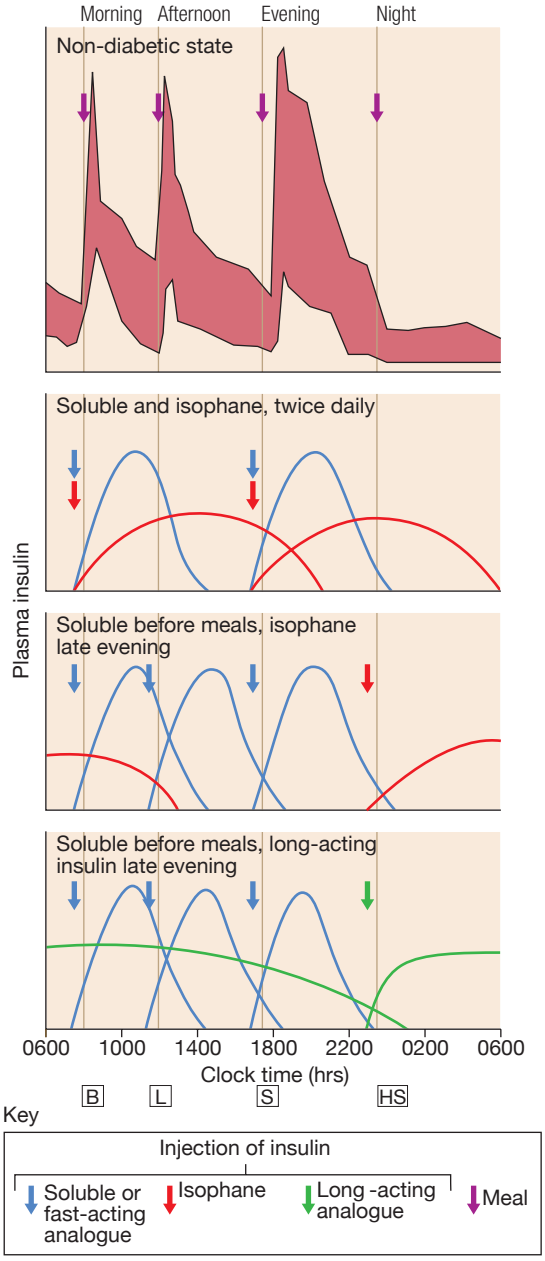
- NPH has a significant peak, making hypoglycemia more common.
- Frequent SMBG (more than three times per day) is absolutely essential for these types of insulin regimens.

Advantages[5]

- The insulin and the food go together, so that meal times and sizes can vary without greatly disturbing metabolic control.
- The flexibility is of great value to patients who have busy jobs, work shifts and travel regularly.
- Strict glucose control from diagnosis in type 1 diabetes prolongs β-cell function, resulting in better glucose levels and less hypoglycaemia.
- Target blood glucose values should normally be 4–7 mmol/L before meals and 4–10 mmol/L after meals, assuming that this can be achieved without troublesome hypoglycaemia.

Caution[5]

Some recovery of endogenous insulin secretion may occur over the first few months (the 'honeymoon period') in type 1 patients and the insulin dose may need to be reduced or even stopped for a period. Requirements rise thereafter.



Figure[1,9]: Profiles of plasma insulin associated with different insulin regimens. [B] breakfast, [L] lunch, [S] supper, [HS] bedtime. The schematic profiles are compared with the insulin responses (mean ± one standard deviation) observed in non-diabetic adults shown in the top panel (shaded area). These are theoretical patterns of plasma insulin and may differ considerably in magnitude and duration of action between individuals.

When to use insulin analogues[5]

Hypoglycaemia between meals and particularly at night is the limiting factor for many patients on multiple-injection regimens. The more expensive rapid-acting insulin analogues are a useful substitute for soluble insulin in some patients, and reduce the frequency of nocturnal hypoglycaemia due to reduced carry-over effect from the daytime.

They are often used on grounds of convenience, since patients can inject shortly before meals, but overall control is unchanged if standard insulins are injected at the same time.

Guide to adjusting insulin dosage according to blood glucose test results[5]

Time	Blood glucose persistently too high	Blood glucose persistently too low
Before breakfast	Increase evening long-acting insulin	Reduce evening long-acting insulin
Before lunch	Increase morning short-acting insulin	Reduce morning short-acting insulin or increase mid-morning snack
Before evening meal	Increase morning long-acting insulin or lunch short-acting insulin	Reduce morning long-acting insulin or lunch short-acting insulin or increase mid-afternoon snack
Before bed	Increase evening short-acting insulin	Reduce evening short-acting insulin

Clinical use[1]

Type 1 diabetes
Most people with type 1 diabetes require two or more injections of insulin daily.

Type 2 diabetes
In type 2 diabetes, insulin is usually initiated as a once-daily long acting insulin, either alone or in combination with oral hypoglycaemic agents. However, in time, more frequent insulin injections are usually required.

Complications of insulin therapy

Complications of insulin therapy are[1] –

- Hypoglycaemia (most importatnt)
- Weight gain
- Peripheral oedema (insulin treatment causes salt and water retention in the short term)
- Insulin antibodies (with animal insulins)
- Local allergy (rare)
- Lipohypertrophy or lipoatrophy at injection sites

A common problem is fasting hyperglycaemia ('the dawn phenomenon'), which arises through a combination of the normal circadian rhythm and release of counter-regulatory hormones (growth hormone and cortisol) during the later part of the night, as well as diminishing levels of overnight isophane insulin.

Hypoglycaemia during insulin treatment[5]

This is the most common complication of insulin therapy and limits what can be achieved with insulin treatment. It is a major cause of anxiety for patients and relatives. It results from an imbalance between injected insulin and a patient's normal diet, activity and basal insulin requirement. The times of greatest risk are before meals, during the night and during exercise. Irregular eating habits, unusual exertion and alcohol excess may precipitate episodes; other cases appear to be due simply to variation in insulin absorption.

Injection site[5]

- Shallow injections result in intradermal insulin delivery and painful, reddened lesions or even scarring.
- Injection site abscesses occur but are extremely rare.
- Fatty lumps, known as lipohypertrophy, may occur as the result of overuse of a single injection site with any type of insulin.

Immunopathology of insulin therapy

At least five molecular classes of insulin antibodies may be produced in diabetics during the course of insulin therapy: IgA, IgD, IgE, IgG, and IgM. There are two major types of immune disorders in these patients:[14]

1. Insulin allergy and
2. Insulin resistance

Insulin allergy[14]
Local allergic responses sometimes occur early in therapy but usually resolve spontaneously.[5] Insulin allergy, an immediate type hypersensitivity, is a rare condition in which local or systemic urticaria results from histamine release from tissue mast cells sensitized by anti-insulin IgE antibodies.
In severe cases, anaphylaxis results but they are exceptionally rare.
Because sensitivity is often to noninsulin protein contaminants, the human and analog insulins have markedly reduced the incidence of insulin allergy, especially local reactions.

Immune insulin resistance
A low titer of circulating IgG anti-insulin antibodies that neutralize the action of insulin to a negligible extent develops in most insulin-treated patients. Rarely, the titer of insulin antibodies leads to insulin resistance and may be associated with other systemic autoimmune processes such as lupus erythematosus.[14] Insulin resistance associated with antibodies directed against the insulin receptor has been reported in patients with acanthosis nigricans.[5]
The most common cause of mild insulin resistance is obesity.[5]
Occasional unstable patients require massive insulin doses, sometimes with a fluctuating requirement. Some patients benefit from use of U500-strength insulin, which allows them to inject the same dose of insulin in one fifth of the usual volume.[5]

Weight gain[5]

Many patients show weight gain on insulin treatment, especially if the insulin dose is increased inappropriately, but this can, to some extent, be overcome by an emphasis on the need for diet and exercise, with the addition of metformin. Patients who are in poor control when insulin is started are more likely to gain weight.

16 Transplantation: Whole-pancreas and pancreatic islet

Whole-pancreas transplantation[1,5]

Whole-pancreas transplantation is carried out in a small number of patients with diabetes each year and has been performed for some 30 years, usually in diabetic patients who require immunosuppression for a kidney transplant.

Surgical advances have greatly improved the outcome of this procedure. In experienced hands, graft function lasts longer with considerable improvement in quality of life.

Patient survival is better in those who receive simultaneous pancreas and kidney grafts, mainly because of the delay involved in waiting for a pancreas to become available following renal transplantation.

There is some evidence of protection against or reversal of some complications of diabetes, but this comes at the cost of long-term immunosuppression. Also, it presents problems relating to exocrine pancreatic secretions.

While results are steadily improving, they remain less favourable than for renal transplantation.

At present, the procedure is usually undertaken only –

1. In patients with end-stage renal failure who require a combined pancreas/kidney transplantation and
2. In whom diabetes control is particularly difficult, e.g. because of recurrent hypoglycaemia.

Islet transplantation[1,5]

Islet transplantation is performed by harvesting pancreatic islets from cadavers (two or three pancreata are usually needed); these are then injected into the portal vein and seed themselves into the liver.

This form of treatment had limited success for many years but improved treatment protocols have now achieved more promising results.

The main indication for islet transplantation is disabling hypoglycaemia.

Progress is being made towards meeting the needs of supply, purification and storage of islets, but the problems of transplant rejection, and of destruction by the patient's autoantibodies against β cells, remain and the main disadvantage is the need for powerful immunosuppressive therapy, with its associated costs and complications.

Nevertheless, the development of methods of inducing tolerance to transplanted islets and the potential use of stem cells means that this may still prove the most promising approach in the long term.

17 Patient education and Self assessment

Educating patients

It is essential that people with diabetes understand their disorder and learn to handle all aspects of their management as comprehensively and quickly as possible. Ideally, this can be achieved by a multidisciplinary team (doctor, dietitian, specialist nurse and podiatrist[1] and fellow patients (peer advisers)[4]) in the outpatient setting.

Randomized trials show that group learning from fellow patients is better at lowering HbA_{1c} than well-run diabetic clinics: we doctors are not all that important![4] Those requiring insulin need to learn how to measure doses of insulin accurately with an insulin syringe or pen device, how to inject, and how to adjust the dose on the basis of blood glucose values and in relation to factors such as exercise, illness and episodic hypoglycaemia.

They must therefore acquire a working knowledge of diabetes, be familiar with the symptoms of hypoglycaemia, and have ready access to medical advice when the need arises.

Information should be provided about driving (national statutory regulations and practical safety measures).

Diabetes and driving[1]

- Licensing regulations vary considerably between countries. In the UK, diabetes requiring insulin therapy or any complication that could affect driving should be declared to the Driver and Vehicle Licensing Agency; ordinary driving licences are 'period-restricted' for insulin-treated drivers; and vocational licences (large goods vehicles and public service vehicles) may be granted but require very strict criteria to be met
- The main risk to driving performance is hypoglycaemia. Visual impairment and other complications may occasionally cause problems
- Insulin-treated diabetic drivers should:
  - Check blood glucose before driving and 2-hourly during long journeys
  - Keep an accessible supply of fast-acting carbohydrate in the vehicle
  - Take regular snacks or meals during long journeys
  - Stop driving if hypoglycaemia develops
  - Refrain from driving until at least 45 mins after treatment of hypoglycaemia (delayed recovery of cognitive function)
  - Carry identification in case of injury

Self-assessment of glycaemic control

In people with type 2 diabetes there is not usually a need for regular self-assessment of blood glucose, unless the patient is treated with insulin, or at risk of hypoglycaemia while taking sulphonylureas.

Blood glucose testing can be used for self-education (i.e. demonstrating how different food and exercise regimes affect blood glucose), and may be useful in acute illness.

Blood glucose targets vary according to individual circumstances, but, in general, pre-meal values between 4 and 7 mmol/L (72 and 126 mg/dL) and 2-hour post-meal values between 4 and 8 mmol/L represent optimal control.

Insulin-treated patients should be taught how to monitor their own blood glucose using capillary blood glucose meters. Immediate knowledge of blood glucose levels can be used by patients to guide their insulin dosing and to manage exercise and illness. This can be supplemented with blood testing for ketones when blood glucose is high and/or during intercurrent illness.

Urine testing for glucose is not recommended because variability in renal threshold means that some patients with inadequate glycaemic control will not find glucose in their urine.

Long-term supervision of diabetes

Diabetes is a complex disorder which progresses in severity with time, so people with diabetes should be seen at regular intervals for the remainder of their lives, either at a specialist diabetic clinic or in primary care where facilities are available and staff are trained in diabetes care.

A checklist for follow-up visits is given below -

How to review a patient in the diabetes clinic[1]

Lifestyle issues

- General health
- Work or school
- Smoking
- Alcohol intake
- Stress or depression
- Sexual health
- Exercise

Body weight and BMI

Blood pressure

- Individualised target of 130–140/70–80 mmHg, depending on risk factors and presence of nephropathy

Urinalysis

- Analyse fasting specimen for glucose, ketones, albumin (both macro- and micro-albuminuria)

Biochemistry

- Renal, liver and thyroid function
- Lipid profile and estimated 10-yr cardiovascular risk to guide need for lipid-lowering therapy

Glycaemic control

- Glycated haemoglobin (HbA_{1c}); individualised target between 48 and 58 mmol/mol (6.5 and 7.5%)
- Inspection of home blood glucose monitoring record (if carried out by patient)

Hypoglycaemic episodes

- Number and cause of severe (requiring assistance for treatment) events and frequency of mild (self-treated) episodes and biochemical hypoglycaemia
- Awareness of hypoglycaemia
- Driving advice

Assessment of injection sites if insulin-treated

Eye examination

- Visual acuities (near and distance)
- Ophthalmoscopy (with pupils dilated) or digital photography

Examination of lower limbs and feet

- Assessment of foot risk

The frequency of visits is variable, ranging from weekly during pregnancy to annually in the case of patients with well-controlled type 2 diabetes.

Therapeutic goals

The target HbA_{1c} depends on the individual patient. Early on in diabetes (i.e. patients managed by diet or one or two oral agents), a target of 48 mmol/mol (6.5%) or less may be appropriate. However, a higher target of 58 mmol/mol (7.5%) may be more appropriate in older patients with pre-existing cardiovascular disease, or those treated with insulin and therefore at risk of hypoglycaemia.

In general, the benefits of lower target HbA_{1c} (primarily a lower risk of microvascular disease) need to be weighed against any increased risks (primarily hypoglycaemia in insulin-treated patients).

Type 2 diabetes is usually a progressive condition (Fig. 21.7), unless there are major diet and lifestyle changes, so that there is usually a need to increase diabetes medication over time to achieve the individualised target HbA_{1c}.

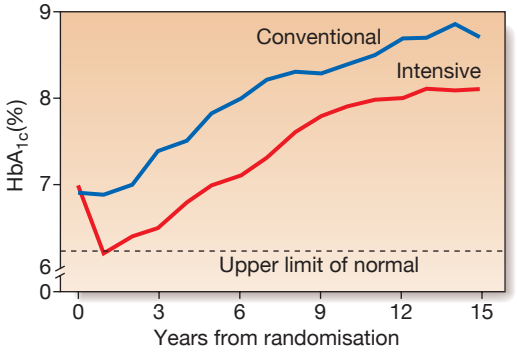


Figure: Time course of changes in HbA_{1c} during the United Kingdom Prospective Diabetes Study (UKPDS). In the UKPDS there was loss of glycaemic control with time in patients receiving monotherapy, independently of their randomisation to conventional or intensive glycaemic control, consistent with progressive decline in β-cell function.[1]

In people with type 2 diabetes, treatment of coexisting hypertension and dyslipidaemia is usually required. This can be decided by assessing absolute risk of a cardiovascular disease event and adjusting targets to individual circumstances.

Assess vascular risk

Target blood pressure <140/80 mmHg.[1,4] In special conditions:

- 130/80 mmHg if: stroke, MI, retinopathy, microalbuminuria (ARB or ACE-i)[4,1]
- <125/<75 with renal disease: creatinine, microalbuminuria, or dipstick proteinuria).[4]

Blood pressure control is critical for preventing macro vascular disease and reducing mortality.4

Check plasma lipids

For lipid-lowering, there is a reduction in cardiovascular risk even with normal cholesterol levels, but statin therapy is usually recommended when the 10-year cardiovascular event risk is at least 20%. As a general rule, this means that anyone with type 2 diabetes who is over the age of 40 years should receive a statin, irrespective of baseline cholesterol levels. Some guidelines do not suggest a target level once the patient is started on a statin but others suggest a total cholesterol of less than 4.0 mmol/L (~150 mg/dL) and an LDL cholesterol of less than 2.0 mmol/L (~75 mg/dL).

Similar targets are appropriate in type 1 diabetes, although there is a shortage of data from clinical trials in this group. Simvastatin 40mg nocte; if triglyceride >4.5mmol/L: Bezalip® 200mg/8h (+Omacor® omega 3 if still increased)[4]

Adjustment of therapy

Patients whose glycaemic control deteriorates after a period of satisfactory control need their therapy to be adjusted. However, this is not a homogeneous group; it includes

- some patients with late-onset type 1 diabetes who develop an absolute deficiency of insulin,
- some with type 2 diabetes whose β-cell failure is advanced, and
- others who are not adhering to the recommended lifestyle changes or medication.

Weight loss suggests worsening β-cell function. During continuing follow-up, the majority of patients will require combinations of anti-diabetic drugs, often with additional insulin replacement, to obtain satisfactory glycaemic control.

Prevention[5]

Genetic predisposition determines whether an individual is susceptible to type 2 diabetes; if and when diabetes develops largely depends on lifestyle.

A dramatic reduction in the incidence of new cases of adult-onset diabetes was documented in the Second World War when food was scarce, and clinical trials in individuals with impaired glucose tolerance have shown that diet, exercise or agents such as metformin have a marked effect in deferring the onset of type 2 diabetes.

Established diabetes can be reversed, even if temporarily, by successful dietary changes and weight loss, or by bariatric surgery.

Diabetes is therefore largely preventable, although the most effective measures would be directed at the whole population and implemented early in life.

Prevention is well worthwhile, for diabetes diagnosed in a man between the ages of 40 and 59 reduces life expectancy by 5–10 years. By contrast, type 2 diabetes diagnosed after the age of 70 has a limited effect on life expectancy.

Diabetes can affect every system in the body. In routine clinical practice, examination of the patient with diabetes is focused on 1 hands, 3 blood pressure, 4 and 5 axillae and neck, 7 eyes, 8 insulin injection sites and 11 feet.

7 Examination of the eyes

Visual acuity

- Distance vision using Snellen chart at 6 metres
- Near vision using standard reading chart

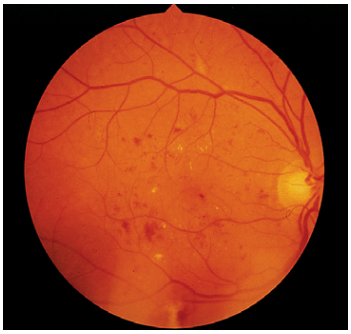
Visual acuity can alter reversibly with acute hyperglycaemia due to osmotic changes affecting the lens. Most patients with retinopathy do not have altered visual acuity, except after a vitreous haemorrhage or in some cases of maculopathy.

Lens opacification

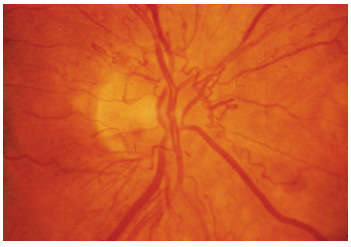
- Look for the red reflex using the ophthalmoscope held 30 cm from the eye

Fundal examination

- Either use a three-field retinal camera or dilate pupils with a mydriatic (e.g. tropicamide) and examine with ophthalmoscope in a darkened room
- Note features of diabetic retinopathy, including photocoagulation scars from previous laser treatment



Background retinopathy.



Proliferative retinopathy.

1 Examination of the hands

Several abnormalities are more common in diabetes:

- Limited joint mobility ('cheiroarthropathy') causes painless stiffness. The inability to extend (to 180°) the metacarpophalangeal or interphalangeal joints of at least one finger bilaterally can be demonstrated in the 'prayer sign'
- Dupuytren's contracture causes nodules or thickening of the skin and knuckle pads
- Carpal tunnel syndrome presents with wrist pain radiating into the hand
- Trigger finger (flexor tenosynovitis)
- Muscle-wasting/sensory changes may be present in peripheral sensorimotor neuropathy, although this is more common in the lower limbs

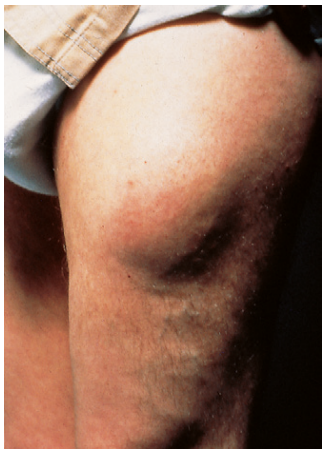
8 Insulin injection sites

Main areas used

- Anterior abdominal wall
- Upper thighs/buttocks
- Upper outer arms

Inspection

- Bruising
- Subcutaneous fat deposition (lipohypertrophy)
- Subcutaneous fat loss (lipoatrophy; associated with injection of unpurified animal insulins – now rare)
- Erythema, infection (rare)



Lipohypertrophy of the upper arm.

11 Examination of the feet

Inspection

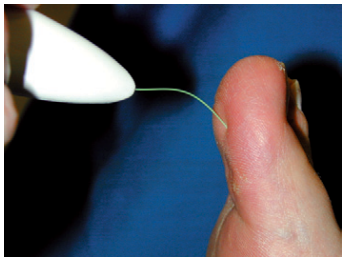
- Look for evidence of callus formation on weight-bearing areas, clawing of the toes (in neuropathy), loss of the plantar arch, discoloration of the skin (ischaemia), localised infection and ulcers
- Deformity may be present, especially in Charcot neuroarthropathy
- Fungal infection may affect skin between toes, and nails

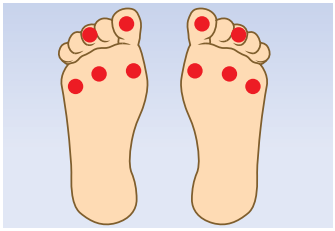
Circulation

- Peripheral pulses, skin temperature and capillary refill may be abnormal

Sensation

- Abnormal in stocking distribution in typical peripheral sensorimotor neuropathy
- Testing light touch with monofilaments is sufficient for risk assessment; test other sensation modalities (vibration, pain, proprioception) only when neuropathy is being evaluated





Monofilaments. The monofilament is applied gently until slightly deformed at 5 points on each foot. Callus should be avoided as sensation is reduced. If the patient feels fewer than 8 out of 10 touches, the risk of foot ulceration is increased 5–10-fold.

Reflexes

- Loss of ankle reflexes in typical sensorimotor neuropathy
- Test plantar and ankle reflexes

Figure: Clinical examination of the patient with diabetes.[1]

18 Psychological Implications[5]

Patients starting tablet or insulin treatment should live as normal a life as possible but this is not always easy. Tact, empathy, encouragement and practical support are needed from all members of the clinical team. Diabetes, like any chronic disease, has psychological sequelae. Most patients will experience periods of not coping, of helplessness, of denial and of acceptance, often fluctuating over time. Other problems include the following:

- **You cannot take a 'holiday' from diabetes** – yet the human psyche is poorly developed to cope with unremitting adversity.
- **Concessions or sympathy are often denied** to the person with diabetes, since its presence is invisible.
- **The treatment is complex and demanding**, and the person with diabetes must make tradeoffs between short-term and long-term wellbeing.
- **Embarrassing loss of control over personal behaviour** or consciousness can occur in insulin-treated patients when minor miscalculation leads to hypoglycaemia.
- **Risk-taking behaviour** is indulged in by all humans when emotion is in conflict with logical thought but its effects can be much greater for the person with diabetes (particularly the risks of unplanned pregnancy, alcohol and tobacco).
- **Poor self-image** is a very common problem.
- **Eating disorders** are more common in people with diabetes – 30–40% of young women will report disordered eating at some stage of their diabetes.
- **Omission of tablets or insulin** is common since non-adherence to treatment regimens is universal in all illness. Between 1 in 4 and 1 in 5 tablets prescribed for diabetes is not consumed within the designated treatment period. Insulin omission is not uncommon in young women, in whom the motivation to stay slim may overcome concerns about long-term complications.

Adolescence

Lapses into poor metabolic control, or dropping out of medical care for a time and re-emerging with complications, are very common in adolescence. Diabetic summer camps (e.g. those run by Diabetes UK) help prevent a feeling of isolation and not knowing anyone else with the same problem. Separate adolescent clinics allow:

- **treatment without marginalization** in a larger group of older people
- **meeting peers with similar problems** in the waiting room
- **gradual separation from parents** and assumption of personal responsibility for the illness
- **age-appropriate literature** to be made available.

Practical aspects

Patients need to inform the driving and vehicle licensing authority and their insurance companies after diagnosis. They would also be wise to inform their family, friends and employers, in case unexpected hypoglycaemia occurs. Insulin treatment can be undertaken by people in most walks of life. A few jobs are unsuitable; these include driving heavy goods or public service vehicles, working at heights, piloting aircraft, or working close to dangerous machinery in motion. Certain professions, such as the police and the armed forces, are barred to all diabetic patients. There are few other limitations, although a considerable amount of illinformed prejudice exists. Doctors can sometimes help support patients in the face of misinformed work practices.

19 Metabolic disturbance and emergencies

Metabolic disturbances

In type 1 diabetes

Patients with type 1 diabetes present when progressive β-cell destruction has crossed a threshold at which adequate insulin secretion and normal blood glucose levels can no longer be sustained.

Above a certain level, high glucose levels may be toxic to the remaining β cells, so that profound insulin deficiency rapidly ensues, causing the metabolic sequelae shown in figure below.

Hyperglycaemia leads to glycosuria and dehydration, causing fatigue, polyuria, nocturia, thirst and polydipsia, susceptibility to urinary and genital tract infections, and later tachycardia and hypotension. Unrestrained lipolysis and proteolysis result in weight loss. Ketoacidosis occurs when generation of ketone bodies exceeds the capacity for their metabolism. Elevated blood H^+ ions drive K^+ out of the intracellular compartment, while secondary hyperaldosteronism encourages urinary loss of K^+.

Thus patients usually present with a short history (typically a few weeks) of hyperglycaemic symptoms (thirst, polyuria, nocturia and fatigue), infections and weight loss, and may have developed ketoacidosis.

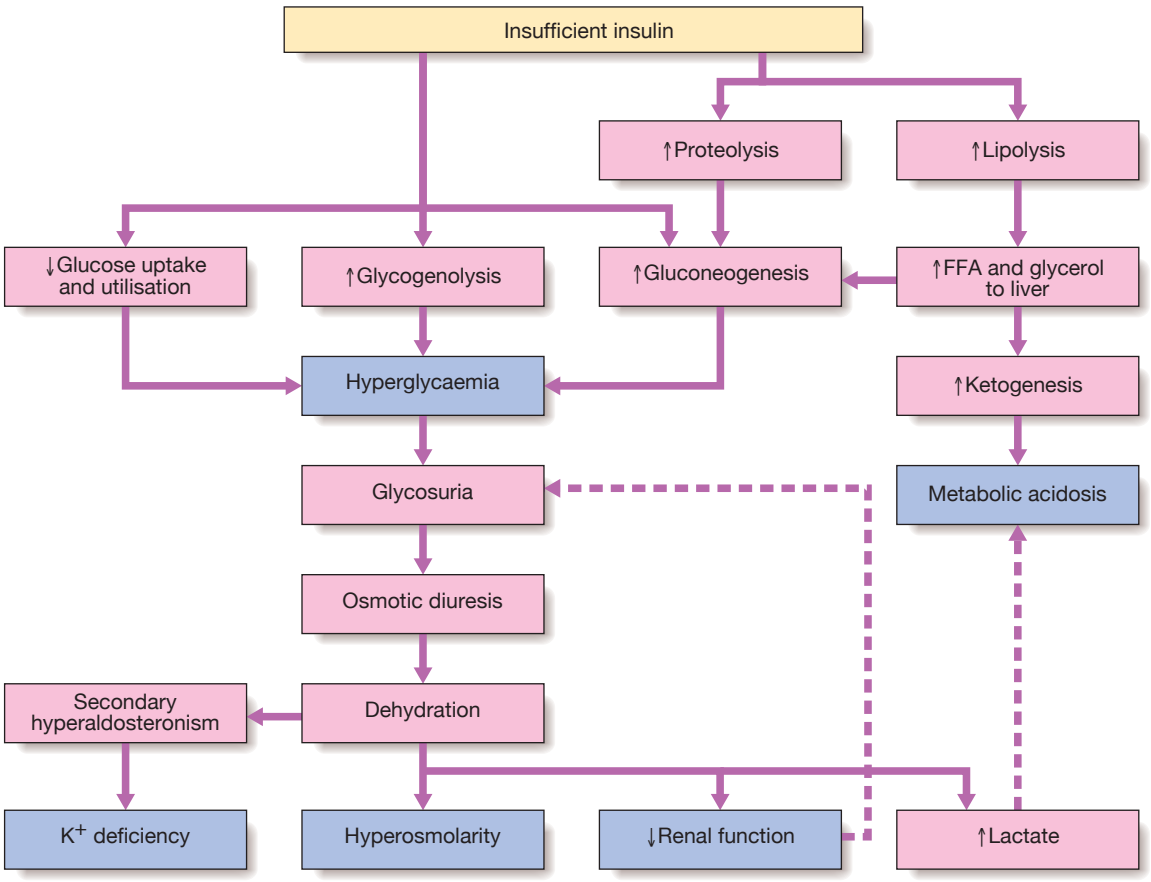


Figure: Acute metabolic complications of insulin deficiency. (FFA = free fatty acids.)[1]

Metabolic disturbances
In type 2 diabetes

Patients with type 2 diabetes have a slow onset of 'relative' insulin deficiency. Relatively small amounts of insulin are required to suppress lipolysis, and some glucose uptake is maintained in muscle, so that, in contrast with type 1 diabetes, lipolysis and proteolysis are not unrestrained and weight loss and ketoacidosis seldom occur.

In type 2 diabetes, hyperglycaemia tends to develop slowly over months or years; because of this insidious onset many cases of type 2 diabetes are discovered coincidentally and a large number are undetected. At diagnosis, patients are often asymptomatic or give a long history (typically many months) of fatigue, with or without 'osmotic symptoms' (thirst and polyuria). In some patients with type 2 diabetes, presentation is late and pancreatic β-cell failure has reached an advanced stage of insulin deficiency. These patients may present with weight loss but ketoacidosis is uncommon. However, in some ethnic groups, such as African Americans, half of those whose first presentation is with diabetic ketoacidosis have type 2 diabetes.

Intercurrent illness, e.g. with infections, increases the production of stress hormones which oppose insulin action, such as cortisol, growth hormone and catecholamines. This can precipitate an acute exacerbation of insulin resistance and insulin deficiency, and result in more severe hyperglycaemia and dehydration (hyperglycaemic hyperosmolar state).

20 Diabetic ketoacidosis (DKA)

Diabetic ketoacidosis (DKA) is a metabolic emergency in which hyperglycaemia is associated with a metabolic acidosis due to greatly raised (>5 mmol/L) ketone levels.[5] It remains a serious cause of morbidity, principally in people with type 1 diabetes.[1] It is the hallmark of type 1 diabetes. It is usually seen in the following circumstances[5]:

- previously undiagnosed diabetes
- interruption of insulin therapy
- the stress of intercurrent illness.

Mortality is low in the UK (approximately 2%) but remains high in developing countries and among non-hospitalised patients. Mortality in DKA is most commonly caused in children and adolescents by cerebral oedema and in adults by hypokalaemia, acute respiratory distress syndrome and comorbid conditions such as acute myocardial infarction, sepsis or pneumonia.[5]

DKA is characteristic of type 1 diabetes and is often the presenting problem in newly diagnosed patients. However, an increasing number of patients presenting with DKA have underlying type 2 diabetes. This appears to be particularly prevalent in African-American and Hispanic populations.[1]

The majority of cases reaching hospital could have been prevented by earlier diagnosis, better communication between patient and doctor, and better patient education.[5] In established type 1 diabetes, DKA may be precipitated by an intercurrent illness because of failure to increase insulin dose appropriately to compensate for the stress response. Sometimes, there is no evidence of a precipitating infection and DKA develops because of errors in self-management.[1] The most common error of management is for patients to reduce or omit insulin because they feel unable to eat, owing to nausea or vomiting.[5] In young patients with recurrent episodes of DKA, up to 20% may have psychological problems complicated by eating disorders.[1] Insulin may need adjusting up or down but should never be stopped.[5]

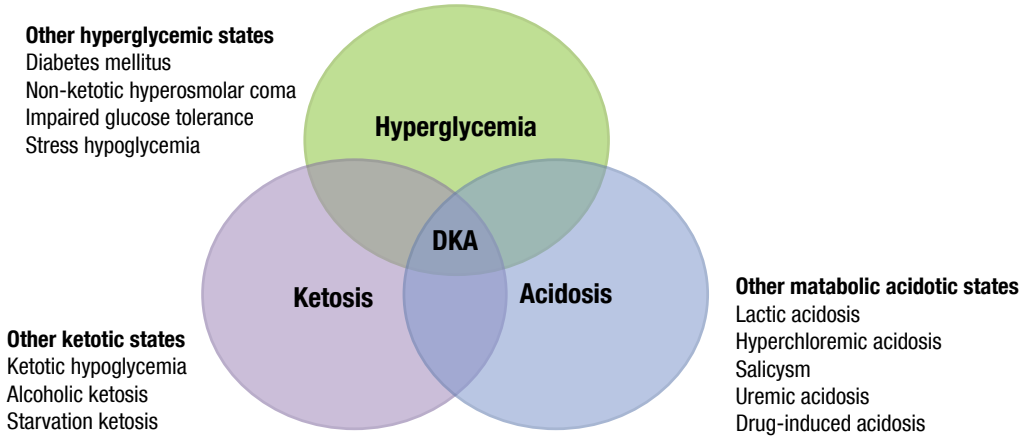
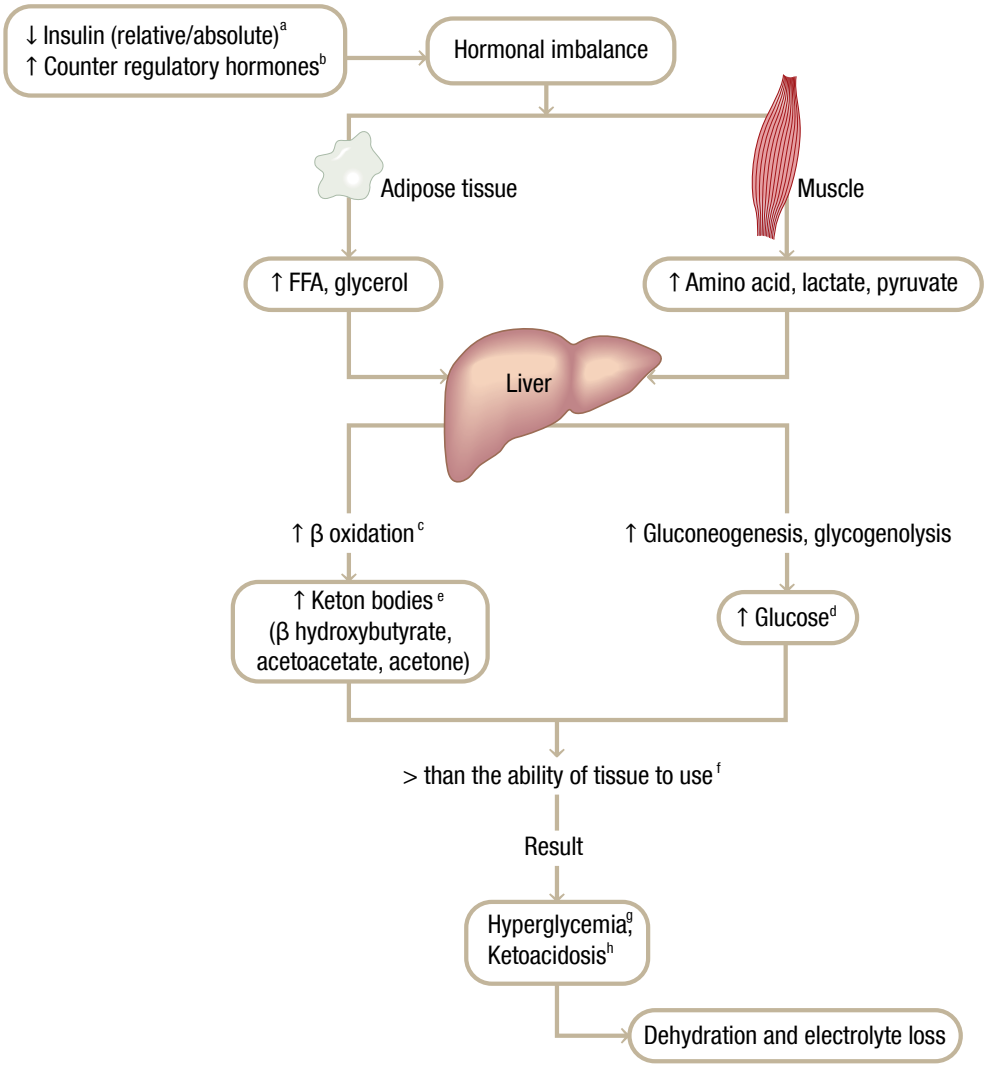


Figure: The triad of DKA (hyperglycemia, acidemia, and ketonemia) and other conditions with which the individual components are associated.[19]

Pathogenesis of DKA[1,5,9,16]

The biochemical features of DKA result from the combined effects of deficient circulating insulin activity and the excessive secretion of counter-regulatory hormones. These hormonal imbalances mobilize the delivery of substrates from muscle (amino acids, lactate, pyruvate) and adipose tissue (free fatty acids, glycerol) to the liver, where they are actively converted to glucose or to ketone bodies. Both are ultimately released into the circulation at rates that greatly exceed the capacity of tissues to use them. The end results are hyperglycemia, ketoacidosis, and an osmotic diuresis that promotes dehydration and electrolyte loss. Ketoacidosis is a state of uncontrolled catabolism associated with insulin deficiency.



a	Insulin deficiency is a necessary precondition since only a modest elevation in insulin levels is sufficient to inhibit hepatic ketogenesis, and stable patients do not readily develop ketoacidosis when insulin is withdrawn.
b	Glucagon, catecholamines, cortisol, and growth hormone.
c	In DKA: ↑Glucagon → activates enzyme carnitine palmitoyltransferase I. This enzyme transports FFA to mitochondria $\xrightarrow{\beta\ oxidation}$ ketone bodies (figure below).
d	↑Glucagon and ↓insulin shift the handling of pyruvate towards glucose synthesis and away from glycolysis.
e	↑Ketone → In urine and in breath (acetone breath).
f	Insulin deficiency reduces level of the GLUT4 glucose transporter, which impairs glucose uptake into skeletal muscle and fat and reduces intracellular glucose metabolism.
g	↑Glucose → osmotic diuresis, fluid and electrolyte loss, dehydration, ↑ plasma osmolarity, ↓ renal perfusion.
h	At physiological pH, ketone bodies exist as ketoacids and neutralized by bicarbonate. ↓Bicarbonate, ↑lactic acid, ↑ketoacids → Metabolic acidosis (it forces hydrogen ions into cells, displacing potassium ions).

The free fatty acids are broken down to acetyl-coenzyme A (CoA) within the liver cells, and this, in turn, is converted to ketone bodies within the mitochondria.

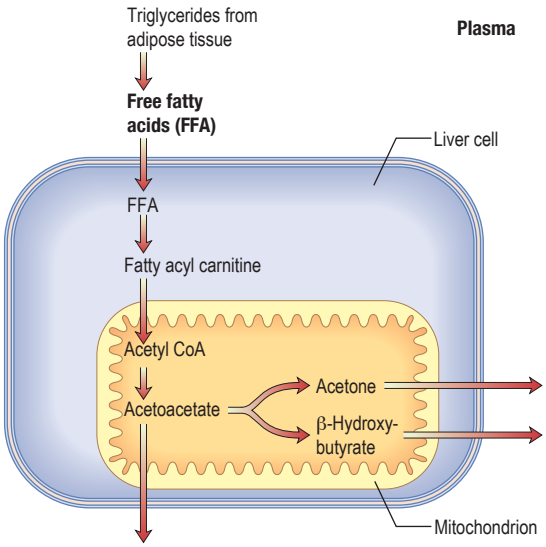


Figure: Ketogenesis.[5]

Outcome

The resulting cardinal biochemical features are[1]:

1. hyperketonaemia (≥ 3 mmol/L) and ketonuria (more than 2+ on standard urine sticks)
2. hyperglycaemia (blood glucose ≥ 11 mmol/L (~200 mg/dL))
3. metabolic acidosis (venous bicarbonate < 15 mmol/L and/or venous pH < 7.3).

The magnitude of the hyperglycaemia does not correlate with the severity of the metabolic acidosis; moderate elevation of blood glucose may be associated with life-threatening ketoacidosis. In some cases, hyperglycaemia predominates and acidosis is minimal, with patients presenting in a hyperosmolar state.

Vomiting leads to further loss of fluid and electrolytes. Respiratory compensation for the acidosis leads to hyperventilation, graphically described as 'air hunger'.

The hyperglycaemia causes a profound osmotic diuresis leading to dehydration and electrolyte loss, particularly of sodium and potassium. Potassium loss is exacerbated by secondary hyperaldosteronism as a result of reduced renal perfusion.

Dehydration occurs during ketoacidosis as a consequence of two parallel processes. Hyperglycaemia results in osmotic diuresis, and hyperketonaemia results in acidosis and vomiting. Plasma osmolality rises and renal perfusion falls and a vicious circle is established as the kidney becomes less able to compensate for the acidosis.

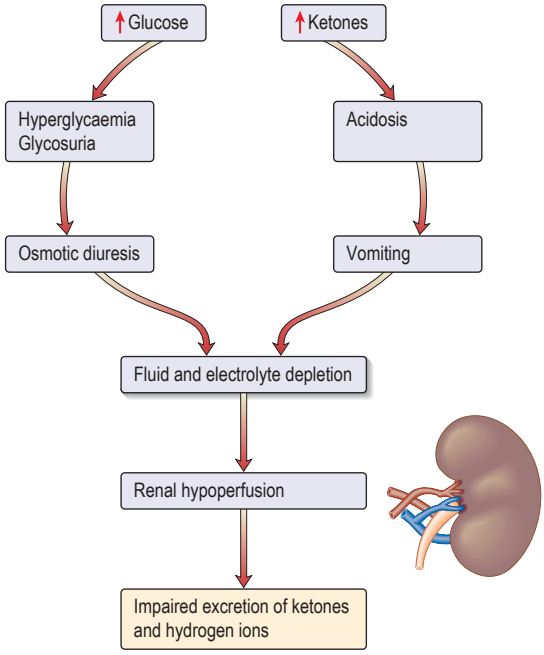


Figure: Dehydration occurs during ketoacidosis as a consequence of two parallel processes.[5]

Progressive dehydration impairs renal excretion of hydrogen ions and ketones, aggravating the acidosis. As the pH falls below 7.0 ([H+] >100 nmol/L), pH-dependent enzyme systems in many cells function less effectively. Untreated, severe ketoacidosis is invariably fatal.

The average loss of fluid and electrolytes in moderately severe DKA in an adult.

Average loss of fluid and electrolytes in adult diabetic ketoacidosis of moderate severity[1]

• Water: 6 L	3 L extracellular
• Sodium: 500 mmol	– replace with saline
• Chloride: 400 mmol	3 L intracellular
• Potassium: 350 mmol	– replace with dextrose

About half the deficit of total body water is derived from the intracellular compartment and occurs comparatively early in the development of acidosis with relatively few clinical features; the remainder represents loss of extracellular fluid sustained largely in the later stages, when marked contraction of extracellular fluid volume occurs, with haemoconcentration, a decreased blood volume, and finally a fall in blood pressure with associated renal ischaemia and oliguria.

Every patient in DKA is potassium-depleted, but the plasma concentration of potassium gives very little indication of the total body deficit. Plasma potassium may even be raised initially due to disproportionate loss of water, catabolism of protein and glycogen, and displacement of potassium from the intracellular compartment by H^+ ions. However, soon after treatment is started, there is likely to be a precipitous fall in the plasma potassium due to dilution of extracellular potassium by administration of intravenous fluids, the movement of potassium into cells induced by insulin, and the continuing renal loss of potassium.

Clinical assessment[1,5,9]

Clinical features of diabetic ketoacidosis[1,9]

Symptoms	
Nausea/vomiting	Weight loss
Thirst/polyuria	Weakness
Abdominal pain	Leg cramps
Shortness of breath	Blurred vision
Physical Findings	
Tachycardia	
Dehydration	
Hypotension (postural or supine)	
Tachypnea/ Kussmaul respirations/ respiratory distress	
Smell of acetone	
Cold extremities/ peripheral cyanosis/ Hypothermia	
Abdominal tenderness (may resemble acute pancreatitis or surgical abdomen)	
Lethargy/ obtundation/ cerebral edema/ confusion/ drowsiness/ possibly coma (10%)	
Precipitating events	
Inadequate insulin administration	
Infection (pneumonia/ UTI/ gastroenteritis/ sepsis)	
Infarction (cerebral, coronary, mesenteric, peripheral)	
Drugs (cocaine)	
Pregnancy	

The symptoms and physical signs of DKA usually develop over 24 hours[9] but may occur in a few hours in 'brittle' diabetes.[16]

DKA may be the initial symptom complex that leads to a diagnosis of type 1 DM, but more frequently, it occurs in individuals with established diabetes.

Nausea and vomiting are often prominent, and their presence in an individual with diabetes warrants laboratory evaluation for DKA.

Abdominal pain is sometimes a feature of DKA, particularly in children. It may be severe and can resemble surgical acute abdomen such as acute pancreatitis or ruptured viscus.

In the fulminating case, the striking features are those of salt and water depletion, with loss of skin turgor, furred tongue and cracked lips, tachycardia, hypotension and reduced intra-ocular pressure.

Hyperglycemia leads to glucosuria, volume depletion, and tachycardia. Hypotension can occur because of volume depletion in combination with peripheral vasodilatation. Evidence of marked dehydration is present and the eyeball is lax to pressure in severe cases.

Hyperventilation is present but becomes less marked in very severe acidosis, owing to respiratory depression. Kussmaul respirations and a fruity odor (sickly-sweet smell of acetone) on the patient's breath (secondary to metabolic acidosis and increased acetone) are classic signs of the disorder.

Some patients are mentally alert at present but lethargy mental apathy, confusion or a reduced conscious level may be present and although coma is uncommon, central nervous system depression may evolve into coma with severe DKA but should also prompt evaluation for other reasons for altered mental status (e.g., infection, hypoxemia).

Cerebral edema, an extremely serious complication of DKA, is seen most frequently in children.

The skin is dry and the body temperature is often subnormal. Signs of infection, which may precipitate DKA, should be sought on physical examination, even in the absence of fever. In infected patients, pyrexia may not be present initially because of vasodilatation secondary to acidosis. Pyrexia may develop later. Tissue ischemia (heart, brain) can also be a precipitating factor.

Serum amylase may be elevated but rarely indicates coexisting pancreatitis.

Omission of insulin because of an eating disorder, mental health disorders, or an unstable psychosocial environment may sometimes be a factor precipitating DKA.

Indeed, a patient with dangerous ketoacidosis requiring urgent treatment may walk into the consulting room. For this reason, the term 'diabetic ketoacidosis' is to be preferred to 'diabetic coma', which implies that there is no urgency until unconsciousness supervenes. In fact, it is imperative that energetic treatment is started at the earliest possible stage.

Diagnosis and laboratory abnormalities

Dignosis is confirmed by demonstrating[5,18] –

1. Ketonaemia ≥ 3.0mmol/L or significant ketonuria (more than 2+ on standard urine sticks)
2. Blood glucose > 11.0mmol/L or known diabetes mellitus
3. Bicarbonate (HCO_3^-) < 15.0mmol/L and/or venous pH < 7.3

Hyperglycaemia is demonstrated by dipstick, while a venous blood sample is sent to the laboratory for confirmation. Ketonaemia is confirmed by centrifuging a blood sample and testing the plasma with a dipstick that measures ketones. Hand-held sensors measuring β-hydroxybutyrate in 30s are available. An arterial blood sample is taken for blood gas analysis.[5]

No time should be lost and treatment is started as soon as the first blood sample has been taken.[5] The following are important but should not delay the institution of intravenous fluid and insulin replacement:[1]

- Venous blood: for urea and electrolytes, glucose and bicarbonate (severe acidosis is indicated by a venous plasma bicarbonate < 12 mmol/L).
- Urine or blood analysis for ketones.
- ECG.
- Infection screen: full blood count, blood and urine culture, C-reactive protein, chest X-ray. Although leucocytosis invariably occurs in DKA, this represents a stress response and does not necessarily indicate infection.

Laboratory values in diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) (Representative ranges at presentation)[9]

	DKA	HHS
Glucose,[a] mmol/L (mg/dL)	13.9–33.3 (250–600)	33.3–66.6 (600–1200)
Sodium, meq/L	125–135	135–145
Potassium[a,b]	Normal to ↑	Normal
Magnesium[a]	Normal	Normal
Chloride[a]	Normal	Normal
Phosphate[a,b]	Normal	Normal
Creatinine	Slightly ↑	Moderately ↑
Osmolality (mOsm/mL)	300–320	330–380
Plasma ketones[a]	++++	+/–
Serum bicarbonate,[a] meq/L	<15	Normal to slightly ↓
Arterial pH	6.8–7.3	>7.3
Arterial Pco_2,[a] mmHg	20–30	Normal
Anion gap [a](Na – [Cl + HCO_3])	↑	Normal to slightly ↑

[a]Large changes occur during treatment of DKA. [b]Although plasma levels may be normal or high at presentation, total-body stores are usually depleted.

Laboratory abnormalities[9]

- Occasionally, the serum glucose is only minimally elevated.
- Serum bicarbonate is frequently <10 mmol/L, and arterial pH ranges between 6.8 and 7.3, depending on the severity of the acidosis.
- Despite a total-body potassium deficit, the serum potassium at presentation may be mildly elevated, secondary to the acidosis.
- Total-body stores of sodium, chloride, phosphorus, and magnesium are reduced in DKA but are not accurately reflected by their levels in the serum because of hypovolemia and hyperglycemia.
- Elevated blood urea nitrogen (BUN) and serum creatinine levels reflect intravascular volume depletion. Interference from acetoacetate may falsely elevate the serum creatinine measurement.
- Leukocytosis, hypertriglyceridemia, and hyperlipoproteinemia are commonly found as well.
- Hyperamylasemia may suggest a diagnosis of pancreatitis, especially when accompanied by abdominal pain. However, in DKA the amylase is usually of salivary origin and thus is not diagnostic of pancreatitis. Serum lipase should be obtained if pancreatitis is suspected.
- The measured serum sodium is reduced as a consequence of the hyperglycemia (1.6-mmol/L [1.6-meq] reduction in serum sodium for each 5.6-mmol/L [100-mg/dL] rise in the serum glucose). A normal serum sodium in the setting of DKA indicates a more profound water deficit.
- In "conventional" units, the calculated serum osmolality (2 × [serum sodium + serum potassium] + plasma glucose [mg/dL]/ 18 + BUN/2.8) is mildly to moderately elevated, although to a lesser degree than that found in HHS.
- The ketone body, β-hydroxybutyrate, is synthesized at a threefold greater rate than acetoacetate; however, acetoacetate is preferentially detected by a commonly used ketosis detection reagent (nitroprusside). Serum ketones are present at significant levels (usually positive at serum dilution of ≥1:8). The nitroprusside tablet, or stick, is often used to detect urine ketones; certain medications such as captopril or penicillamine may cause false-positive reactions. Serum or plasma assays for β-hydroxybutyrate are preferred because they more accurately reflect the true ketone body level.
- The metabolic derangements of DKA exist along a spectrum, beginning with mild acidosis with moderate hyperglycemia evolving into more severe findings.
- The degree of acidosis and hyperglycemia do not necessarily correlate closely because a variety of factors determine the level of hyperglycemia (oral intake, urinary glucose loss).
- Ketonemia is a consistent finding in DKA and distinguishes it from simple hyperglycemia.

Assessment of severity[5,18]

The presence of one or more of the following may indicate severe DKA.

- Blood ketones > 6mmol/L
- Bicarbonate level < 5mmol/L
- Venous/arterial pH > 7.0
- Hypokalaemia on admission (< 3.5mmol/L)
- GCS < 12 or abnormal AVPU scale ('Alert, Voice, Pain, Unresponsive' scale)
- Oxygen saturation < 92% on air (assuming normal baseline respiratory function)
- Systolic BP < 90mmHg
- Pulse > 100 or < 60bpm
- Anion gap > 16
  [Anion Gap = (Na+ + K+) – (Cl- + HCO3 -)]

Differential diagnosis[9,17]

The differential diagnosis of DKA includes –

- starvation ketosis,
- alcoholic ketoacidosis (bicarbonate usually >15 meq/L), and
- other forms of increased anion-gap acidosis including lactic acidosis, ingestion of drugs such as salicylate, methanol, ethylene glycol, and paraldehyde, and chronic renal failure (which is more typically hyperchloremic acidosis rather than high-anion gap acidosis).

Management

DKA is a medical emergency which should be treated in hospital, preferably in a high-dependency area. If available, the diabetes specialist team should be involved. Regular clinical and biochemical review is essential, particularly during the first 24 hours of treatment.[1]

New principles in the management of DKA by JBDS:[18]

1. Aim to treat the cause of the acidosis, i.e. the ketonaemia
2. Insulin is to be given as a standard dose per kg until the ketones are cleared
3. Use bedside meters (Trust approved only) for glucose and ketone measurements
4. Use blood gas machines on HDU/EAU for venous pH (there no significant difference from arterial pH), venous HCO_3^-, and U&Es.
5. Use 0.9% sodium chloride solution for resuscitation, not colloid. Do not use Hartmann's (however, ITU patients may differ).
6. Only use a variable rate intravenous insulin infusion with 10% glucose when the blood glucose is <14mmol/L
7. Give both 0.9% sodium chloride and glucose together if ketones are present (>1.0mmol/L and glucose <14mmol/L)
8. Patients should be seen by the diabetes specialist team within one working day of admission
9. Upon discharge patients should be offered appropriate outpatient follow up, have access to psychological support and be offered structured education

Guideline for management of DKA–

Management of diabetic ketoacidosis*,[1]

Time: 0–60 mins

1. Commence 0.9% sodium chloride
   - If systolic BP > 90 mmHg, give 1 L over 60 mins
   - If systolic BP < 90 mmHg, give 500 mL over 10–15 mins, then re-assess. If BP remains < 90 mmHg, seek senior review
2. Commence insulin treatment
   - 50 U human soluble insulin in 50 mL 0.9% sodium chloride infused intravenously at 0.1 U/kg body weight/hr
   - Continue with SC basal insulin analogue if usually taken by patient
3. Perform further investigations: see text
4. Establish monitoring schedule
   - Hourly capillary blood glucose and ketone testing
   - Venous bicarbonate and potassium after 1 and 2 hrs, then every 2 hrs
   - Plasma electrolytes every 4 hrs
   - Clinical monitoring of O_2 saturation, pulse, BP, respiratory rate and urine output every hour
5. Treat any precipitating cause

Time: 60 mins to 12 hrs

- IV infusion of 0.9% sodium chloride with potassium chloride added as indicated below
  - 1 L over 2 hrs
  - 1 L over 2 hrs
  - 1 L over 4 hrs
  - 1 L over 4 hrs
  - 1 L over 6 hrs
- Add 10% glucose 125 mL/hr IV when glucose < 14 mmol/L
- Be more cautious with fluid replacement in elderly, young people, pregnant patients and those with renal or heart failure. If plasma sodium is > 155 mmol/L, 0.45% sodium chloride may be used.
- Adjust potassium chloride infusion

Plasma potassium (mmol/L)	Potassium replacement (mmol/L of infusion)
> 5.5	Nil
3.5–5.5	40
< 3.5	Senior review – additional potassium required

Time: 12–24 hrs

- Ketonaemia and acidosis should have resolved (blood ketones < 0.3 mmol/L, venous bicarbonate > 18 mmol/L). Request senior review if not improving
- If patient is not eating and drinking
  - Continue IV insulin infusion at lower rate of 2–3 U/kg/hr
  - Continue IV fluid replacement and biochemical monitoring
- If ketoacidosis has resolved and patient is able to eat and drink
  - Re-initiate SC insulin with advice from diabetes team. Do not discontinue IV insulin until 30 mins after SC short-acting insulin injection

Additional procedures

- Catheterisation if no urine passed after 3 hrs
- Central venous line if cardiovascular system compromised, to allow fluid replacement to be adjusted accurately – also consider in elderly, pregnant, renal or cardiac failure, other serious comorbidities, severe DKA
- Measure arterial blood gases and repeat chest X-ray if O_2 saturation < 92%
- ECG monitoring in severe cases
- Thromboprophylaxis with low molecular weight heparin

*Adapted from Joint British Diabetes Societies guideline, NHS Diabetes (2010), See the end of this section for updated 2013 guideline.

Insulin[1]

Rate
A fixed-rate intravenous insulin infusion of 0.1 U/kg body weight/hr is recommended.

Alternative
Exceptionally, if intravenous administration is not feasible, soluble insulin can be given by intramuscular injection (loading dose of 10–20 U, followed by 5 U hourly), or a fast-acting insulin analogue can be given hourly by subcutaneous injection (initially 0.3 U/kg body weight, then 0.1 U/kg hourly).

Target
The blood glucose concentration should fall by 3–6 mmol/L (approximately 55–110 mg/dL) per hour, or blood ketone concentrations fall by at least 0.5 mmol/L/hr.

Caution
A more rapid decrease in blood glucose should be avoided, as this might precipitate hypoglycaemia and the serious complication of cerebral oedema, particularly in children.

Failure of blood glucose to fall within 1 hour of commencing insulin infusion should lead to a re-assessment of insulin dose.

Cause of failure
Ketosis, dehydration, acidaemia, infection and stress combine to produce severe insulin resistance in some cases, but most will respond to a low-dose insulin regimen.

After blood glucose falls
When the blood glucose has fallen, 10% dextrose infusion is introduced and insulin infusion continued to encourage glucose uptake into cells and restoration of normal metabolism.

In recent years, it has also become increasingly common to continue with the use of long-acting insulin analogues administered subcutaneously during the initial management of DKA; this provides background insulin for when the intravenous insulin is discontinued.

Follow-up
Restoration of the usual insulin regimen, by subcutaneous injection, should not be instituted until the patient is both biochemically stable and able to eat and drink normally.

Fluid replacement[1]

Duration
In adults, rapid fluid replacement in the first few hours is usually recommended.

Caution
Caution is recommended in children and young adults because of the risk of cerebral oedema.

Replacement fluid
Most current guidelines favour correction of the extracellular fluid deficit with isotonic saline (0.9% sodium chloride).

If the plasma sodium is greater than 155 mmol/L, 0.45% saline may be used initially.

Potassium[1]

Objective
Careful monitoring of potassium is essential to the management of diabetic ketoacidosis because both hypo and hyperkalaemia can occur and are potentially life-threatening.

Duration
Potassium replacement is not usually recommended with the initial litre of fluid because prerenal failure may be present secondary to dehydration.

Replacement fluid
Treatment with 0.9% sodium chloride with potassium chloride 40 mmol/L is recommended if the serum potassium is below 5.5 mmol/L and the patient is passing urine.

Caution
If the potassium falls below 3.5 mmol/L, the potassium replacement regimen needs to be reviewed.

Cardiac rhythm should be monitored in severe DKA because of the risk of electrolyte-induced cardiac arrhythmia.

Bicarbonate[1]

Adequate fluid and insulin replacement should resolve the acidosis. The use of intravenous bicarbonate therapy is currently not recommended.

Acidosis may reflect an adaptive response, improving oxygen delivery to the tissues, and so excessive bicarbonate may induce a paradoxical increase in cerebrospinal fluid acidosis and has been implicated in the pathogenesis of cerebral oedema in children and young adults.

Subsequent management[5]

The mortality of DKA is around 5% and is increased in older patients. Its treatment is incomplete without a careful enquiry into the causes of the episode and advice as to how to avoid its recurrence.

Problems of management[5]

Hypotension
This may lead to renal shutdown. Sodium chloride 0.9% is the fluid of choice to increase circulating volume and thus blood pressure and renal perfusion. A central venous pressure line is useful in this situation. A bladder catheter is inserted if no urine is produced within 2 h but routine catheterization is not necessary.

Coma
It is essential to pass a nasogastric tube to prevent aspiration, since gastric stasis is common and carries the risk of aspiration pneumonia if a drowsy patient vomits.

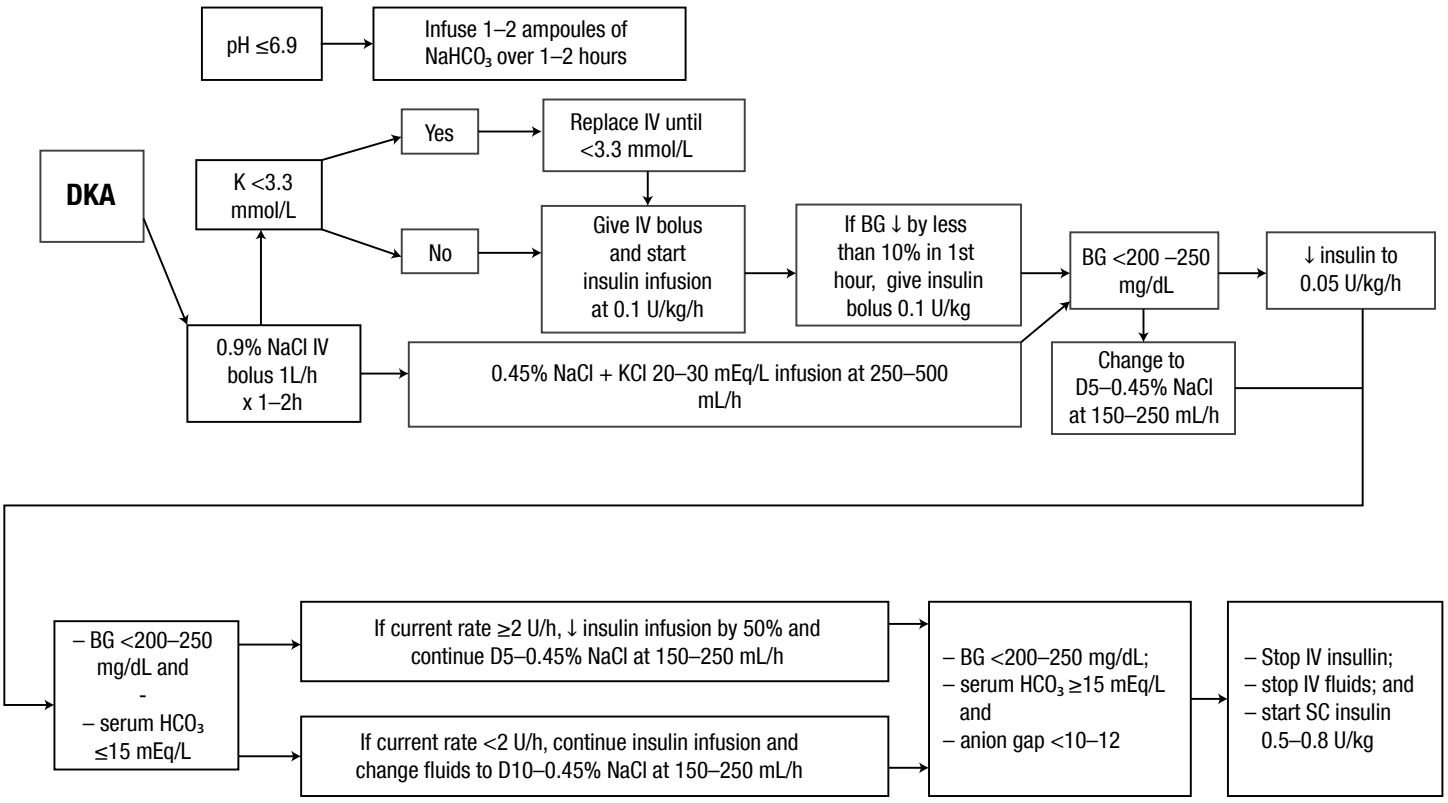
Cerebral oedema
This is a rare but serious complication and has mostly been reported in children or young adults. Excessive rehydration and use of hypertonic fluids such as 8.4% bicarbonate may sometimes be responsible. The mortality is high.

Hypothermia
Severe hypothermia with a core temperature <33°C may occur and can be overlooked unless a rectal temperature is taken with a low-reading thermometer.

Late complications
These include pneumonia and deep-vein thrombosis and occur especially in the comatose or elderly patient.

Complications of therapy
These include hypoglycaemia and hypokalaemia, due to loss of K+ in the urine from osmotic diuresis. Over-enthusiastic fluid replacement may precipitate pulmonary oedema in the very young or the very old. Hyperchloraemic acidosis may develop in the course of treatment since patients have lost a large variety of negatively charged electrolytes, which are replaced with chloride. The kidneys usually correct this spontaneously within a few days.

Protocol for the management of adult patients with DKA[19]



Joint British Diabetes Societies guideline, NHS Diabetes (2013)[18]

Management of diabetic ketoacidosis

A. Hour 1: Immediate management upon diagnosis: 0 to 60 minutes.
T = 0 at time intravenous fluids are commenced. If there is a problem with intravenous access, critical care support should be requested immediately

Aims

- Commence IV 0.9% sodium chloride solution
- Commence a FRIII but only after fluid therapy has been commenced
- Establish monitoring regime appropriate to patient; generally hourly blood glucose (BG) and hourly ketone measurement, with at least 2 hourly serum potassium and bicarbonate for the first six hours
- Clinical and biochemical assessment of the patient
- Involve the diabetes specialist team at the earliest possible stage

Action 1 - Intravenous access and initial investigations

- Rapid ABC (Airway, Breathing, Circulation)
- Large bore IV cannula (use ports to reduce infection risk) and commence IV fluid replacement (See Action 2)
- Clinical assessment
- Respiratory rate; temperature; blood pressure; pulse; oxygen saturation
- Glasgow Coma Scale. NB: a drowsy patient in the context of DKA is serious and the patient requires critical care input. Consider an NG tube with airway protection to prevent aspiration
- Full clinical examination
- Initial investigations should include:

Blood ketones	Full blood count	Continuous cardiac monitoring
Capillary blood glucose	Blood cultures	Continuous pulse oximetry
Venous plasma glucose	ECG	Consider precipitating causes and treat appropriately
Urea and electrolytes	Chest radiograph if clinically indicated	Establish usual medication for diabetes
Venous blood gases	Urinalysis and culture	Pregnancy test in women of child bearing age

Action 2 – Restoration of circulating volume

Assess the severity of dehydration using pulse and blood pressure. As a guide 90mmHg may be used as a measure of hydration but take age, gender and concomitant medication into account.

Systolic BP (SBP) on admission below 90mmHg Hypotension is likely to be due to low circulating volume, but consider other causes such as heart failure, sepsis, etc.

- Give 500ml of 0.9% sodium chloride solution over 10-15 minutes. If SBP remains below 90mmHg this may be repeated whilst awaiting senior input. In practice most patients require between 500 to 1000ml given rapidly.
- If there has been no clinical improvement reconsider other causes of hypotension and seek an immediate senior assessment. Consider involving the ITU/critical care team.
- Once SBP above 90mmHg follow fluid replacement as shown below

Systolic BP on admission 90mmHg and over

Below is a table outlining a typical fluid replacement regimen for a previously well 70kg adult. This is an illustrative guide only. A slower infusion rate should be considered in young adults.

Fluid	Volume
0.9% sodium chloride 1L *	1000ml over 1st hour
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000ml over next 6 hours
Re-assessment of cardiovascular status at 12 hours is mandatory, further fluid may be required *Potassium chloride may be required if more than 1 litre of sodium chloride has been given already to resuscitate hypotensive patients	

Exercise caution in patients - Young people aged 18-25 years, Elderly, Pregnant, Heart or kidney failure, Other serious co-morbidities. In these situations admission to a Level 2/HDU facility should be considered. Fluids should be replaced cautiously, and if appropriate, guided by the central venous pressure measurements.

Action 3 - Potassium replacement

Hypokalaemia and hyperkalaemia are life threatening conditions and are common in DKA. Serum potassium is often high on admission (although total body potassium is low) but falls precipitously upon treatment with insulin. Regular monitoring is mandatory.

Potassium level in first 24 hours (mmol/L)	Potassium replacement in mmol/L of infusion solution
> 5.5	Nil
3.5–5.5	40
< 3.5	Senior review as additional potassium needs to be given

... Cont.

Action 4 - Commence a fixed rate intravenous insulin infusion (FRIII)	• If a weight is not available from the patient, estimate it in kilograms • If the patient is pregnant, use her present weight and call for immediate senior obstetric help as well • Start a continuous FRIII via an infusion pump. This is made of 50 units of human soluble insulin (Actrapid®, Humulin S®) made up to 50ml with 0.9% sodium chloride solution. Ideally this should be provided as a ready-made infusion • Infuse at a fixed rate of 0.1 unit/kg/hr (i.e. 7ml/hr if weight is 70kg) • Only give a bolus (stat) dose of intramuscular insulin (0.1 unit/kg) if there is a delay in setting up a FRIII • If the patient normally takes Lantus®, Levemir® or Tresiba® subcutaneously continue this at the usual dose and usual time (although the option exists to continue human basal insulin as well) • Insulin may be infused in the same line as the intravenous replacement fluid provided that a Y connector with a one way, anti-siphon valve is used and a large-bore cannula has been placed
B. 60 minutes to 6 hours	
Aims	• Clear the blood of ketones and suppress ketogenesis • Achieve a rate of fall of ketones of at least 0.5mmol/L/hr • In the absence of ketone measurement, bicarbonate should rise by 3.0mmol/L/hr and blood glucose should fall by 3.0mmol/L/hr • Maintain serum potassium in the normal range • Avoid hypoglycaemia
Action 1 – Re-assess patient, monitor vital signs	• During this time, patients should be reviewed hourly initially to ensure that adequate progress is being made in reducing the ketone and/or glucose concentrations • Consider urinary catheterisation if the patient is incontinent or anuric (i.e. not passed urine by 60 minutes) • Consider naso-gastric tube insertion if the patient is obtunded or persistently vomiting • If the oxygen saturation falls, then perform an arterial blood gas measurement and request a repeat chest radiograph • Regular observations and Early Warning Score (EWS) charting as appropriate • Maintain an accurate fluid balance chart, the minimum urine output should be no less than 0.5ml/kg/hr • Continuous cardiac monitoring in those with severe DKA • Give low molecular weight heparin as per NICE guidance
Action 2 – Review metabolic parameters	• Measure blood ketones and capillary glucose hourly (note: if meter reads “blood glucose over 20mmol/L" or “Hi” venous blood should be sent to the laboratory hourly or measured using venous blood in a blood gas analyser until the bedside meter is within its QA range) • Review patient’s response to FRIII hourly by calculating the rate of change of ketone level fall (or rise in bicarbonate or fall in glucose). • Assess the resolution of ketoacidosis – If blood ketone measurement is available and blood ketones are not falling by at least 0.5mmol/L/hr call a prescribing clinician to increase the insulin infusion rate by 1.0 unit/hr increments hourly until the ketones are falling at target rates (also check infusion**) – If blood ketone measurement is not available, use venous bicarbonate. If the bicarbonate is not rising by at least 3.0mmol/L/hr call a prescribing clinician to increase the insulin infusion rate by 1 unit/hr increments hourly until the bicarbonate is rising at this rate** – Alternatively use plasma glucose. If the glucose is not falling by at least 3.0mmol/L/hr call a prescribing clinician to increase the insulin infusion rate by 1.0 unit/hr increments hourly until glucose falls at this rate. Glucose level is not an accurate indicator of resolution of acidosis in euglycaemic ketoacidosis, so the acidosis resolution should be verified by venous gas analysis** ** If ketones and glucose are not falling as expected always check the insulin infusion pump is working and connected and that the correct insulin residual volume is present (to check for pump malfunction) • Measure venous blood gas for pH, bicarbonate and potassium at 60 minutes, 2 hours and 2 hourly thereafter • If the potassium is outside the reference range, assess the appropriateness of the potassium replacement and check it hourly. If it remains abnormal after a further hour, seek immediate senior medical advice (see Action 3) • Continue the FRIII until the ketone measurement is less than 0.6mmol/L, venous pH over 7.3 and/or venous bicarbonate over 18mmol/L • Do not rely on urinary ketone clearance to indicate resolution of DKA, because these will still be present when the DKA has resolved • If the glucose falls below 14.0mmol/L, commence 10% glucose given at 125ml/hour alongside the 0.9% sodium chloride solution • Monitor and replace potassium because it may fall rapidly
Action 3	• Identify and treat precipitating factors
Action 4	Patients presenting with newly diagnosed type 1 diabetes should be given Lantus® or Levemir® (or human NPH insulin, depending on local policy) at a dose of 0.25 units/Kg subcutaneously once daily to mitigate against rebound ketosis when they are taken off the FRIII
C. 6 to 12 hours	
Aim	• Ensure that clinical and biochemical parameters are improving • Continue IV fluid replacement • Continue insulin administration • Assess for complications of treatment e.g. fluid overload, cerebral oedema • Continue to treat precipitating factors as necessary • Avoid hypoglycaemia
Action 1 – Re-assess patient, monitor vital signs	• If the patient is not improving then seek senior advice • Ensure a referral has been made to the specialist diabetes team

... Cont.

Action 2 – Review biochemical and metabolic parameters	• At 6 hours check the venous pH, bicarbonate, potassium, as well as blood ketones and glucose • Resolution of DKA is defined as ketones less than 0.6mmol/L and venous pH over 7.3 (do not use bicarbonate as a surrogate at this stage because the hyperchloraemic acidosis associated with large volumes of 0.9% sodium chloride will lower bicarbonate levels) • If DKA resolved go to section E. • If DKA not resolved refer to Action 2 in Section B.
D. 12 to 24 hours	
Expectation	• By 24 hours the ketonaemia and acidosis should have resolved
Aim	• Ensure that the clinical and biochemical parameters are improving or have normalised • Continue IV fluids if the patient is not eating and drinking • If the patient is not eating and drinking and there is no ketonaemia move to a VRIII as per local guidelines • Re-assess for complications of treatment e.g. fluid overload, cerebral oedema • Continue to treat any precipitating factors as necessary • Transfer to subcutaneous insulin if the patient is eating and drinking normally. Ensure that the subcutaneous insulin is started before the IV insulin is discontinued. Ideally give the subcutaneous fast acting insulin at a meal and discontinue IV insulin one hour later
Action 1	Re-assess patient, monitor vital signs
Action 2 – Review biochemical and metabolic parameters	• At 12 hours check venous pH, bicarbonate, potassium, as well as blood ketones and glucose • Resolution of DKA is defined as ketones less than 0.6mmol/L, and venous pH over 7.3 • If DKA resolved go to section E. • If DKA not resolved refer to Action 2 in Section B and seek senior specialist advice as a matter of urgency. • Note: Do not rely on bicarbonate alone to assess the resolution of DKA at this point due to the possible hyperchloraemia secondary to high volumes of 0.9% sodium chloride solution. The hyperchloraemic acidosis will lower the bicarbonate and thus lead to difficulty is assessing whether the ketosis has resolved. The hyperchloraemic acidosis may cause renal vasoconstriction and be a cause of oliguria. • Expectation: Patients should be eating and drinking and back on normal insulin. If this expectation is not met within this time period it is important to identify and treat the reasons for the failure to respond to treatment. It is unusual for DKA not to have resolved by 24 hours with appropriate treatment and requires senior and specialist input.
E. Conversion to subcutaneous insulin	
	The patient should be converted to an appropriate subcutaneous regime when biochemically stable (blood ketones less than 0.6mmol/L, pH over 7.3) and the patient is ready and able to eat. Conversion to subcutaneous insulin is ideally managed by the diabetes specialist team. If the patient is newly diagnosed, it is essential they are seen by a member of the specialist team prior to discharge. **Specialist diabetes team input** In line with the Best Practice Tariff, if they are not already involved, the local diabetes team should be informed and the patient reviewed within 24 hours of admission. Specialist diabetes team input is important to allow re-education, to reduce the chance of recurrence, and to facilitate appropriate follow up.

21 Hyperglycaemic hyperosmolar state

This condition, in which severe hyperglycaemia develops without significant ketosis, is the characteristic metabolic emergency of uncontrolled type 2 diabetes.[5] It was previously referred to as hyperosmolar non-ketotic (HONK) coma but, as in DKA, coma is not invariable.[1] Patients present in middle or later life, often with previously undiagnosed diabetes. Common precipitating factors include consumption of glucose-rich fluids, concurrent medication such as thiazide diuretics or steroids, and intercurrent illness.[5]

DKA and HHS

The hyperosmolar hyperglycaemic state and ketoacidosis represent two ends of a spectrum rather than two distinct disorders. The biochemical differences may partly be explained as follows:

Age
The extreme dehydration characteristic of the hyperosmolar hyperglycaemic state may be related to age. Old people experience thirst less acutely and become dehydrated more readily. In addition, the mild renal impairment associated with age results in increased urinary losses of fluid and electrolytes.

The degree of insulin deficiency
This is less severe in the hyperosmolar hyperglycaemic state. Endogenous insulin levels are sufficient to inhibit hepatic ketogenesis but insufficient to inhibit hepatic glucose production.[5]

Hyperglycaemic hyperosmolar state

Hyperglycaemic hyperosmolar state (HHS) is characterised by[1] –

1. Severe hyperglycaemia (> 30 mmol/L (600 mg/dL)),
2. Hyperosmolality (serum osmolality > 320 mOsm/kg),
3. Dehydration
4. Absence of significant hyperketonaemia (< 3 mmol/L) or acidosis (pH > 7.3, bicarbonate > 15 mmol/L).

Incidence

Although typically occurring in the elderly, HHS is increasingly seen in younger adults. Mortality rates are higher than in DKA, up to 20% in the USA, mainly because of the age and more frequent presence of comorbidities.[1,5]

Predisposing factors

Common precipitating factors include[1]

- Infection,
- Myocardial infarction,
- Cerebrovascular events or
- Drug therapy (e.g. corticosteroids).

Clinical features

The prototypical patient with HHS is an elderly individual with type 2 DM, with a several-week history of polyuria, weight loss, and diminished oral intake that culminates in mental confusion, lethargy, or coma.[9] The characteristic clinical features on presentation are dehydration and stupor or coma. Impairment of consciousness is directly related to the degree of hyperosmolality.[5]

The physical examination reflects profound dehydration and hyperosmolality and reveals hypotension, tachycardia, and altered mental status. Notably absent are symptoms of nausea, vomiting, and abdominal pain and the Kussmaul respirations characteristic of DKA.[9]

HHS is often precipitated by a serious, concurrent illness such as myocardial infarction or stroke. Sepsis, pneumonia, and other serious infections are frequent precipitants and should be sought. In addition, a debilitating condition (prior stroke or dementia) or social situation that compromises water intake usually contributes to the development of the disorder.[9]

Pathogenesis

As with DKA, there is glycosuria, leading to an osmotic diuresis, with loss of water, sodium, potassium and other electrolytes. However, in HHS, hyperglycaemia usually develops over a longer period (a few days to weeks), causing more profound hyperglycaemia and dehydration (fluid loss may be 10–22 litres in a person weighing 100 kg).[1]

The reason that patients with HHS do not develop significant ketoacidosis is that while DKA is a state of near absolute insulinopenia, there is sufficient amount of insulin present in HHS to prevent lipolysis and ketogenesis but not adequate to cause glucose utilization (as it takes 1/10 as much insulin to suppress lipolysis as it does to stimulate glucose utilization). In addition, in HHS there is a smaller increase in counter regulatory hormones.[1,19]

A mixed picture of HHS and DKA can occur.[1]

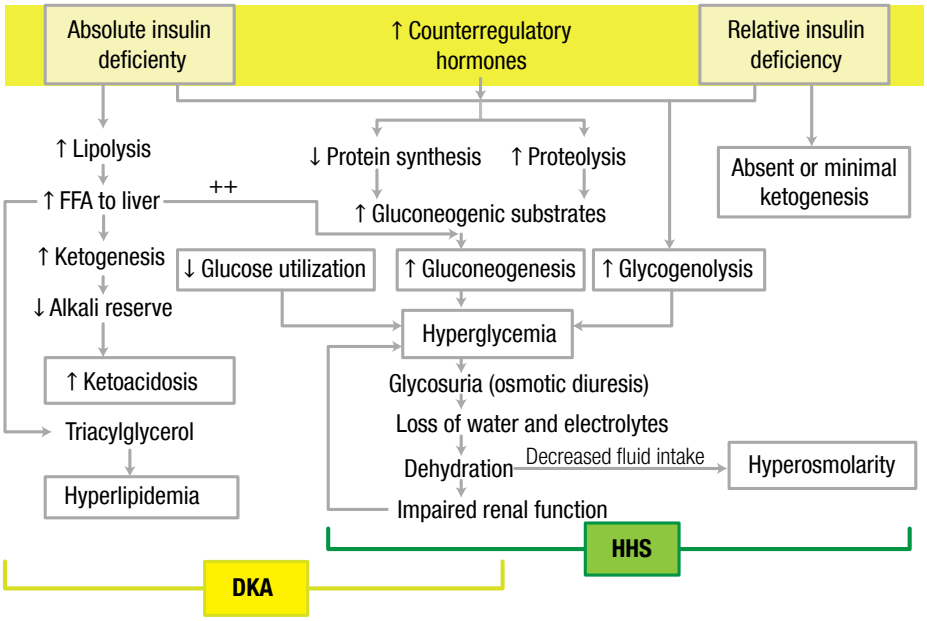


Figure: Pathogenesis of DKA and HHS: stress, infection, or insufficient insulin.[19,20]

Laboratory features[9]

In the laboratory features in HHS, most notable are the marked hyperglycemia (plasma glucose may be >55.5 mmol/L [1000 mg/dL]), hyperosmolality (>350 mosmol/L), and prerenal azotemia.

The measured serum sodium may be normal or slightly low despite the marked hyperglycemia. The corrected serum sodium is usually increased (add 1.6 meq to measured sodium for each 5.6-mmol/L [100-mg/dL] rise in the serum glucose).

In contrast to DKA, acidosis and ketonemia are absent or mild. A small anion-gap metabolic acidosis may be present secondary to increased lactic acid. Moderate ketonuria, if present, is secondary to starvation.

Admission biochemical data with HHS or DKA[20]

	HHS	DKA
Glucose (mg/dl)	930 ± 83	616 ± 36
Na^+ (mEq/l)	149 ± 3.2	134 ± 1.0
K^+ (mEq/l)	3.9 ± 0.2	4.5 ± 0.13
BUN (mg/dl)	61 ± 11	32 ± 3
Creatinine (mg/dl)	1.4 ± 0.1	1.1 ± 0.1
pH	7.3 ± 0.03	7.12 ± 0.04
Bicarbonate (mEq/l)	18 ± 1.1	9.4 ± 1.4
3-β-hydroxybutyrate (mmol/l)	1.0 ± 0.2	9.1 ± 0.85
Total osmolality*	380 ± 5.7	323 ± 2.5
IRI (nmol/l)	0.08 ± 0.01	0.07 ± 0.01
C-peptide (nmol/l)	1.14 ± 0.1	0.21 ± 0.03
Free fatty acids (nmol/l)	1.5 ± 0.19	1.6 ± 0.16
Human growth hormone (ng/ml)	1.9± 0.2	6.1 ± 1.2
Cortisol (ng/ml)	570 ± 49	500 ± 61
IRI (nmol/l)†	0.27 ± 0.05	0.09 ± 0.01
C-peptide (nmol/l)†	1.75 ± 0.23	0.25 ± 0.05
Glucagon (ng/ml)	689 ± 215	580 ± 147
Catacholamines (ng/ml)	0.28 ± 0.09	1.78 ± 0.4
Growth hormone (ng/ml)	1.1	7.9
ΔGap: anion gap − 12 (mEq/l)	1 1	17

*According to the formula 2(Na + K) + urea (mmol/l) + glucose (mmol/l). †Values following intravenous administration of tolbutamide. IRI, immunoreactive insulin.

Management[1]

The principles of management

- Measure or calculate serum osmolality frequently
- Give fluid replacement with 0.9% sodium chloride (IV). Use 0.45% sodium chloride only if osmolality is increasing, despite positive fluid balance. Target fall in plasma sodium is ≤ 10 mmol/L at 24 hours
- Aim for positive fluid balance of 3–6 L by 12 hours, and replacement of remaining estimated loss over next 12 hours
- Initiate insulin IV infusion (0.05 U/kg body weight/hour) only when blood glucose is not falling with 0.9% sodium chloride alone OR if there is significant ketonaemia (3β-hydroxybutyrate > 1 mmol/L or urine ketones > 2+). Reduce blood glucose by no more than 5 mmol/L/hour
- Treat coexisting conditions
- Give prophylactic anticoagulation
- Assume high risk of foot ulceration

Aim of therapy

The aims are to –

- normalise osmolality,
- replace fluid and electrolyte losses, and
- normalise blood glucose,

at the same time preventing complications such as

- arterial or venous thrombosis,
- cerebral oedema and
- central pontine demyelinosis

Comorbidities also need to be taken into account; for example, rapid fluid replacement may precipitate cardiac failure in patients with coronary artery disease.

Management

Historically, management of HHS has followed DKA guidelines, but increasing recognition of the differences between HHS and DKA has led to new approaches in HHS. In particular, rapid shifts in osmolality should be avoided through more measured fluid replacement regimens that are guided by serial calculations of serum osmolality.

A key recommendation is that 0.9% sodium chloride solution alone is used for initial treatment, and that insulin is introduced only when the rate of fall in blood glucose has plateaued.

Calculation of osmolarity

If osmolality cannot be measured frequently, osmolarity can be calculated as follows and used as a surrogate (based on plasma values in mmol/L):

$$\textbf{Plasma osmolarity} = 2[Na^+] + [\textbf{glucose}] + [\textbf{urea}]$$

The normal value is 280–290 mmol/L and consciousness is impaired when it is high (> 340 mmol/L), as commonly occurs in HHS.

Poor prognostic signs

Poor prognostic signs include –

- hypothermia,
- hypotension (systolic blood pressure < 90 mmHg),
- tachy- or bradycardia,
- severe hypernatraemia (sodium > 160 mmol/L),
- serum osmolality > 360 mOsm/kg, and
- the presence of other serious comorbidities.

22 Complications of Diabetes

Patients with long-standing diabetes are at risk of developing a variety of complications. Moreover, as many as 25% of people with type 2 diabetes have evidence of diabetic complications at the time of initial diagnosis. Thus, diabetes may be first suspected when a patient visits an optometrist or podiatrist, or presents with hypertension or a vascular event such as an acute myocardial infarction or stroke. Blood glucose should therefore be checked in all patients presenting with such pathology.

Despite all the treatments now available, the outcome for patients with diabetes remains disappointing. Long-term complications of diabetes still cause significant morbidity and mortality.[1] The major cause of death in treated patients is cardiovascular problems (60–70%) followed by renal failure (10%) and infections (6%). There is no doubt that the duration and degree of hyperglycaemia play a major role in the production of complications. Improved glucose control can reduce the rate of progression of both nephropathy and retinopathy, and the DCCT trial showed a 60% reduction in developing complications over 9 years when the HbA_{1c} was kept at around 7% in type 1 diabetes.[5]

Complications of diabetes[1]

Microvascular/neuropathic

Retinopathy, cataract
- Impaired vision

Nephropathy
- Renal failure

Peripheral neuropathy
- Sensory loss
- Pain
- Motor weakness

Autonomic neuropathy
- Gastrointestinal problems (gastroparesis; altered bowel habit)
- Postural hypotension

Foot disease
- Ulceration
- Arthropathy

Macrovascular

Coronary circulation
- Myocardial ischaemia/infarction

Cerebral circulation
- Transient ischaemic attack
- Stroke

Peripheral circulation
- Claudication
- Ischaemia

Excess mortality in diabetes is caused mainly by large blood vessel disease, particularly myocardial infarction and stroke. Macrovascular disease also causes substantial morbidity from myocardial infarction, stroke, angina, cardiac failure and intermittent claudication.

The pathological changes of atherosclerosis in diabetic patients are similar to those in the non-diabetic population but occur earlier in life and are more extensive and severe. Diabetes amplifies the effects of the other major cardiovascular risk factors: smoking, hypertension and dyslipidaemia.

Mortality in diabetes[1]

Risk versus non-diabetic controls (mortality ratio)	
• Overall	2.6
• Coronary heart disease Cerebrovascular disease Peripheral vascular disease	2.8
• All other causes, including renal failure	2.7
Causes of death in diabetes (approximate proportion)	
• Cardiovascular disease	70%
• Renal failure	10%
• Cancer	10%
• Infections	6%
• Diabetic ketoacidosis	1%
• Other	3%

Risk factors for increased morbidity and mortality in diabetes

- Duration of diabetes
- Early age at onset of disease
- High glycated haemoglobin (HbA_{1c})
- Raised blood pressure
- Proteinuria; microalbuminuria
- Dyslipidaemia
- Obesity

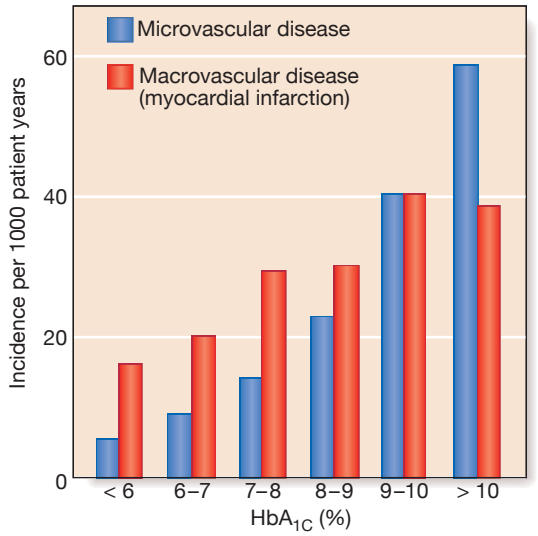


Figure: Association between HbA_{1c} and risk of microvascular and macrovascular diabetes complications. These data were obtained amongst participants in the UK Prospective Diabetes Study and were adjusted for effects of age, sex and ethnicity; the incidences show what could be expected amongst white men aged 50–54 years at diagnosis of type 2 diabetes, followed up for 10 years. Microvascular disease included retinopathy requiring photocoagulation, vitreous haemorrhage and renal failure. Macrovascular disease included fatal and non-fatal myocardial infarction and sudden death. A 1% change in HbA_{1c} is equivalent to a reduction of 11 mmol/mol.[1]

Moreover, patients with type 2 diabetes are more likely to have additional cardiovascular risk factors, which co-segregate with insulin resistance in the metabolic syndrome.

Pathophysiology[5]

The mechanisms leading to damage are ill defined. The following are consequences of hyperglycaemia and may play a role:

- **Non-enzymatic glycosylation** of a wide variety of proteins, such as haemoglobin, collagen, low-density lipoprotein (LDL) and tubulin in peripheral nerves. This leads to an accumulation of advanced glycosylated end-products, causing injury and inflammation via stimulation of pro-inflammatory factors, such as complement and cytokines.
- **Polyol pathway**. The metabolism of glucose by increased intracellular aldose reductase leads to accumulation of sorbitol and fructose. This causes changes in vascular permeability, cell proliferation and capillary structure via stimulation of protein kinase C and transforming growth factor beta (TGF-β).
- **Abnormal microvascular blood flow**. This impairs the supply of nutrients and oxygen. Microvascular occlusion is due to vasoconstrictors, such as endothelins and thrombogenesis, and leads to endothelial damage.
- **Other factors**. These include the formation of reactive oxygen species and stimulation of growth factors TGF-β and vascular endothelial growth factor (VEGF). These growth factors are released by ischaemic tissues and cause endothelial cells to proliferate.
- **Haemodynamic changes**. These take place, for example, in the kidney.

It has been proposed that all of the above mechanisms stem from a single hyperglycaemiainduced process of overproduction of superoxide by the mitochondrial electron chain. This paradigm offers an integrated explanation of how complications of diabetes develop.

Macrovascular complications[5]

Diabetes is a risk factor for the development of atherosclerosis. This risk is related to that of the background population. For example, people with diabetes in Japan are less likely than European patients to develop atherosclerosis, but more likely to develop it than non-diabetic Japanese.

Diabetic risk factors for macrovascular complications

- Duration
- Increasing age
- Systolic hypertension
- Hyperinsulinaemia due to insulin resistance associated with obesity and the metabolic syndrome
- Hyperlipidaemia, particularly hypertriglyceridaemia/low high-density lipoprotein (HDL)
- Proteinuria (including microalbuminuria)
- Other factors as for the general population

Several large trials have shown that intensive glucose-lowering treatment of diabetes has a relatively minor effect on cardiovascular risk; it is vital to tackle all cardiovascular risk factors together in diabetes, and not just to focus on glucose levels. Other associated factors are –

Hypertension

The UKPDS demonstrated that aggressive treatment of hypertension produces a marked reduction in adverse cardiovascular outcomes, both microvascular and macrovascular. To achieve the target for blood pressure, the UKPDS found that one-third of patients needed three or more antihypertensive drugs in combination, and two-thirds of treated patients needed two or more.

Smoking

This is the avoidable risk factor. Efforts to help patients stop smoking should never be given up.

Lipid abnormalities

Clinical trials suggest that there is no 'safe' cut-off for serum cholesterol. It seems best to aim for the lowest achievable level, and in practice this means that almost all people with type 2 diabetes will be treated with a statin.

Low-dose aspirin

Low-dose aspirin can reduce macrovascular risk but is associated with a morbidity and mortality from bleeding. The benefits of aspirin outweigh the bleeding risk when the risk of a cardiovascular end-point is >30% in the next 10 years. This risk is reached in patients aged under 45 with three strong additional cardiovascular risk factors, those aged 45–54 with three additional risk factors, those aged 54–65 with two additional risk factors, or those aged over 65 with just one additional risk factor.

ACE inhibitors/angiotensin II receptor antagonists

Treating people with diabetes and at least one other major cardiovascular risk factor with an ACE inhibitor produces a 25–35% lowering of the risk of heart attack, stroke, overt nephropathy or cardiovascular death. Angiotensin II receptor antagonists are sometimes preferred initially and are also used for those intolerant to ACE inhibitors. The two agents are not used together.

Microvascular complications[5]

In contrast to macrovascular disease, which is prevalent in the West as a whole, disease of small blood vessels is a specific complication of diabetes and is termed diabetic microangiopathy.[1,5] Small blood vessels throughout the body are affected but the disease process is of particular danger in three sites[5]:

1. retina
2. renal glomerulus
3. nerve sheaths

Diabetic microangiopathy contributes to[1] –

- mortality through renal failure caused by diabetic nephropathy, and
- substantial morbidity and disability by
    - blindness from diabetic retinopathy,
    - difficulty in walking, chronic ulceration of the feet from peripheral neuropathy, and
    - bowel and bladder dysfunction from autonomic neuropathy.

Diabetic retinopathy, nephropathy and neuropathy tend to manifest 10–20 years after diagnosis in young patients but may present earlier in older patients, probably because these individuals have had unrecognized diabetes for months or even years prior to diagnosis.[5]

Genetic factors appear to contribute to the susceptibility to microvascular disease. Diabetic siblings of diabetic patients with renal and eye disease have a three- to fivefold increased risk of the same complication in both type 1 and type 2 patients.[5]

There are racial differences in the overall prevalence of nephropathy. In the USA, prevalence is: Pima American Indian > Hispanic/Mexican > US black > US white patients.[5]

The risk of microvascular disease is positively correlated with the duration and degree of sustained hyperglycaemia, however caused and at whatever age it develops.[1]

Pathophysiology[1]

The histopathological hallmark of diabetic microangiopathy is thickening of the capillary basement membrane, with associated increased vascular permeability, which occurs throughout the body.

The development of the characteristic clinical syndromes of diabetic retinopathy, nephropathy, neuropathy and accelerated atherosclerosis is thought to result from the local response to generalised vascular injury. For example, in the wall of large vessels, increased permeability of arterial endothelium, particularly when combined with hyperinsulinaemia and hypertension, may increase the deposition of atherogenic lipoproteins. The mechanisms linking hyperglycaemia to these pathological changes are, however, poorly characterised.

Preventing diabetes complications

The microvascular complications of both type 1 and type 2 DM result from chronic hyperglycemia. Evidence implicating a causative role for chronic hyperglycemia in the development of macrovascular complications is less conclusive. CHD events and mortality rate are two to four times greater in patients with type 2 DM and correlate with fasting and postprandial plasma glucose levels as well the HbA_{1c}. Other factors such as dyslipidemia and hypertension also play important roles in macrovascular complications.[9]

Glycaemic control[1]

The evidence that improved glycaemic control decreases the risk of developing microvascular complications of diabetes was established by the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes, and the UK Prospective Diabetes Study (UKPDS) in type 2 diabetes.

The DCCT was a large study that lasted 9 years. There was a 60% overall reduction in the risk of developing diabetic complications in patients with type 1 diabetes on intensive therapy with strict glycaemic control, compared with those on conventional therapy.

Glycaemic control in type 1 diabetes[1]

'In patients with type 2 diabetes, strict glycaemic control (mean HbA_{1c} 53 mmol/mol (7%)) reduced the development of retinopathy and other microvascular complications by 76% compared with conventional therapy (mean HbA_{1c} 75 mmol/mol (9%)). On longer-term follow-up, strict glycaemic control also reduced cardiovascular events, including myocardial infarction, stroke and death from cardiovascular disease.'

- Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329:977–986.
- Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. N Engl J Med 2005; 353:2643–2653.

For further information: www.diabetes.niddk.nih.gov/dm/pubs/control/

No single factor other than glycaemic control had a significant effect on outcome. However, the group who were intensively treated to lower blood glucose had three times the rate of severe hypoglycaemia.

The UKPDS showed that, in type 2 diabetes, the frequency of diabetic complications is lower and progression is slower with good glycaemic control and effective treatment of hypertension, irrespective of the type of therapy used.

Extrapolation from the UKPDS suggests that, for every 11 mmol/mol (1%) reduction in HbA_{1c}, there is a 21% reduction in death related to diabetes, a 14% reduction in myocardial infarction and 30–40% reduction in risk of microvascular complications. These landmark trials demonstrated that diabetic complications are preventable and that the aim of treatment should be 'near-normal' glycaemia. However, more recent studies, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD), showed increased mortality in a subgroup of patients who were aggressively treated to lower HbA_{1c} to a target of less than 48 mmol/mol (6.5%). The patients in this study had poor glycaemic control at baseline, a long duration of diabetes and a high prevalence of cardiovascular disease. It appears that, whilst a low target HbA_{1c} is appropriate in younger patients with earlier diabetes who do not have underlying cardiovascular disease, aggressive glucose-lowering is not beneficial in older patients with long duration of diabetes and multiple comorbidities.

Glycaemic control in type 2 diabetes[1]

'In patients with type 2 diabetes, intensive glycaemic control (mean HbA_{1c} 53 mmol/mol (7%)) with oral anti-diabetic drugs or insulin reduced the development of microvascular complications, particularly retinopathy, by 25% compared with conventional treatment (mean HbA_{1c} 64 mmol/mol (8%)). On longer-term follow-up, there was a significant reduction in myocardial infarction and all-cause mortality in intensively controlled patients.'

- UKPDS Group. Lancet 1998; 352:837–853, 854–865.
- Holman RR, et al. N Engl J Med 2008; 359:1577–1589.

For further information: www.dtu.ox.ac.uk

Diabetes management in old age[1]

- **Glycaemic control**: the optimal target for glycaemic control in older people has yet to be determined. Strict glycaemic control should be avoided in frail patients with comorbidities and in older patients with long duration of diabetes.
- **Cognitive function and affect**: may benefit from improving glycaemic control.
- **Hypoglycaemia**: older people have reduced symptomatic awareness of hypoglycaemia and limited knowledge of symptoms, and are at greater risk of, and from, hypoglycaemia.
- **Mortality**: the mortality rate of older people with diabetes is more than double that of age-matched non-diabetic people, largely because of increased deaths from cardiovascular disease.

Control of other risk factors[1]

Randomised controlled trials have shown that aggressive management of blood pressure minimises the microvascular and macrovascular complications of diabetes. Angiotensin-converting enzyme (ACE) inhibitors are valuable in improving outcome in heart disease and in treating diabetic nephropathy.

The management of dyslipidaemia with a statin limits macrovascular disease in people with diabetes. This often results in the necessary use of multiple medications, which exacerbates the problem of adherence to therapy by patients; it is not unusual for a patient to be taking two or more diabetes therapies, two or more blood pressure drugs and a statin.

23 Ophthalmologic complications

At least 90% of young patients with type 1 diabetes will develop retinal changes but these only progress to sight-threatening retinopathy in a minority.[5] The gravity of this problem is highlighted by the finding that individuals with DM are 25 times more likely to become legally blind than individuals without DM. Severe vision loss is primarily the result of progressive diabetic retinopathy and clinically significant macular edema.[9] Diabetic retinopathy (DR) is one of the most common causes of blindness in adults between 30 and 65 years of age in developed countries. The prevalence of DR increases with duration of diabetes, and almost all individuals with type 1 diabetes and the majority of those with type 2 diabetes will have some degree of DR after 20 years.[1] Some 30–50% will require laser photocoagulation to prevent or limit progression to proliferative retinopathy, and good control of blood pressure is essential.[5]

Diabetes affects the eye in a variety of ways:[5]

1. **Cataract** is denaturation of the protein and other components of the lens of the eye, which renders it opaque.
2. **Diabetic retinopathy** is damage to the retina and iris caused by diabetes, which can lead to blindness.
3. **External ocular palsies** most commonly affect the sixth and the third nerves. Third nerve palsy is not associated with pain. These nerve palsies usually recover spontaneously within a period of 3–6 months.

Causes of visual loss in people with diabetes[1]

Causes of visual loss in patient with diabetes are –

1. Diabetic retinopathy,
2. Cataract,
3. Age-related macular degeneration,
4. Retinal vein occlusion,
5. Retinal arterial occlusion,
6. Non-arteritic ischaemic optic neuropathy and
7. Glaucoma.

Around 50% of visual loss in people with type 2 diabetes results from causes other than diabetic retinopathy.

Some of these conditions are to be expected in this group, as they relate to cardiovascular risk factors (e.g. hypertension, hyperlipidaemia and smoking), all of which are prevalent in people with type 2 diabetes.

Diabetic retinopathy

Diabetic retinopathy is the most commonly diagnosed diabetes-related complication. Its prevalence increases with the duration of diabetes. Some 20% of people with type 1 diabetes will have retinal changes after 10 years, rising to >95% after 20 years; 20–30% of people with type 2 diabetes have retinopathy at diagnosis. The metabolic consequences of poorly controlled diabetes cause intramural pericyte death, and thickening of the basement membrane in the small blood vessels of the retina. This leads initially to increased permeability of the vascular walls, and later to occlusion of the vessels (capillary closure). This process has somewhat different consequences in the peripheral retina and in the macular area.[5]

Pathogenesis[1]

Hyperglycaemia increases retinal blood flow and disrupts intracellular metabolism in retinal endothelial cells and pericytes (pericytes wrap around the outside of the capillary wall and influence blood flow and capillary permeability). This leads to impaired vascular autoregulation, increased production of vasoactive substances and endothelial cell proliferation.

The resulting capillary hypoperfusion and closure cause chronic retinal ischaemia, stimulating the production of growth factors, including vascular endothelial growth factor (VEGF), which further stimulates deleterious endothelial cell growth (causing new vessel formation) and increased vascular permeability (causing retinal leakage and exudation).

Natural history and clinical features[1]

DR is a progressive condition, often classified into two stages:

1. non-proliferative ('background') and
2. proliferative.

Non-proliferative DR

The earliest signs of non-proliferative DR are microaneurysms and retinal haemorrhages, sometimes inaccurately called 'dot' and 'blot' haemorrhages, respectively (Fig. A and B).

As DR progresses and there is continuing capillary hypoperfusion, cotton wool spots, venous beading and intra-retinal microvascular abnormalities can be seen (Fig. C–E); this stage is referred to as pre-proliferative DR.

Proliferative DR

The disease may then progress to proliferative DR, which is characterised by growth of new blood vessels on the retina or optic disc (Fig. F and G).

The new vessels are abnormal and often bleed, leading to vitreous haemorrhage, subsequent fibrosis and scarring, and finally tractional retinal detachment.

Macular oedema

In addition to proliferative and non-proliferative DR, patients may also develop clinically significant macular oedema (CSMO; see Fig. C). This can occur at any stage of DR and is characterised by increased vascular permeability and deposition of hard exudates in the central retina.

CSMO is the most common cause of loss of vision in people with diabetes.

Rubeosis iridis

Proliferative retinopathy and severe ocular ischaemia may stimulate new vessels to grow on the anterior surface of the iris: 'rubeosis iridis'. These vessels may obstruct the drainage angle of the eye and the outflow of aqueous fluid, causing secondary glaucoma.

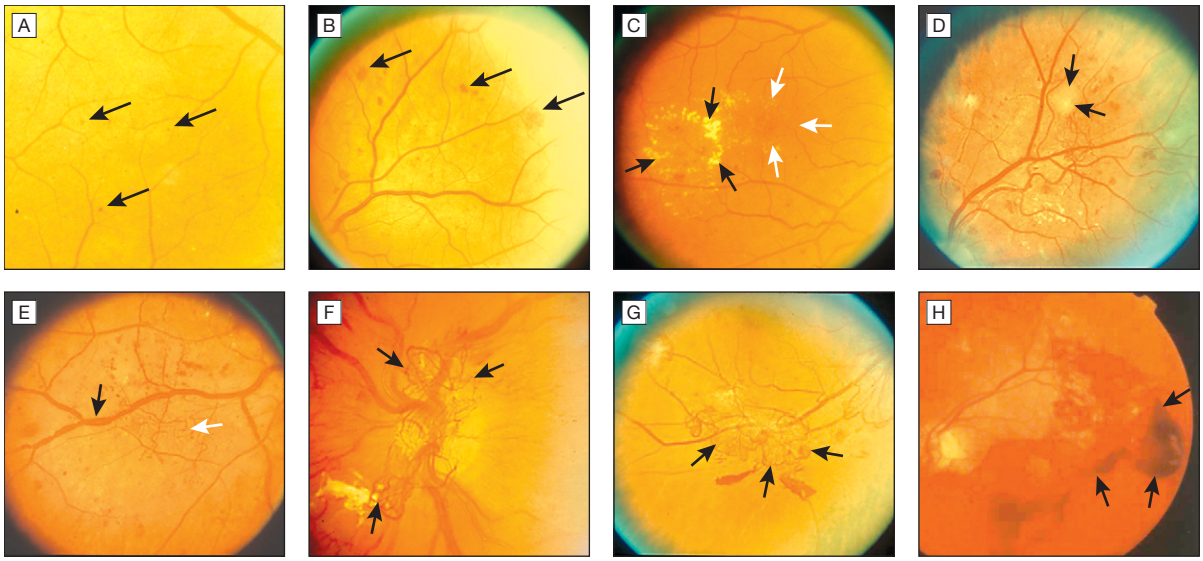


Figure: Diabetic retinopathy.[1]

[A] Microaneurysms. Usually the earliest clinical abnormality, these tiny aneurysms arise mainly from the venous end of capillaries and appear as discrete, circular, dark red dots near to, but apparently separate from, the retinal vessels and no wider than a vessel at the optic disc margin (arrows).

[B] Haemorrhages. Larger than a microaneurysm, with indistinct margins and at least as wide as a vessel at the optic disc margin, these occur in deeper layers of the retina (arrows). They result either from microaneurysms that have burst or from leaky capillaries. Superficial flame-shaped haemorrhages in the nerve fibre layer may also occur, particularly if the patient is hypertensive.

[C] Hard exudates. These irregularly shaped lesions are formed from leaking of cholesterol, often through microaneurysms (black arrows). They can be associated with retinal oedema; if this affects the centre of the macula, it can cause clinically significant macular oedema (CSMO, white arrows), which is sight-threatening.

[D] Cotton wool spots. These white, feathery, fluffy lesions indicate capillary infarcts within the nerve fibre layer (arrows). They are most often seen in rapidly advancing retinopathy or in association with uncontrolled hypertension.

[E] Venous beading. In extensive retinal ischaemia, walls of veins develop saccular bulges, looking like a string of sausages (black arrow). Intra-retinal microvascular anomalies (IRMA) are spidery vessels, often with sharp corners that indicate dilatations of pre-existing capillaries (white arrow).

[F] and [G] Neovascularisation. New vessel formation in response to widespread retinal ischaemia may arise from the venous circulation either on the optic disc (NVD, arrows in F) or elsewhere in the retina (NVE, arrows in G). Initially, fine tufts of delicate vessels form arcades on the surface of the retina; later, they may extend forwards on to the posterior surface of the vitreous. Leaking of serous products from new vessels stimulates a connective tissue reaction, with gliosis and fibrosis, that first appears as a white, cloudy haze among the network of new vessels and later extends to obliterate the area with a dense white sheet.

[H] Vitreous haemorrhage. New vessels are fragile and liable to rupture during vitreous movement, causing a pre-retinal ('subhyaloid') or a vitreous haemorrhage (arrows), which may lead to sudden visual loss.

Loss of visual acuity[1]

Microaneurysms, abnormalities of the veins, and small haemorrhages and exudates situated in the periphery will not interfere with vision. However, if these changes are observed near the macula, and in particular if they are accompanied by loss of visual acuity, CSMO should be suspected.

Macular oedema can cause impairment of visual acuity even if this is associated with only mild peripheral non-proliferative retinopathy and no other obvious pathology. Macular oedema can only be confirmed or excluded on slit lamp retinal biomicroscopy.

Sudden visual loss occurs with vitreous haemorrhage or retinal detachment.

In pre-proliferative and proliferative retinopathy, whether or not visual acuity is impaired, prompt laser treatment is important to reduce the risk of haemorrhage, fibrosis/gliosis and severe irreversible visual impairment.

Risk factors[1]

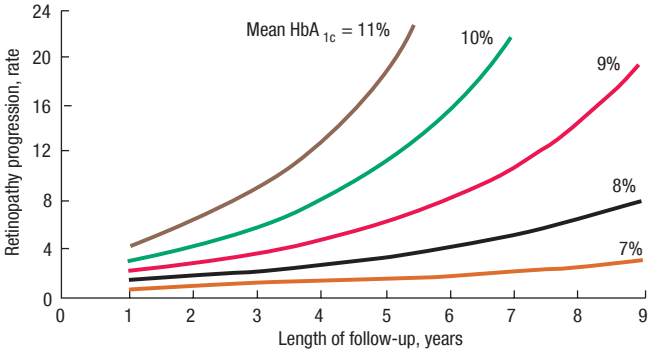
Risk factors for diabetic retinopathy –

- Long duration of diabetes
- Poor glycemic control
- Hypertension
- Hyperlipidaemia
- Pregnancy
- Nephropathy/renal disease
- Others: obesity, smoking

Prevention[1]

Glycaemic control

Many epidemiological studies have shown a clear relationship between glycaemic control and the incidence of DR. Large randomised controlled trials have shown convincingly that improved glycaemic control, particularly in the early stages of disease, reduces both the incidence and progression of DR in type 1 and type 2 diabetes.



Figure[9]: Relationship of glycemic control and diabetes duration to diabetic retinopathy. The progression of retinopathy in individuals in the Diabetes Control and Complications Trial is graphed as a function of the length of follow-up with different curves for different HbA_{1c} values.

When blood glucose is lowered, there can be a transient deterioration of retinopathy. This relates to loss of hyperglycaemia-induced hyperperfusion in the retinal circulation and a consequent increase in ischaemia. However, this effect wears off within 18 months. Improvement in glycaemic control should therefore be effected gradually in patients with retinopathy, particularly when glycaemic control is initially poor.

Blood pressure control

Evidence from randomised controlled trials suggests that blood pressure control is also warranted to reduce the incidence and progression of DR. Early trials suggested specific benefit from angiotensin II receptor antagonists, but later studies indicate that other antihypertensive agents are similarly effective. Most guidelines recommend achieving a blood pressure of less than 130/80 mmHg.

Lipid profile control

Observational studies suggest that hyperlipidaemia is a risk factor for DR, but intervention trials have not been conclusive.

Screening

Annual screening for retinopathy is essential in all diabetic patients, as the disease is asymptomatic in the early stages, when treatment is most effective. Screening is particularly important in those with risk factors. It should be undertaken by trained personnel in an organised and audited programme.

The preferred method is a digital photographic system for retinal imaging, with prompt referral of patients with sight threatening retinopathy to an ophthalmologist for examination with slit lamp biomicroscopy. If direct ophthalmoscopy is used, the pupils should be dilated for adequate examination.

Unfortunately, many people with diabetes receive no regular supervision and do not attend for eye screening.

Development or progression of retinopathy may be accelerated by rapid improvement in glycaemic control, by pregnancy and by nephropathy, and these groups need frequent monitoring.[5]

Criteria for a successful local screening scheme for sight-threatening diabetic retinopathy[5]

1. Clearly defined geographical area for the screening programme
2. Adequate number of people with diabetes for viability (>12 000)
3. Identified screening programme manager
4. Identified clinical screening lead
5. Identified hospital eye service for diagnosis and laser treatment
6. Computer software capable of supporting call/recall of patients and image grading
7. Centralized appointment administration
8. Single collated list of all people with diabetes in the area over the age of 12
9. Equipment to obtain adequate disc- and macula-centred images of each eye
10. Single image grading centre
11. Process to manage people with poor-quality images
12. Clear route of referral for treatment, and for feedback from treatment centre to screening unit
13. Accreditation of screening staff
14. Annual reporting of service performance

Management

The most effective therapy for diabetic retinopathy is prevention. Good glycaemic (HbA_{1c} around 53 mmol/mol (7%)) control and an appropriate blood pressure (< 130/ 80 mmHg) should be maintained to prevent onset and delay progression of diabetic eye disease.[1]

Paradoxically, during the first 6–12 months of improved glycemic control, established diabetic retinopathy may transiently worsen. Fortunately, this progression is temporary, and in the long term, improved glycemic control is associated with less diabetic retinopathy.[5]

Fluorescein angiography (a fluorescent dye is injected into an arm vein and photographed in transit through the retinal vessels) is used to define the extent of the potentially sight-threatening diabetic retinopathy. Ocular coherence tomography (OCT) is used to image the content of the layers of the retina at the macula, and in particular to measure retinal thickness. It can detect macular oedema and other macular abnormalities.[5]

Ranibizumab

Novel agents are emerging, including ranibizumab, a monoclonal antibody fragment that binds to VEGF-A and is antiangiogenic; it is used for diabetic macular oedema.

Retinal photocoagulation

Individuals with known retinopathy may be candidates for prophylactic laser photocoagulation when initiating intensive therapy. Once advanced retinopathy is present, improved glycemic control imparts less benefit, although adequate ophthalmologic care can prevent most blindness.[1]

Retinal photocoagulation (laser treatment) is indicated in[1]-

- Severe proliferative or very severe nonproliferative retinopathy;
- New vessels elsewhere with vitreous haemorrhage;
- New vessels without vitreous haemorrhage in type 2 diabetes; or
- CSMO.

Photocoagulation is used[1] –

- to treat leaking microaneurysms and areas of retinal thickening in the macular area, and to reduce macular oedema (focal laser)
- to destroy areas of retinal ischaemia and hence lower intraocular levels of VEGF, which play a major role in the development of neovascularisation
- to reduce the risk of recurrent haemorrhage by inducing gliosis and fibrosis of new vessels (pan-retinal photocoagulation (PRP)).

Argon laser photocoagulation is the usual method. This simple procedure can be carried out under topical anaesthesia. Patients should be reviewed regularly to look for further development of new vessels and/or maculopathy. Extensive bilateral photocoagulation can cause significant visual field loss, which may interfere with driving ability and reduce night vision.[1]

Laser photocoagulation is very successful in preserving vision. Proliferative retinopathy is usually treated with panretinal laser photocoagulation, whereas macular edema is treated with focal laser photocoagulation and anti–vascular endothelial growth factor therapy (ocular injection).[9]

Vitrectomy

Vitrectomy is used in selected cases of advanced diabetic eye disease due to type 1 diabetes where visual loss has been caused by[1] –

- recurrent vitreous haemorrhage that has failed to clear or
- by tractional retinal detachment threatening the macula.

The value of vitrectomy in type 2 diabetes is less certain. Rubeosis iridis is a severe complication requiring early and extensive PRP.

Grading and management of pathological changes in diabetic retinopathy[5]

Retinopathy grade	Retinal abnormality (cause)	Action needed
Peripheral retina		
Background (R1)	1. Dot haemorrhages (capillary microaneurysms) (usually appear first) 2. Blot haemorrhages (leakage of blood into deeper retinal layers) 3. Hard exudates (exudation of plasma rich in lipids and protein)[a] 4. Cotton wool spots/cytoid bodies[b]	Annual screening only
Preproliferative (R2)	1. Venous beading/loops 2. Intraretinal microvascular abnormalities (IRMAs) 3. Multiple deep, round haemorrhages	Non-urgent referral to an ophthalmologist
Proliferative (R3)	1. New blood-vessel formation/neovascularization 2. Preretinal or subhyaloid haemorrhage 3. Vitreous haemorrhage	Urgent referral to an ophthalmologist
Advanced retinopathy	1. Retinal fibrosis 2. Traction retinal detachment	Urgent referral to an ophthalmologist – but much vision already lost
Central retina		
Maculopathy (M1)	1. Hard exudates within 1 disc-width of macula 2. Lines or circles of hard exudates within 2 disc-widths of macula 3. Microaneurysms or retinal haemorrhages within 1 disc-width of macula if associated with an unexplained visual acuity 6/12 or worse	Prompt referral to an ophthalmologist

[a]Hard exudates have a bright yellowish-white colour and are often irregular in outline with a sharply defined margin.
[b]Cotton-wool spots are greyish-white and have indistinct margins and a dull matt surface, unlike the glossy appearance of hard exudates. Peripheral

Cataract

Cataract is a permanent lens opacity and is a common cause of visual deterioration in the elderly.[1] Cataract develops earlier in people with diabetes than in the general population.[5]

Pathogenesis

The lens thickens and opacifies with age; with diabetes, the increased metabolic insult to the lens causes these changes to accelerate and occur prematurely.[1]

A rare type of 'snow-flake' cataract occurs in young patients with poorly controlled diabetes. It comes on rapidly. This does not usually affect vision but tends to make fundal examination difficult.[1]

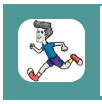
Fluctuations in blood glucose concentration can cause refractive variability, as a result of osmotic changes within the lens (the absorption of water into the lens causes temporary hypermetropia). This presents as fluctuating difficulty in reading. It resolves with better metabolic control of the diabetes.[5]

Treatment

Extraction and intraocular lens implantation is indicated if the cataract is causing visual disability or an inability to view the retina adequately. Cataract extraction is straightforward if there is no retinopathy present. Pre-existing retinopathy may worsen after cataract extraction.[5]

Indication for cataract extraction[1] –

- The indications for cataract extraction are similar to those for the non-diabetic population and depend on the degree of visual impairment.
- An additional indication in diabetes is when adequate assessment of the fundus, or laser treatment to the retina, is prevented.



Bedside eye examination[5]

Visual acuity should be checked using both a pinhole and the patient's distance spectacles. The ocular movements are assessed to detect any ocular motor palsies. The iris is examined for rubeosis and then the pupils dilated with 1% tropicamide. About 20 minutes later, the eye is examined for the presence of a cataract by looking at the lens with a +10.00 lens in the ophthalmoscope and viewing the lens against the red reflex. The retina is then examined systematically looking at the disc, then all four quadrants, and finally the macula. The macula is examined last because this induces the greatest discomfort, and pupillary constriction.

24 Renal complications of diabetes

The kidney may be damaged by diabetes in three main ways[5]:

1. glomerular damage
2. ischaemia resulting from hypertrophy of afferent and efferent arterioles
3. ascending infection.

Diabetic nephropathy is an important cause of morbidity and mortality.[1] It is the leading cause of chronic kidney disease (CKD), ESRD, and CKD requiring renal replacement therapy. Furthermore, the prognosis of diabetic patients on dialysis is poor, with survival comparable to many forms of cancer. Albuminuria in individuals with DM is associated with an increased risk of cardiovascular disease. Individuals with diabetic nephropathy commonly have diabetic retinopathy.[9]

Common causes of end-stage renal failure[1]

Disease	Proportion	Comments
Congenital and inherited	5%	Polycystic kidney disease, Alport's syndrome
Renovascular disease	5%	Mostly atheromatous, may be more common
Hypertension	5–20%	Causality controversial, much may be renal disease
Glomerular diseases	10–20%	IgA nephropathy is most common
Interstitial diseases	20–30%	Often drug-induced
Systemic inflammatory diseases	5–10%	Systemic lupus erythematosus, vasculitis
Diabetes mellitus	20–40%	Large racial and geographical differences
Unknown	5–20%	

Epidemiology[1]

About 30% of patients with type 1 diabetes have developed diabetic nephropathy 20 years after diagnosis, but the risk after this time falls to less than 1% per year, and from the outset the risk is not equal in all patients (see the risk factors).

Indeed, some patients do not develop nephropathy, despite having long-standing, poorly controlled diabetes, suggesting that they are genetically protected from it. Whilst variants in a few genes have been implicated in diabetic nephropathy, the major differences in individual risk remain unexplained.

Epidemiological data have indicated that the overall incidence is declining as standards of glycaemic and blood pressure control have improved.

Risk factors[1]

Risk factors for diabetic nephropathy are –

- Poor glycaemic control
- Long duration of diabetes
- Presence of other microvascular complications
- Ethnicity (e.g. Asians, Pima Indians)
- Pre-existing hypertension
- Family history of diabetic nephropathy
- Family history of hypertension

Pathology[5]

The earliest functional abnormality in the diabetic kidney is renal hypertrophy associated with a raised GFR. This appears soon after diagnosis and is related to poor glycaemic control.

As the kidney becomes damaged by diabetes, the afferent arteriole becomes vasodilated to a greater extent than the efferent glomerular arteriole. This increases the intraglomerular filtration pressure, further damaging the glomerular capillaries. This raised intraglomerular pressure also leads to increased local shearing forces, which are thought to contribute to mesangial cell hypertrophy and increased secretion of extracellular mesangial matrix

material. This process eventually leads to glomerular sclerosis.

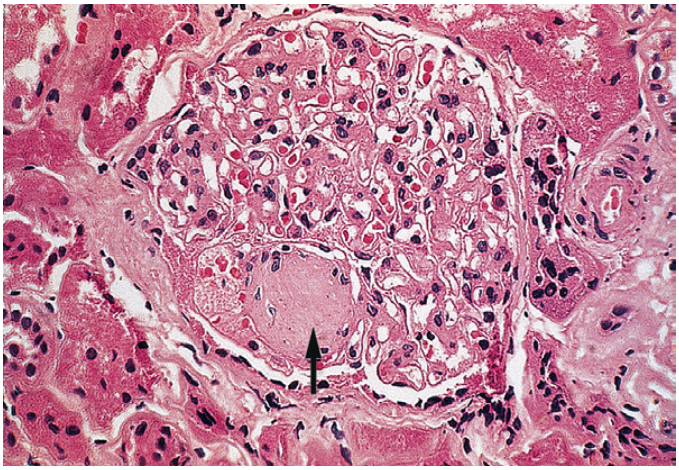
The initial structural lesion in the glomerulus is thickening of the basement membrane. Associated changes result in disruption of the protein cross-linkages that normally make the membrane an effective filter. In consequence, there is a progressive leak of large molecules (particularly protein) into the urine.

Albuminuria

The earliest evidence of this is 'microalbuminuria' – amounts of urinary albumin so small as to be undetectable by standard dipsticks. Microalbuminuria may be tested for with radio immunoassay or special dipsticks. It is a predictive marker of progression to nephropathy in type 1 diabetes, and of increased cardiovascular risk in type 2 diabetes.

Microalbuminuria may, after some years, progress to intermittent albuminuria followed by persistent proteinuria. Light-microscopic changes of glomerulosclerosis become manifest; both diffuse and nodular glomerulosclerosis can occur. The latter is sometimes known as the Kimmelstiel–Wilson lesion.

At the later stage of glomerulosclerosis, the glomerulus is replaced by hyaline material. At the stage of persistent proteinuria, the plasma creatinine is normal but the average patient is only some 5–10 years from end-stage kidney disease. The proteinuria may become so heavy as to induce a transient nephrotic syndrome, with peripheral oedema and hypoalbuminaemia. Patients with nephropathy typically show a normochromic normocytic anaemia and a raised erythrocyte sedimentation rate (ESR).



Figure[1]: Nodular diabetic glomerulosclerosis. There is thickening of basement membranes and mesangial expansion, and a Kimmelstiel–Wilson nodule (arrow), which is pathognomonic of diabetic kidney disease.

Hypertension is a common development and may itself damage the kidney still further.

A rise in plasma creatinine is a late feature that progresses inevitably to renal failure, although the rate of progression may vary widely between individuals.

The pattern of progression of renal abnormalities in diabetes is shown schematically below[1] –

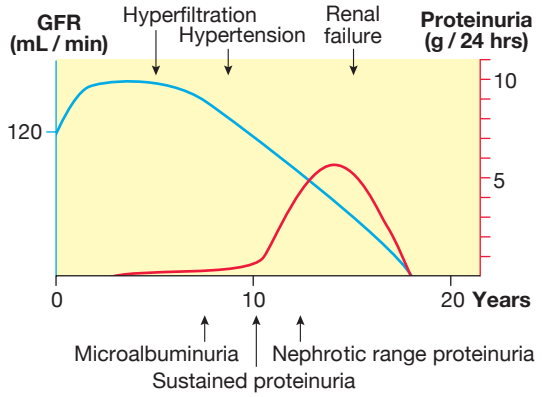


Figure: Natural history of diabetic nephropathy.[1] In the first few years of type 1 diabetes mellitus, there is hyperfiltration, which declines fairly steadily to return to a normal value at approximately 10 years (blue line). In susceptible patients (about 30%), after about 10 years, there is sustained proteinuria, and by approximately 14 years it has reached the nephrotic range (red line). Renal function continues to decline, with the end stage being reached at approximately 16 years.

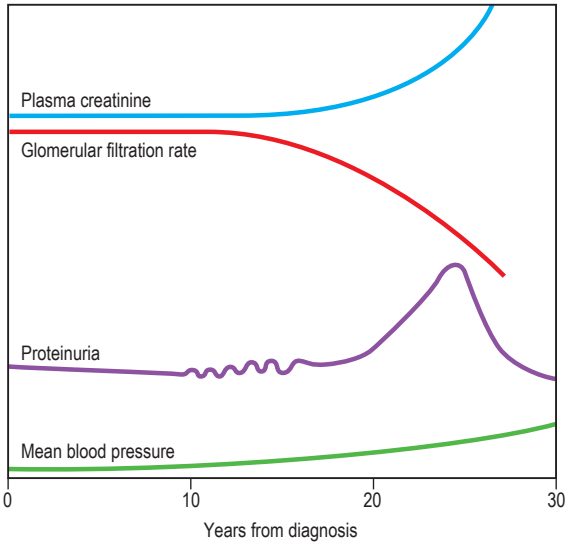


Figure: Schematic representation of the natural history of nephropathy.[5] The typical onset is 15 years after diagnosis. Intermittent proteinuria leads to persistent proteinuria. In time, the plasma creatinine rises as the glomerular filtration rate falls.

Ischaemic lesions

Arteriolar lesions, with hypertrophy and hyalinization of the vessels, can occur in patients with diabetes. The appearances are similar to those of hypertensive disease and lead to ischaemic damage to the kidneys.

Infective lesions

Urinary tract infections are relatively more common in women with diabetes, but not in men. Ascending infection may occur because of bladder stasis resulting from autonomic neuropathy, and infections more easily become established in damaged renal tissue. Autopsy material frequently reveals interstitial changes suggestive of infection, but ischaemia may produce similar changes and

the true frequency of pyelonephritis in diabetes is uncertain. Untreated infections in diabetics can result in renal papillary necrosis, in which renal papillae are shed in the urine, but this complication is now very rare.

Diagnosis and screening

Microalbuminuria is the presence in the urine of small amounts of albumin, at a concentration below that detectable using a standard urine dipstick.

Quantifying proteinuria in random urine samples [1]

ACR[1]	PCR[2]	Typical dipstick results[3]	Significance
< 3.5 (female) < 2.5 (male)		–	Normal
~3.5–15		–	Microalbuminuria
~15–50	~15–50	+ to ++	Dipsticks positive; equivalent to 24-hr protein excretion < 0.5 g
50–200	> 250	++ to +++	Glomerular disease more likely
> 200	> 300	+++ to ++++	Nephrotic range: always glomerular disease, equivalent to 24-hr protein excretion > 3 g

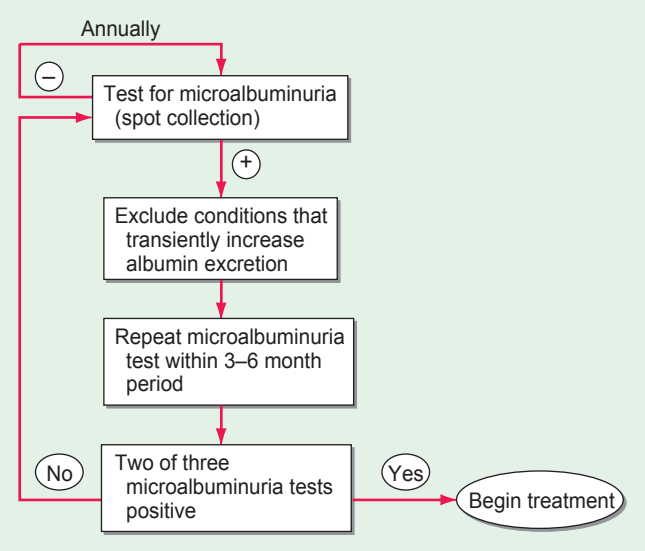
[1]Urinary albumin (mg/L)/urine creatinine (mmol/L). [2]Urine protein (mg/L)/urine creatinine (mmol/L). (If urine creatinine is measured in mg/dL, reference values for PCR and ACR can be derived by dividing by 11.31.)
[3]Dipstick results are affected by urine concentration and are occasionally weakly positive on normal samples.

Overt nephropathy is defined as the presence of macroalbuminuria (albumin to creatinine ratio (ACR) > 300 mg/mmol; detectable on urine dipstick).

Screening for microalbuminuria [1]

- Identifies incipient nephropathy in type 1 and type 2 diabetes; is an independent predictor of macrovascular disease in type 2 diabetes
- Risk factors include high blood pressure, poor glycaemic control, smoking
- Who to screen:
  - Patients with type 1 diabetes annually from 5 yrs after diagnosis
  - Patients with type 2 diabetes annually from time of diagnosis
- Early morning urine measured for albumin : creatinine ratio (ACR). Microalbuminuria present if:
  - Males ACR 2.5–30 mg/mmol creatinine
  - Females ACR 3.5–30 mg/mmol creatinine
- An elevated ACR should be followed by a repeat test:
  - Established microalbuminuria if 2 out of 3 tests positive
  - An ACR > 30 mg/mmol creatinine is consistent with overt nephropathy

Microalbuminuria is a good predictor of progression to nephropathy in type 1 diabetes. It is a less reliable predictor of nephropathy in older patients with type 2 diabetes, in whom it may be accounted for by other diseases, although it is a potentially useful marker of an increased risk of macrovascular disease.



Figure[9]: Screening for microalbuminuria flow chart. Non-diabetes-related conditions that might increase microalbuminuria are urinary tract infection, hematuria, heart failure, febrile illness, severe hyperglycemia, severe hypertension, and vigorous exercise.

Management[1]

The management of diabetic nephropathy is similar to that of other causes of chronic kidney disease, with the following provisos[5]:

- Aggressive treatment of blood pressure with a target <130/80 mmHg has been shown to slow the rate of deterioration of renal failure considerably.
- Oral hypoglycaemic agents partially excreted via the kidney (e.g. glibenclamide and metformin) should be avoided.
- Insulin sensitivity increases and drastic reductions in insulin dosage may be needed.
- Associated diabetic retinopathy tends to progress rapidly, and frequent ophthalmic supervision is essential.

The presence of established microalbuminuria or overt nephropathy should prompt vigorous efforts to reduce the risk of progression of nephropathy and of cardiovascular disease by:

1. aggressive reduction of blood pressure
2. aggressive cardiovascular risk factor reduction.

Blood pressure reduction

- In type 1 diabetes, ACE inhibitors have been shown to provide greater protection than equal blood pressure reduction achieved with other drugs.

- In type 2 diabetes, subsequent studies have shown similar benefits from angiotensin II receptor blockers (ARBs).

An ACE inhibitor or angiotensin II receptor antagonist is the drug of choice. These drugs should also be used in normotensive patients with persistent microalbuminuria. Reduction in albuminuria occurs with this treatment.[5]

Blockade of the renin– angiotensin system

This benefit from blockade of the renin– angiotensin system arises from a reduction in the angiotensin II-mediated vasoconstriction of efferent arterioles in glomeruli.

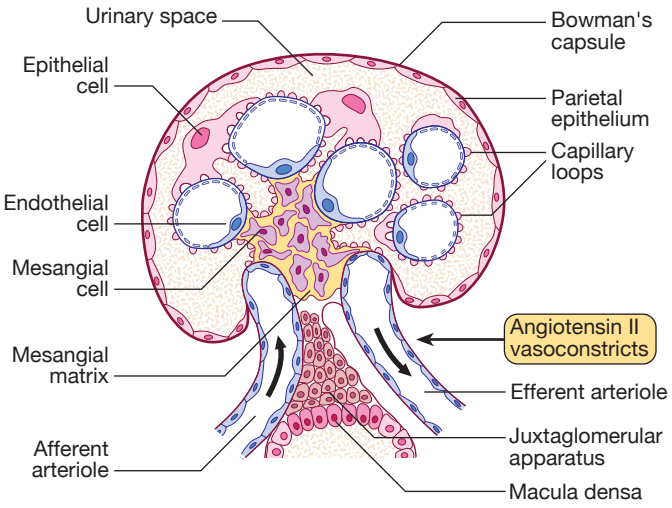


Figure: Schematic cross-section of a glomerulus showing site of angiotensin II-mediated vasoconstriction of efferent arterioles.[1]

The resulting dilatation of these vessels decreases glomeruli filtration pressure and therefore the hyperfiltration and protein leak.

Risks

Both ACE inhibitors and ARBs increase risk of hyperkalaemia and, in the presence of renal artery stenosis, may induce marked deterioration in renal function. Therefore, electrolytes and renal function should be checked after initiation or each dose increase.

Alternative

Non-dihydropyridine calcium antagonists (diltiazem, verapamil) may be suitable alternatives.

Halving the amount of albuminuria with an ACE or ARB results in a nearly 50% reduction in long-term risk of progression to end-stage renal disease. However, some patients do progress, with worsening renal function. Renal replacement therapy may benefit diabetic patients at an earlier stage than other patients with end-stage renal failure.

Renal replacement therapy

Renal transplantation dramatically improves the life of many, and any recurrence of diabetic nephropathy in the allograft is usually too slow to be a serious problem, but associated macrovascular and microvascular disease elsewhere may still progress.

Pancreatic transplantation

Pancreatic transplantation (generally carried out at the same time as renal transplantation) can produce insulin independence and delay or reverse microvascular disease, but the supply of organs is limited and this option is available to few.

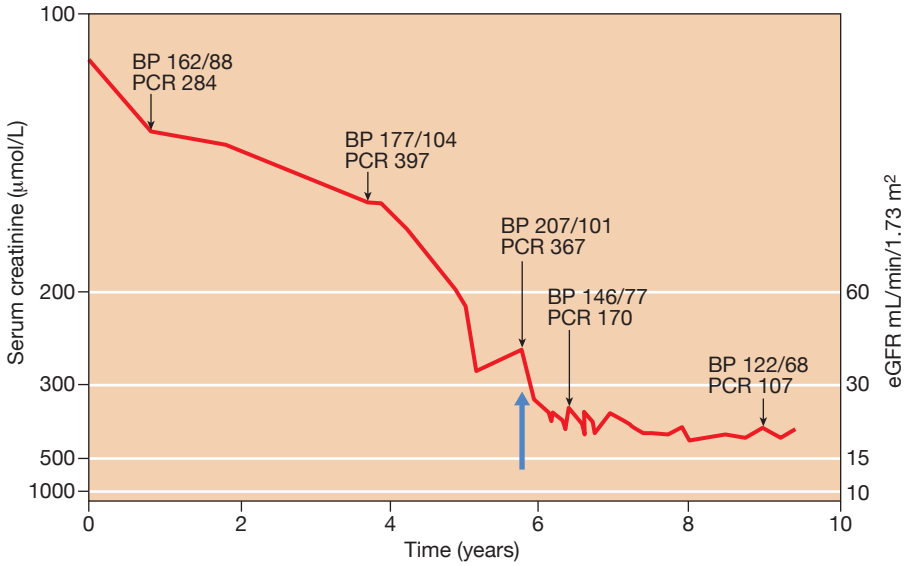


Figure: Plot of the reciprocal of serum creatinine concentration against time in a patient with type 1 diabetes mellitus. After approximately 6 years of monitoring (blue arrow), he entered an aggressive treatment programme aimed at optimising blood pressure (BP) and glycaemic control. The reduction in blood pressure was accompanied by a fall in proteinuria (protein : creatinine ratio, PCR; mg/mmol) and a stabilisation in renal function.[1]

25 Diabetic neuropathy

Diabetic neuropathy causes substantial morbidity and increases mortality. Depending on the criteria used for diagnosis, it affects between 50 and 90% of patients with diabetes, and of these, 15–30% will have painful diabetic neuropathy (PDN).[1] Diabetic neuropathy may manifest as polyneuropathy, mononeuropathy, and/or autonomic neuropathy.[9]

As with other complications of DM, the development of neuropathy correlates with the duration of diabetes and glycemic control. Additional risk factors are body mass index (BMI) (the greater the BMI, the greater the risk of neuropathy) and smoking. The presence of CVD, elevated triglycerides, and hypertension is also associated with diabetic peripheral neuropathy.[9]

Both myelinated and unmyelinated nerve fibers are lost. Because the clinical features of diabetic neuropathy are similar to those of other neuropathies, the diagnosis of diabetic neuropathy should be made only after other possible etiologies are excluded.[9]

Although there is some evidence that the central nervous system is affected in long-term diabetes, the clinical impact of diabetes is mainly manifest in the peripheral nervous system.[1]

Pathological features can occur in any peripheral nerves. They include axonal degeneration of both myelinated and unmyelinated fibres, with thickening of the Schwann cell basal lamina, patchy segmental demyelination, and abnormal intraneural capillaries (with basement membrane thickening and microthrombi).[1] The earliest functional change in diabetic nerves is delayed nerve conduction velocity; the earliest histological change is segmental demyelination, caused by damage to Schwann cells. In the early stages, axons are preserved, implying prospects of recovery; at a later stage, irreversible axonal degeneration develops.[5]

Classifications

Various classifications of diabetic neuropathy have been proposed. One classification is[5] –

- symmetrical, mainly sensory polyneuropathy (distal)
- acute painful neuropathy
- mononeuropathy and mononeuritis multiplex
    - cranial nerve lesions
    - isolated peripheral nerve lesions
- diabetic amyotrophy (asymmetrical motor diabetic neuropathy)
- autonomic neuropathy.

Another classification is shown in Box below, but motor, sensory and autonomic nerves may be involved in varying combinations so that clinically mixed syndromes usually occur.[1]

Classification of diabetic neuropathy[1]

Somatic

- Polyneuropathy
  Symmetrical, mainly sensory and distal
  Asymmetrical, mainly motor and proximal (including amyotrophy)
- Mononeuropathy (including mononeuritis multiplex)

Visceral (autonomic)

- Cardiovascular
- Gastrointestinal
- Genitourinary
- Sudomotor
- Vasomotor
- Pupillary

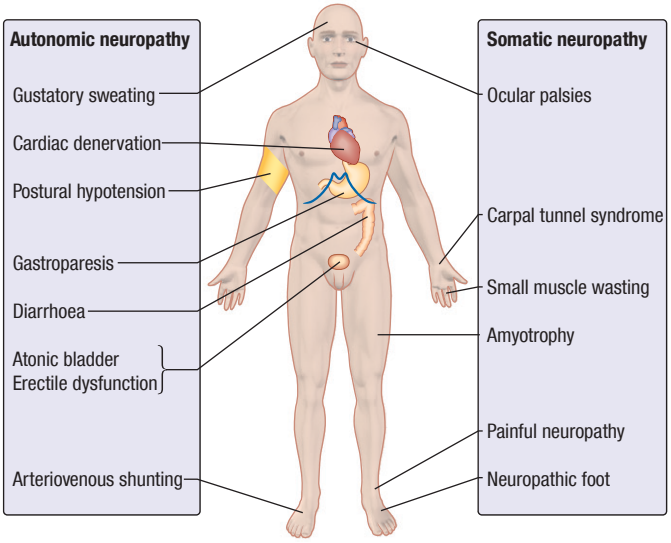


Figure: The neuropathic man.[5]

Symmetrical sensory polyneuropathy[1]

This is frequently asymptomatic. The most common clinical signs are diminished perception of vibration sensation distally, 'glove and stocking' impairment of all other modalities of sensation, and loss of tendon reflexes in the lower limbs.

In symptomatic patients, sensory abnormalities are predominant. Symptoms include

1. paraesthesiae in the feet (and, rarely, in the hands),
2. pain in the lower limbs (dull, aching and/or lancinating, worse at night, and mainly felt on the anterior aspect of the legs),
3. burning sensations in the soles of the feet,
4. cutaneous hyperaesthesia and an abnormal gait (commonly wide-based),
5. often associated with a sense of numbness in the feet.

Weakness and atrophy, in particular of the interosseous muscles, may develop, leading to structural changes in the foot with

1. loss of lateral and transverse arches,
2. clawing of the toes and exposure of the metatarsal heads. This results in increased pressure on the plantar aspects of the metatarsal heads, with the development of callus skin at these and other pressure points.

Electrophysiological tests

Electrophysiological tests demonstrate slowing of both motor and sensory conduction, and tests of vibration sensitivity and thermal thresholds are abnormal.

A diffuse small-fibre neuropathy

A diffuse small-fibre neuropathy causes altered perception of pain and temperature, and is associated with symptomatic autonomic neuropathy; characteristic features include foot ulcers and Charcot neuroarthropathy.

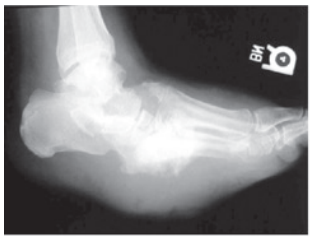


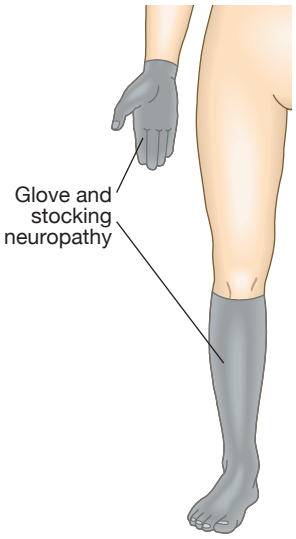
Figure: Charcot foot[1]

Asymmetrical motor diabetic neuropathy[1]

It is sometimes called diabetic amyotrophy.

Presentation

- This presents as severe and progressive weakness and wasting of the proximal muscles of the lower (and occasionally the upper) limbs.
- It is commonly accompanied by severe pain, mainly felt on the anterior aspect of the leg, and hyperaesthesia and paraesthesiae.
- Sometimes there may also be marked loss of weight ('neuropathic cachexia').
- The patient may look extremely ill and be unable to get out of bed.
- Tendon reflexes may be absent on the affected side(s).
- Sometimes there are extensor plantar responses and the cerebrospinal fluid protein is often raised.



Pathogenesis

This condition is thought to involve acute infarction of the lower motor neurons of the lumbosacral plexus.

Other lesions involving this plexus, such as neoplasms and lumbar disc disease, must be excluded.

Prognosis

Although recovery usually occurs within 12 months, some deficits are permanent.

Management

Management is mainly supportive.

Mononeuropathy[1]

Either motor or sensory function can be affected within a single peripheral or cranial nerve.

Presentation

- Unlike the gradual progression of distal symmetrical and autonomic neuro pathies, mononeuropathies are severe and of rapid onset, but they eventually recover.
- The nerves most commonly affected are the 3rd and 6th cranial nerves (resulting in diplopia), and the femoral and sciatic nerves.
- Rarely, involvement of other single nerves results in paresis and paraesthesiae in the thorax and trunk (truncal radiculopathies).
- Nerve compression palsies are more common in diabetes, frequently affecting the median nerve, giving the clinical picture of carpal tunnel syndrome, and less commonly the ulnar nerve.
- Lateral popliteal nerve compression occasionally causes foot drop.
- Compression palsies may be more common because of glycosylation and thickening of connective tissue and/or because of increased susceptibility of nerves affected by diabetic microangiopathy.

Autonomic neuropathy[1]

This is not necessarily associated with peripheral somatic neuropathy. Parasympathetic or sympathetic nerves may be predominantly affected in one or more visceral systems. The resulting symptoms and signs are listed in Box below –

Clinical features of autonomic neuropathy[1]

Cardiovascular

- Postural hypotension
- Resting tachycardia
- Fixed heart rate

Gastrointestinal

- Dysphagia, due to oesophageal atony
- Abdominal fullness, nausea and vomiting, unstable glycaemia, due to delayed gastric emptying ('gastroparesis')
- Nocturnal diarrhoea ± faecal incontinence
- Constipation, due to colonic atony

Genitourinary

- Difficulty in micturition, urinary incontinence, recurrent infection, due to atonic bladder
- Erectile dysfunction and retrograde ejaculation

Sudomotor

- Nocturnal sweats without hypoglycaemia
- Gustatory sweating
- Anhidrosis; fissures in the feet

Vasomotor

- Feet feel cold, due to loss of skin vasomotor responses
- Dependent oedema, due to loss of vasomotor tone and increased vascular permeability
- Bullous formation

Pupillary

- Decreased pupil size
- Resistance to mydriatics
- Delayed or absent reflexes to light

Tests of autonomic function

How to test cardiovascular autonomic function[1]

Simple reflex tests

	Normal	Borderline	Abnormal
Heart rate responses			
To Valsalva manœuvre (15 secs)[1]: ratio of longest to shortest R–R interval	≥ 1.21		≤ 1.20
To deep breathing (6 breaths over 1 min): maximum–minimum heart rate	≥ 15	11–14	≤ 10
To standing after lying: ratio of R–R interval of 30th to 15th beats	≥ 1.04	1.01–1.03	≤ 1.00
Blood pressure response[2]			
To standing: systolic BP fall (mmHg)	≤ 10	11–29	≥ 30

Specialised tests

- Heart rate and blood pressure responses to sustained handgrip
- Heart rate variability using power spectral analysis of ECG monitoring
- Heart rate and blood pressure variability using time–domain analysis of ambulatory monitoring
- MIBG (met-iodobenzylguanidine) scan of the heart

[1]Omit in patients with previous laser therapy for proliferative retinopathy.
[2]Avoid arm with arteriovenous fistula in dialysed patients.

Pathogenesis

The development of autonomic neuropathy is less clearly related to poor metabolic control than somatic neuropathy, and improved control rarely results in improved symptoms.

Progression

- Within 10 years of developing overt symptoms of autonomic neuropathy, 30–50% of patients are dead, many from sudden cardiorespiratory arrest.
- Patients with postural hypotension (a drop in systolic pressure of 30 mmHg or more on standing from the supine position) have the highest subsequent mortality.

The cardiovascular system[5]

Vagal neuropathy results in tachycardia at rest and loss of sinus arrhythmia. At a later stage, the heart may become denervated (resembling a transplanted heart). Cardiovascular reflexes, such as the Valsalva manoeuvre, are impaired. Postural hypotension occurs owing to loss of sympathetic tone to peripheral arterioles. A warm foot with a bounding pulse is often seen in a polyneuropathy as a result of peripheral vasodilatation.

The gastrointestinal tract[5]

Vagal damage can lead to gastroparesis, often asymptomatic but sometimes leading to intractable vomiting. Implantable devices that stimulate gastric emptying, and injections of botulinum toxin into the

pylorus (to paralyse the sphincter partly), have each shown benefit in cases of this previously intractable problem. Autonomic diarrhoea characteristically occurs at night, accompanied by urgency and incontinence. Diarrhoea and steatorrhoea may be present, owing to small bowel bacterial overgrowth; treatment is with antibiotics such as tetracycline.

Bladder involvement[5]

Loss of tone, incomplete emptying and stasis (predisposing to infection) can occur and may ultimately result in an atonic, painless, distended bladder. Treatment is with intermittent self-catheterization, permanent catheterization if that fails, and prophylactic antibiotic therapy for those prone to recurrent infection.

Erectile dysfunction

Erectile failure (impotence) affects 30% of diabetic males and is often multifactorial.

Although neuropathy and vascular causes are common, psychological factors, including depression, anxiety and reduced libido, may be partly responsible. Alcohol and antihypertensive drugs, such as thiazide diuretics and β-adrenoceptor antagonists (β-blockers), may cause sexual dysfunction and patients have an endocrine cause such as testosterone deficiency or hyperprolactinaemia.

Causes of erectile dysfunction[1]

With reduced libido
• Hypogonadism • Depression
With intact libido
• Psychological problems, including anxiety • Vascular insufficiency (atheroma) • Neuropathic causes (diabetes mellitus, alcohol excess, multiple sclerosis) • Drugs (β-blockers, thiazide diuretics)

Management[1]

Management of neuropathies is outlined in Box below –

Management options for peripheral sensorimotor and autonomic neuropathies[1]

Pain and paraesthesiae from peripheral somatic neuropathies
• Intensive insulin therapy (strict glycaemic control) • Anticonvulsants (gabapentin, pregabalin, carbamazepine, phenytoin) • Tricyclic antidepressants (amitriptyline, imipramine) • Other antidepressants (duloxetine) • Substance P depleter (capsaicin – topical) • Opiates (tramadol, oxycodone) • Membrane stabilisers (mexiletine, IV lidocaine) • Antioxidant (α-lipoic acid)
Postural hypotension
• Support stockings • Fludrocortisone • NSAIDs • α-adrenoceptor agonist (midodrine)
Gastroparesis
• Dopamine antagonists (metoclopramide, domperidone) • Erythromycin • Gastric pacemaker; percutaneous enteral (jejunal) feeding
Diarrhoea
• Loperamide • Broad-spectrum antibiotics • Clonidine • Octreotide
Constipation
• Stimulant laxatives (senna)
Atonic bladder
• Intermittent self-catheterisation
Excessive sweating
• Anticholinergic drugs (propantheline, poldine, oxybutinin) • Clonidine • Topical antimuscarinic agent (glycopyrrolate cream)
Erectile dysfunction
• Phosphodiesterase type 5 inhibitors (sildenafil, vardenafil, tadalafil) – oral • Dopamine agonist (apomorphine) – sublingual • Prostaglandin E1 (alprostadil) – injected into corpus cavernosum or intra-urethral administration of pellets • Vacuum tumescence devices • Implanted penile prosthesis • Psychological counselling; psychosexual therapy
(NSAIDs = non-steroidal anti-inflammatory drugs)

Additional insights

Causes of polyneuropathy[1]

Genetic

- Charcot–Marie–Tooth disease (CMT)
- Hereditary neuropathy with liability to pressure palsies (HNPP)
- Hereditary sensory ± autonomic neuropathies (HSN, HSAN)
- Familial amyloid polyneuropathy
- Hereditary neuralgic amyotrophy

Drugs

- Amiodarone
- Antibiotics (dapsone, isoniazid, metronidazole, ethambutol)
- Antiretrovirals
- Chemotherapy (cisplatin, vincristine, thalidomide)
- Phenytoin

Toxins

- Alcohol
- Nitrous oxide (recreational use)
- Rarely: lead, arsenic, mercury, organophosphates, solvents

Vitamin deficiencies

- Thiamin
- Pyridoxine
- Vitamin B_{12}
- Vitamin E

Infections

- HIV
- Leprosy
- Brucellosis

Inflammatory

- Guillain–Barré syndrome
- Chronic inflammatory demyelinating polyradiculoneuropathy
- Vasculitis (polyarteritis nodosa, granulomatosis with polyangiitis (also known as Wegener's granulomatosis), rheumatoid arthritis, SLE)
- Paraneoplastic (antibody-mediated)

Systemic medical conditions

- Diabetes
- Renal failure
- Sarcoidosis

Malignant disease

- Infiltration

Others

- Paraproteinaemias
- Amyloidosis
- Critical illness polyneuropathy/myopathy

Common causes of axonal and demyelinating chronic polyneuropathies[1]

Axonal

- Diabetes mellitus
- Alcohol
- Uraemia
- Cirrhosis
- Amyloid
- Myxoedema
- Acromegaly
- Paraneoplastic
- Drugs and toxins
- Deficiency states
- Hereditary
- Infection
- Idiopathic

Demyelinating

- Chronic inflammatory demyelinating polyradiculoneuropathy
- Multifocal motor neuropathy
- Paraprotein-associated demyelinating neuropathy
- Charcot–Marie–Tooth disease type I and type X

26 Diabetic Foot disease

The foot is a frequent site of complications in patients with diabetes and for this reason foot care is particularly important. Treatment of the foot complications of diabetes accounts for more inpatient days than any other diabetes-related complication.[1] A total of 10–15% of diabetic patients develop foot ulcers at some stage in their lives. Diabetic foot problems are responsible for nearly 50% of all diabetes-related hospital admissions. Many diabetic limb amputations could be delayed or prevented by more effective patient education and medical supervision.[5] Tissue necrosis in the feet is a common reason for hospital admission in diabetic patients.[1] Ischaemia, infection and neuropathy combine to produce tissue necrosis. Although all these factors may coexist, the ischaemic and the neuropathic foot can be distinguished. In rural India, foot ulcers are commonly due to neuropathic and infective causes rather than vascular causes.[5]

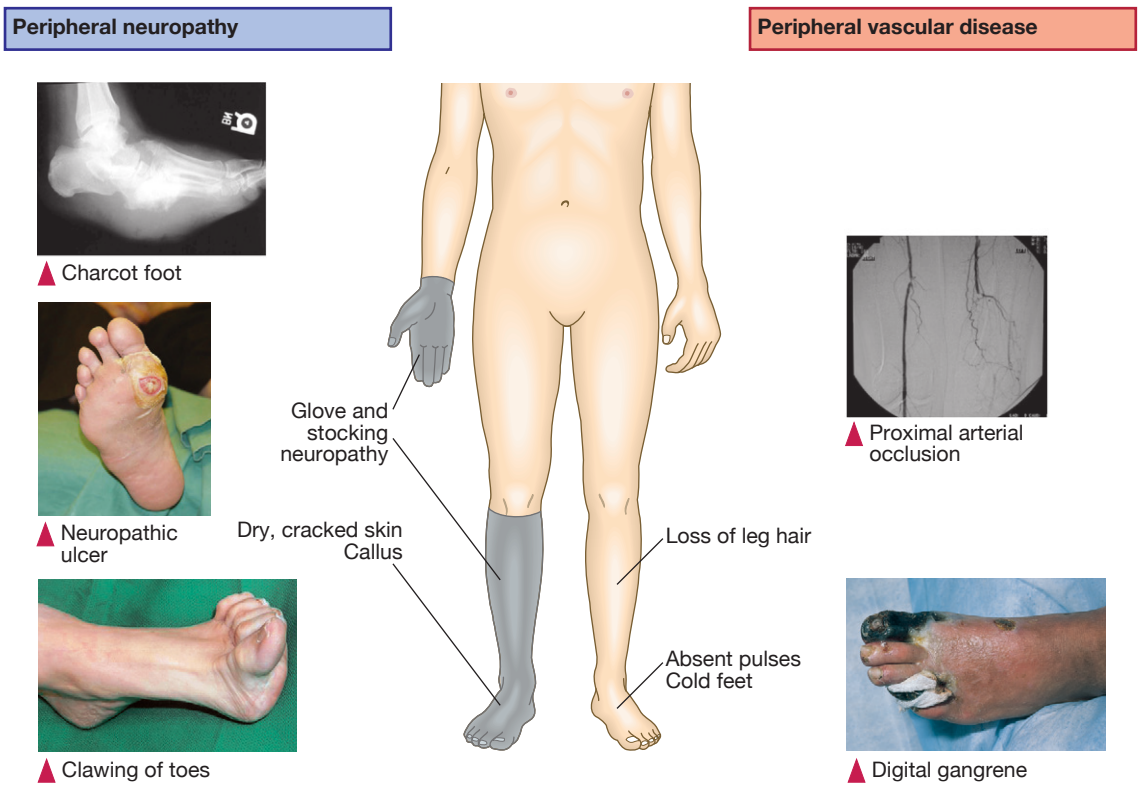


Figure: Diabetic foot disease.[1] Patients with diabetes can have neuropathy, peripheral vascular disease or both. Clawing of the toes is thought to be caused by intrinsic muscle atrophy and subsequent imbalance of muscle function, and causes increased pressure on the metatarsal heads and pressure on flexed toes, leading to increased callus and risk of ulceration. A Charcot foot occurs only in the presence of neuropathy, and results in bony destruction and ultimately deformity (this X-ray shows a resulting 'rocker bottom foot'). The angiogram shows disease of the superficial femoral arteries (occlusion of the left and stenosis of the right).

Aetiology

Foot ulceration occurs as a result of trauma (often trivial) in the presence of neuropathy and/or peripheral vascular disease, with infection occurring as a secondary phenomenon following disruption of the protective epidermis.

Most ulcers develop at the site of a plaque of callus skin, beneath which tissue necrosis occurs and eventually breaks through to the surface. In many cases, multiple components are involved, but sometimes neuropathy or ischaemia predominates.

Ischaemia alone accounts for a minority of foot ulcers in diabetic patients, with most being either neuropathic or neuro-ischaemic.

Clinical features

Clinical features of the diabetic foot[1]

	Neuropathy	Ischaemia
Symptoms	None Paraesthesiae Pain Numbness	None Claudication Rest pain
Structural damage	Ulcer Sepsis Abscess Osteomyelitis Digital gangrene Charcot joint	Ulcer Sepsis Gangrene

Distinguishing features between ischaemia and neuropathy in the diabetic foot

Distinguishing ischemia and neuropathy[5]

Features	Neuropathy	Ischemia
Symptoms	Usually painless	Claudication
	Sometimes painful neuropathy	Rest pain
Inspection	High arch	Dependent rubor
	Clawing of toes No trophic changes	Trophic changes
Palpation	Warm	Cold
	Bounding pulses	Pulseless
Ulceration	Painless	Painful
	Plantar	Heels and toes

Management

Management can be divided into –

1. primary prevention and
2. treatment of an active problem.

Primary prevention

All patients should be educated in preventive measures

Care of the feet in patients with diabetes [1]

- Preventive advice to all diabetic patients includes:
  - Inspect feet every day
  - Wash feet every day
  - Moisturise skin if dry
  - Cut or file toenails regularly
  - Change socks or stockings every day
  - Avoid walking barefoot
  - Check footwear for foreign bodies
  - Wear suitable, well-fitting shoes
  - Cover minor cuts with sterile dressings
  - Do not burst blisters
  - Avoid over-the-counter corn/callus remedies
- Advice to moderate- and high-risk patients is as above plus:
  - Do not attempt corn removal
  - Avoid high and low temperatures
- A podiatrist is an integral part of the diabetes team to ensure regular and effective podiatry and to educate patients in care of the feet
- Specially manufactured and fitted orthotic footwear is required to prevent recurrence of ulceration and to protect the feet of patients with Charcot neuroarthropathy

The feet of patients with diabetes should be screened annually, following the steps of clinical examination of the patient with diabetes.

Two simple tests are required to grade a patient's risk:

1. A 10g monofilament should be used to assess sensation at five points on each foot, and
2. Foot pulses should be palpated (dorsalis pedis and/or posterior tibial).

Combined with the clinical scenario, these tests guide appropriate referral and monitoring (Figure below).

Removal of callus skin with a scalpel is usually best done by a podiatrist who has specialist training and experience in diabetic foot problems.

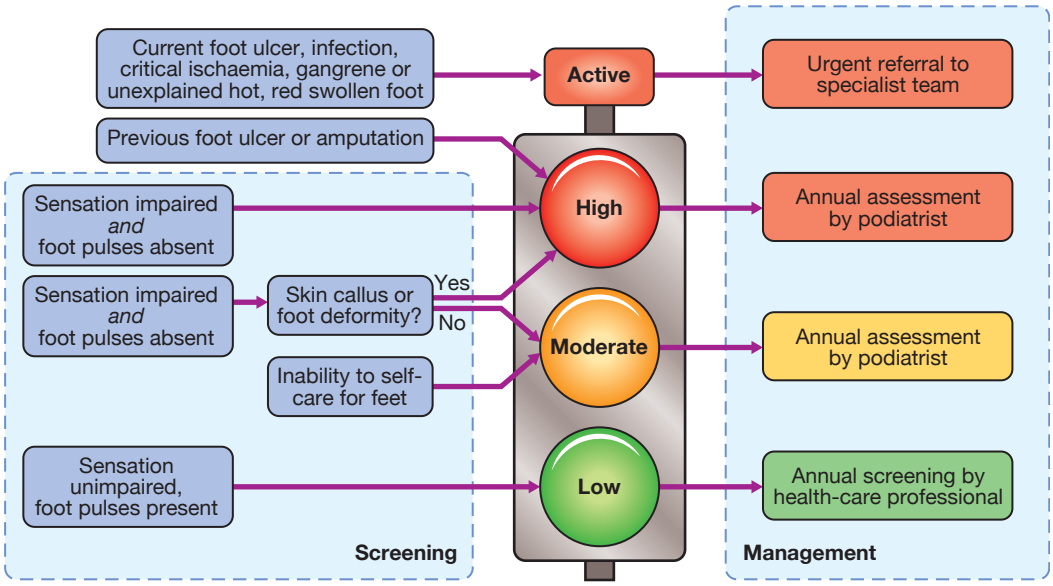


Figure: Risk assessment and management of foot problems in diabetes.[1]

Foot ulcer

Once a foot ulcer develops, patients should ideally be referred to a multidisciplinary foot team, involving a diabetes specialist, a podiatrist, a vascular surgeon and an orthotist.

Treatment

Treatment involves:

1. débridement of dead tissue;
2. prompt, often prolonged, treatment with antibiotics if required, as infection can accelerate tissue necrosis and lead to gangrene;
3. pressure relief using dressings;
4. use of specialised bespoke orthotic footwear; and
5. sometimes total contact plaster cast or irremovable aircast boot.

In neuro-ischaemic ulcer

If an ulcer is neuro-ischaemic, a vascular assessment is often carried out, by ultrasound or angiography, as revascularisation by angioplasty or surgery may be required to allow the ulcer to heal.

In severe secondary infection or gangrene

In cases of severe secondary infection or gangrene, an amputation may be required. This can be limited to the affected toe or involve more extensive limb amputation.

Charcot foot

Charcot neuro-arthropathy is a progressive condition affecting the bones and joints of the foot; it is characterised by early inflammation and then joint dislocation, subluxation, and pathological fractures of the foot of neuropathic patients, often resulting in debilitating deformity.

Charcot neuroarthropathy can arise in any condition that causes neuropathy (including syphilis, spinal cord injury, syringomyelia and so on) but diabetes is the most common cause.

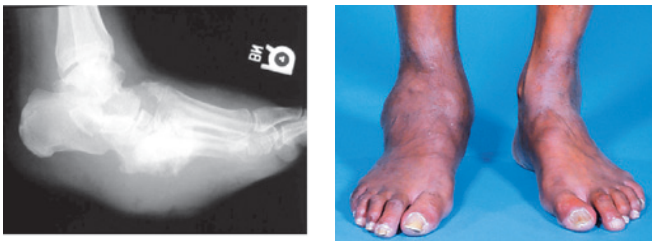


Figure: Charcot neuro-arthropathy.[1]

Pathology

The pathophysiological mechanisms remain poorly understood, but may involve unperceived trauma leading to progressive destruction (the 'neurotraumatic' theory), and/or increased blood flow resulting in a mismatch of bone destruction and synthesis (the 'neurovascular' theory).

More recent evidence points to disordered inflammation mediated via the nuclear factor kappa B (NFκB)/receptor activator of NFκB ligand (RANKL) pathway, opening the way for trials of the RANKL inhibitor, denosumab.

Presentation

Acute Charcot arthropathy almost always presents with signs of inflammation – a hot, red, swollen foot.

Investigation

1. Initial X-ray may show bony destruction but is often normal. As about 40% of patients with a Charcot joint also have a foot ulcer, it can be difficult to differentiate from osteomyelitis.
2. Magnetic resonance imaging (MRI) of the foot is often helpful.

Treatment

The mainstay of treatment for an active Charcot foot is immobilisation and, ideally, avoidance of weight-bearing on the affected foot.

The rationale is that if no pressure is applied through the foot, the destructive process involving the bones will not result in significant deformity when the acute inflammatory process subsides.

Immobilisation is often achieved by a total contact plaster cast or 'aircast' boot. The acute phase often lasts 3–6 months and sometimes longer.

In the post-acute phase, there is consolidation and remodelling of fracture fragments, eventually resulting in a stable foot.

Additional insights

Diabetic vascular disease: the 'diabetic foot' [1]

Feature	Difficulty
Arterial calcification	Spuriously high ABPI due to incompressible ankle vessels. Inability to clamp arteries for the purposes of bypass surgery. Resistant to angioplasty
Immunocompromise	Prone to rapidly spreading cellulitis, gangrene and osteomyelitis
Multisystem arterial disease	Coronary and cerebral arterial disease increase the risks of intervention
Distal disease	Diabetic vascular disease has a predilection for the calf vessels. Although vessels in the foot are often spared, performing a satisfactory bypass or angioplasty to these small vessels is a technical challenge
Sensory neuropathy	Even severe ischaemia and/or tissue loss may be completely painless. Diabetic patients often present late with extensive destruction of the foot. Loss of proprioception leads to abnormal pressure loads and worsens joint destruction (Charcot joints)
Motor neuropathy	Weakness of the long and short flexors and extensors leads to abnormal foot architecture, abnormal pressure loads, callus formation and ulceration
Autonomic neuropathy	Leads to a dry foot deficient in sweat that normally lubricates the skin and is antibacterial. Scaling and fissuring create a portal of entry for bacteria. Abnormal blood flow in the bones of the ankle and foot may also contribute to osteopenia and bony collapse

(ABPI = ankle–brachial pressure index)

27 Other complications of diabetes

Infection

Individuals with DM have a greater frequency and severity of infection. The reasons for this include incompletely defined abnormalities in cell-mediated immunity and phagocyte function associated with hyperglycemia, as well as diminished vascularization.[9] One reason why poor control leads to infection is that chemotaxis and phagocytosis by polymorphonuclear leucocytes are impaired because, at high blood glucose concentrations, neutrophil superoxide generation is impaired.[5]

Hyperglycemia aids the colonization and growth of a variety of organisms (*Candida* and other fungal species). Many common infections are more frequent and severe in the diabetic population, whereas several rare infections are seen almost exclusively in the diabetic population. Examples of this latter category include rhinocerebral mucormycosis, emphysematous infections of the gallbladder and urinary tract, and "malignant" or invasive otitis externa. Invasive otitis externa is usually secondary to *P. aeruginosa* infection in the soft tissue surrounding the external auditory canal, usually begins with pain and discharge, and may rapidly progress to osteomyelitis and meningitis. These infections should be sought, in particular, in patients presenting with severe hyperglycemia[9]

Pneumonia, urinary tract infections, and skin and soft tissue infections are all more common in the diabetic population. In general, the organisms that cause pulmonary infections are similar to those found in the nondiabetic population; however, gram-negative organisms, *S. aureus*, and *Mycobacterium tuberculosis* are more frequent pathogens. Urinary tract infections (either lower tract or pyelonephritis) are the result of common bacterial agents such as *Escherichia coli*, although several yeast species (*Candida* and *Torulopsis glabrata*) are commonly observed. Complications of urinary tract infections include emphysematous pyelonephritis and emphysematous cystitis. Bacteriuria occurs frequently in individuals with diabetic cystopathy. Susceptibility to furunculosis, superficial candidal infections, and vulvovaginitis are increased. Poor glycemic control is a common denominator in individuals with these infections. Diabetic individuals have an increased rate of colonization of *S. aureus* in the skinfolds and nares. Diabetic patients also have a greater risk of postoperative wound infections.[9]

There is no evidence that diabetic patients with good glycaemic control are more prone to infection than normal subjects. However, poorly controlled diabetes entails increased susceptibility to the following infections[5]:

Skin

- staphylococcal infections (boils, abscesses, carbuncles)
- mucocutaneous candidiasis

Gastrointestinal tract

- periodontal disease
- rectal and ischiorectal abscess formation (when control is very poor)

Urinary tract

- urinary tract infections (in women)
- pyelonephritis
- perinephric abscess

Lungs

- staphylococcal and pneumococcal pneumonia
- Gram-negative bacterial pneumonia
- tuberculosis

Bone

- spontaneous staphylococcal spinal osteomyelitis.

Infections may lead to loss of glycaemic control and precipitate hyperglycaemic emergencies. Insulin-treated patients need to increase their dose by up to 25% in the face of infection, and non-insulin-treated patients may need insulin cover while the infection lasts. Patients should be told never to omit their insulin dose, even if they are nauseated and unable to eat; instead, they should test their blood glucose frequently and seek urgent medical advice. Patients should receive pneumococcal vaccine and yearly influenza vaccine.[5]

Diabetes and cancer[5]

Certain types of cancer are more common in type 2 diabetes. The risk of carcinoma of the uterus and of the pancreas is approximately doubled, and there is a 20–50% increase in the risk of colorectal and breast cancer. These associations appear to be mediated by obesity, which confers similar levels of risk in the absence of hyperglycaemia, although there is also an element of reverse causation with carcinoma of the pancreas, which can precipitate or cause diabetes.

Metformin-treated patients have been reported to have a lower cancer risk than those on other therapies, and this agent is under investigation for possible anti-tumour properties.

Joints[5]

Joint contractures in the hands are a common consequence of childhood diabetes. The sign may be demonstrated by asking the patient to join the hands as if in prayer; the metacarpophalangeal and interphalangeal joints cannot be opposed.

Thickened, waxy skin can be noted on the backs of the fingers. These features may be due to glycosylation of collagen and are not progressive. The condition is sometimes referred to as diabetic cheiroarthropathy.

Osteopenia in the extremities is also described in type 1 diabetes but rarely has clinical consequences.

Skin[9]

The most common skin manifestations of DM are xerosis and pruritus and are usually relieved by skin moisturizers.

Protracted wound healing and skin ulcerations are also frequent complications.

Diabetic dermopathy, sometimes termed pigmented pretibial papules, or “diabetic skin spots,” begins as an erythematous macule or papule that evolves into an area of circular hyperpigmentation. These lesions result from minor mechanical trauma in the pretibial region and are more common in elderly men with DM.

Bullous diseases, such as bullosa diabeticorum (shallow ulcerations or erosions in the pretibial region), are also seen.

Necrobiosis lipoidica diabeticorum is an uncommon disorder, accompanying diabetes in predominantly young women. This usually begins in the pretibial region as an erythematous plaque or papules that gradually enlarge, darken, and develop irregular margins, with atrophic centers and central ulceration. They are often painful.

Vitiligo occurs at increased frequency in individuals with type 1 DM. *Acanthosis nigricans* (hyperpigmented velvety plaques seen on the neck, axilla, or extensor surfaces) is sometimes a feature of severe insulin resistance and accompanying diabetes. Generalized or localized granuloma annulare (erythematous plaques on the extremities or trunk) and scleredema (areas of skin thickening on the back or neck at the site of previous superficial infections) are more common in the diabetic population.

Lipoatrophy and lipohypertrophy can occur at insulin injection sites but are now unusual with the use of human insulin.

28 Special situations in diabetes

Diabetes in pregnancy

Pregnancy in diabetes was, in the past, associated with high fetal mortality, which has been dramatically reduced by meticulous metabolic control of the diabetes and careful obstetric management. Despite this, the rates of congenital malformation and perinatal mortality remain several times higher than in the non-diabetic population. Type 2 diabetes is now much more prevalent in the maternal population as a result of the changing natural history of this condition.[5]

During pregnancy, maternal glucose metabolism changes to optimise glucose and other nutrient delivery to the fetus. This is particularly apparent in the second half of pregnancy, when there is an increase in maternal tissue insulin resistance, such that glucose is preferentially supplied to the fetus rather than maternal tissue. This is largely driven by the maternal hormonal environment, with increased oestrogens and progestogens, and, in particular, human placental lactogen (hPL). The delivery of the placenta results in rapid decline in hPL with a rapid reversal of insulin resistance soon after birth.

During pregnancy, fasting plasma glucose decreases slightly, while post-prandial blood glucose may be increased. The renal threshold for glycosuria is reduced in pregnancy.

Incidence

4% of pregnancies are complicated by DM: either pre-existing type 1 or 2 DM (<0.5%), or new-onset gestational diabetes (GDM) (>3.5%).[4]

Risks [4]

All forms carry an increased risk to mother and foetus:

1. miscarriage,
2. pre-term labour,
3. pre-eclampsia,
4. congenital malformations,
5. macrosomia, and
6. a worsening of diabetic complications, eg retinopathy, nephropathy.

Obstetric and fetal problems

Obstetric problems

Congenital malformations associated with maternal diabetes affect cardiac and skeletal development, of which the caudal regression syndrome is an example. Poorly controlled diabetes later in gestation is associated with stillbirth, shoulder dystocia owing to fetal macrosomia, polyhydramnios and pre-eclampsia. Ketoacidosis in pregnancy carries a 50% fetal mortality, but maternal hypoglycaemia, although highly undesirable, is relatively well tolerated by the fetus.[5]

Fetal macrosomia

In the fetus, insulin secretion is driven by fetal blood glucose levels, which are determined by the maternal glucose concentrations. Thus, maternal hyperglycaemia drives fetal hyperinsulinaemia. Since insulin is a major fetal growth factor, hyperinsulinaemia in turn drives increased fetal growth, resulting in increased birth weight ('macrosomia').[1]

The infant of a diabetic mother is more susceptible to hyaline membrane disease than nondiabetic infants of similar maturity. In addition, neonatal hypoglycaemia may occur. The mechanism is as follows: maternal glucose crosses the placenta but insulin does not; the fetal islets hypersecrete to combat maternal hyperglycaemia, and a rebound to hypoglycaemic levels occurs when the umbilical cord is cut. These complications are due to hyperglycaemia in the third trimester.[5]

Gestational diabetes

Definition

Gestational diabetes is defined as diabetes with first onset or recognition during pregnancy.

This definition will include

- a few patients who develop type 1 diabetes during pregnancy, where prompt action and early insulin treatment will be required, and
- some patients who develop type 2 diabetes, or had unknown preexisting type 2 diabetes, in whom the diabetes does not remit after pregnancy.

Pathogenesis

The majority of gestational diabetes develops due to an inability to increase insulin secretion adequately to compensate for pregnancy-induced insulin resistance, and most women can expect to return to normal glucose tolerance immediately after pregnancy.

Diagnostic basis

In contrast to non-gestational diabetes, for which the diagnostic thresholds for diabetes are based upon risk of microvascular complications, the diagnosis of gestational diabetes is based upon maternal blood glucose measures that are associated with increased fetal growth.

An international consensus recommended that glucose values diagnostic of gestational diabetes should be lower than those for non-gestational diabetes.

Identifying patients with gestational diabetes[1]

Women at high risk of gestational diabetes

- BMI > 30 kg/m^2
- A previous macrosomic baby weighing ≥ 4.5 kg at birth
- Previous gestational diabetes
- A first-degree relative with diabetes
- A high-risk ethnicity – South Asian, black Caribbean or Middle Eastern (Non-Caucasian[4])
- HIV +ve [4]

Diagnosis

- High-risk women should have a 75 g oral glucose tolerance test before 28 weeks' gestation
- Gestational diabetes is diagnosed when:
  - Fasting plasma glucose ≥ 5.1 mmol/L (92 mg/dL) or
  - 1-hr plasma glucose (after glucose load) ≥ 10 mmol/L (180 mg/dL) or
  - 2-hr plasma glucose (after glucose load) ≥ 8 mmol/L (144 mg/dL)
- Consider testing high-risk women at first booking visit with an HbA_{1c} or fasting blood glucose

Screening

Controversy remains about who should be screened, and in part the screening strategy depends on the population risk.

It is widely accepted that women at high risk for gestational diabetes should have an oral glucose tolerance test at 24–28 weeks (16-18 weeks if previous GDM[4]), with some guidelines recommending that all are screened by measuring HbA_{1c}, fasting blood glucose or random blood glucose at the first booking visit[1], OGTT if risk associated with factors[4].

With the increasing use of HbA_{1c} to diagnose diabetes, it should be noted that HbA_{1c} is unreliable after early pregnancy, when it falls due to increased red cell turnover.

Management

The aim is to normalise the maternal blood glucose and thereby reduce excessive fetal growth.

Dietary modification

The first element of management is dietary modification, in particular by reducing consumption of quick-acting refined carbohydrate.

Women with gestational diabetes should undertake regular pre- and post-prandial self-monitoring of blood glucose, aiming for

- pre-meal blood glucose levels of less than 5.5 mmol/L (100 mg/dL) or
- postmeal blood glucose levels of less than 7.0 mmol/L (125 mg/dL).

Drugs

If treatment is necessary, metformin or glibenclamide is considered safe to use in pregnancy. Glibenclamide should be used rather than other sulphonylureas because it does not cross the placenta.

Other oral therapies or injectable incretin-based therapies should not be given in pregnancy.

Insulin may be required, especially in the later stages of pregnancy.

Complication

If the maternal blood glucose is not well controlled prior to, and during, delivery, the resulting fetal hyperinsulinaemia leads to neonatal hyperinsulinaemia, which in turn can cause neonatal hypoglycaemia.

Follow up and prognosis

After delivery, maternal glucose usually rapidly returns to pre-pregnancy levels. Woman should be tested at least 6 weeks post-partum with an oral glucose tolerance test.

In women with persistent mild fasting hyperglycaemia (glucose over 5.5 mmol/L (100 mg/ dL)) who have a small increment (less than 3.5 mmol/L) in plasma glucose 2 hours after oral glucose, monogenic diabetes due to a mutation in GCK (encoding glucokinase) should be considered.

Those who have returned to normal glucose tolerance remain at considerable risk for developing type 2 diabetes, with a 5-year risk between 15 and 50%, depending on the population.

Therefore, all women who have had gestational diabetes should be given diet and lifestyle advice to reduce their risk of developing type 2 diabetes.

Pregnancy in women with established diabetes

Maternal hyperglycaemia early in pregnancy (during the first 6 weeks post-conception) can adversely affect fetal development. Consequences include –

- Cardiac malformations,
- renal malformations and
- skeletal malformations, of which the caudal regression syndrome is the most characteristic.

Epidemiology

The risk of fetal anomaly is about 2% for non-diabetic women, about 4% for women with well-controlled diabetes (HbA_{1c} below 53 mmol/mol (7%)), but more than 20% for those with poor glycaemic control (HbA_{1c} greater than 97 mmol/mol (11%)).

While the outlook for mother and child has been vastly improved over recent years, pregnancy outcomes are still not equivalent to those of non-diabetic mothers.

Perinatal mortality rates remain 3–4 times those of the non-diabetic population (at around 30–40 per 1000 pregnancies) and the rate of congenital malformation is increased 5–6-fold overall.

Pregnancy associated risks

Pregnancy is also associated with an increased potential for ketosis, particularly, but not exclusively, in women with type 1 diabetes.

Ketoacidosis during pregnancy is dangerous for the mother and is associated with a high rate (10–35%) of fetal mortality.

Pregnancy is associated with a worsening of diabetic complications, most notably retinopathy and nephropathy, so careful monitoring of eyes and kidneys is required throughout pregnancy.

If heavy proteinuria and/or renal dysfunction exist prior to pregnancy, there is a marked increase in the risk of pre-eclampsia, and renal function can deteriorate irreversibly during pregnancy.

These risks need to be carefully discussed before a woman with diabetes is considering pregnancy.

Management

Pre-conception:

- Offer general advice, and discuss risks. [1,4]
- Control/reduce weight, [4]
- Aim to achieve excellent glycaemic control before becoming pregnant. [1,4]
- In addition, high-dose folic acid (5 mg, rather than the usual 400 µg, daily) should be initiated before conception to reduce the risk of neural tube defects[1] (continue until 12 weeks[4]).

Conception

- As for gestational diabetes, mothers should attempt to maintain near-normal blood glucose levels whilst avoiding hypoglycaemia throughout their pregnancy, as this minimises excessive fetal growth and neonatal hypoglycaemia. However, this is often difficult to achieve. [1]
- Oral hypoglycaemics other than metformin should be discontinued. Metformin may be used as an adjunct or alternative to insulin in type 2 DM or GDM.[4]

Postpartum

- 6 weeks postpartum, do a fasting glucose. Even if negative, 50% will eventually go on to develop DM.[4]

Surgery and diabetes

Patients with diabetes are reported to have up to 50% higher peri-operative mortality than patients without diabetes.

Pathophysiology

Surgery causes catabolic stress and secretion of counter-regulatory hormones (including catecholamines and cortisol) in both normal and diabetic subjects. This results in increased glycogenolysis, gluconeogenesis, lipolysis, proteolysis and insulin resistance. Starvation exacerbates this process by increasing lipolysis.

In the non-diabetic person, these metabolic effects lead to a secondary increase in the secretion of insulin, which exerts a controlling influence. In diabetic patients, either there is absolute deficiency of insulin (type 1 diabetes) or insulin secretion is delayed and impaired (type 2 diabetes), so that in untreated or poorly controlled diabetes, the uptake of metabolic substrate into tissues is significantly reduced, catabolism is increased and, ultimately, metabolic decompensation in the form of diabetic ketoacidosis may develop in both types of diabetes.

In addition, hyperglycaemia impairs wound healing and innate immunity, leading to increased risk of infection. Patients with diabetes are also more likely to have underlying pre-operative morbidity, especially cardiovascular disease. Finally, management errors with diabetes may cause dangerous hyperglycaemia or hypoglycaemia.

Careful pre-operative assessment and peri-operative management are therefore essential, ideally with support from the diabetes specialist team.

Pre-operative assessment

Unless a surgical intervention is an emergency, patients with diabetes should be assessed well in advance of surgery so that poor glycaemic control and other risk factors can be addressed.

How to carry out pre-operative assessment of patients with diabetes[1]

- Assess glycaemic control
  - Consider delaying surgery and referral to the diabetes team if HbA_{1c} > 75 mmol/mol (9%). This should be weighed against the need for surgery
- Assess cardiovascular status
  - Optimise blood pressure
  - ECG for evidence of (possibly silent) ischaemic heart disease and to assess QTc
- Assess foot risk
  - Patients with high-risk feet should have suitable pressure relief provided during post-operative nursing
- For minor/moderate operations where only one meal will be omitted, plan for the patient to be first on the list

There is good evidence that higher HbA_{1c} is associated with adverse perioperative outcome. In general, an upper limit for an acceptable HbA_{1c} should be between 64 and 75 mmol/ mol (8 and 9%).

However, since optimisation of care may take weeks or months to achieve, the benefits need to be weighed against the need for early surgical intervention.

Peri-operative management

Following figure outlines a general approach to peri-operative management of diabetes, although this may need to be adapted according to the patient, the surgical procedure and local guidelines.

Date of admission:

Patients with diabetes who are considered low-risk can attend as day cases or be admitted on the day of surgery. However, patients are often admitted the night before to ensure optimal management, and to begin intravenous insulin to optimise blood glucose, if required.

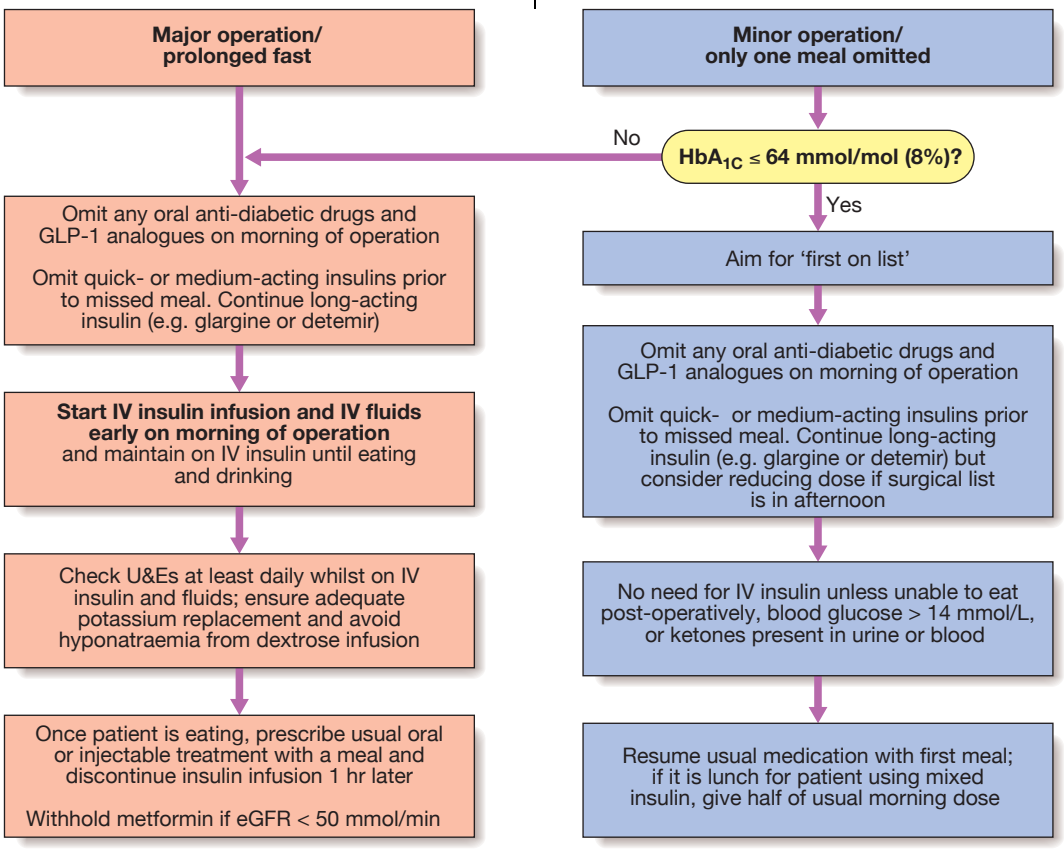


Figure: Management of diabetic patients undergoing surgery and general anaesthesia. (Glucose > 14 mmol/L ≅ 250 mg/dL) (eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide 1).[1]

Post-operative management

Patients who need to continue fasting after surgery should be maintained on intravenous insulin and fluids until they are able to eat and drink. During this time, care must be taken with fluid balance and electrolyte levels.

Insulin infusion necessitates dextrose infusion to maintain a supply of glucose, but this combination drives down plasma potassium and can result in hyponatraemia. Intravenous fluids during prolonged insulin infusion should therefore include saline and potassium supplementation. UK guidelines recommend use of dextrose/saline (0.45% saline with 5% dextrose and 0.15% potassium chloride).

Once a patient's usual treatment has been reinstated, care must be taken to continue to control the blood glucose, ideally between 4 and 10 mmol/L (70–180 mg/ dL), in order to optimise wound healing and recovery.

Patients normally controlled on tablets may require temporary subcutaneous insulin treatment until the increased 'stress' of surgery, wound healing or infection has resolved.

Children, adolescents and young adults with diabetes

The management of diabetes in children and adolescents presents particular challenges, which should be addressed in specialised clinics.

Diabetes in adolescence [1]

- **Type of diabetes**: type 1 diabetes is predominant in children and adolescents, but type 2 diabetes is now presenting in unprecedented numbers of obese, inactive teenagers. Monogenic diabetes (MODY) should also be considered
- **Physiological changes**: hormonal, physical and lifestyle changes in puberty affect dietary intake, exercise patterns and sensitivity to insulin, necessitating alterations in insulin regimen.
- **Emotional changes**: adolescence is a phase of transition into independence (principally from parental care). Periods of rebellion against parental control, experimentation (e.g. with alcohol) and a more chaotic lifestyle are common, and often impact adversely on control of diabetes.
- **Glycaemic control**: a temporary deterioration in control is common, although not universal. It is sometimes more important to maintain contact and engagement with a young person than to insist on tight glycaemic control.
- **Diabetic ketoacidosis**: a few adolescents and young adults present with frequent episodes of DKA, often because of non-adherence to insulin therapy. This is more common in females. Motivating factors may include weight loss, rebellion, and manipulation of family or schooling circumstances.
- **Adolescent diabetes clinics**: these challenges are best tackled with support from a specialised multidisciplinary team, including paediatricians, physicians, nurses and psychologists. Support is required for the patient and parents.

Hyperglycaemia in acute myocardial infarction

Hyperglycaemia is often found in patients who have sustained an acute myocardial infarction.

Cause:

1. In some, this represents stress hyperglycaemia,
2. some have previously undiagnosed diabetes, and
3. many have established diabetes.

Many patients with stress hyperglycaemia will have impaired glucose tolerance on a subsequent glucose tolerance test.

Management

Over and above the standard management of myocardial infarction, hyperglycaemia should be treated with insulin rather than oral anti-diabetic agents in the peri-infarct period, aiming for near-normalisation of blood glucose.

Studies have suggested that good glycaemic control using insulin therapy in hyperglycaemic patients with acute myocardial infarction may reduce their long-term mortality from coronary heart disease.

29 Hypoglycaemia

Hypoglycemia (blood glucose < 3.5 mmol/L (63 mg/ dL))[1] is most commonly caused by drugs used to treat diabetes mellitus or by exposure to other drugs, including alcohol. However, a number of other disorders, including critical organ failure, sepsis and inanition, hormone deficiencies, non-β-cell tumors, insulinoma, and prior gastric surgery, can cause hypoglycemia.[9]

Hypoglycemia is most convincingly documented by Whipple's triad[9]:

1. Symptoms consistent with hypoglycemia,
2. A low plasma glucose concentration measured with a precise method (not a glucose monitor), and
3. Relief of symptoms after the plasma glucose level is raised.

The lower limit of the fasting plasma glucose concentration is normally ~70 mg/dL (~3.9 mmol/L), but lower venous glucose levels occur normally, late after a meal, during pregnancy, and during prolonged fasting (>24 h). Hypoglycemia can cause serious morbidity; if severe and prolonged, it can be fatal. It should be considered in any patient with episodes of confusion, an altered level of consciousness, or a seizure.[9]

Incidence and awareness of hypoglycaemia

Hypoglycaemia can be a frequent occurrence in the lives of people with type 1 diabetes and has a major impact on their willingness and ability to achieve target glucose levels.

For most individuals, the glucose level (threshold) at which they first become aware of hypoglycaemia is not constant but varies according to the circumstances in which hypoglycaemia arises (e.g. during the night or during exercise). In addition, with longer duration of disease, and particularly in response to frequent hypoglycaemia, the threshold for generation of symptom responses to hypoglycaemia shifts to a lower glucose concentration. This cerebral adaptation has a similar effect on the counter-regulatory hormonal response to hypoglycaemia.

Taken together, this means that individuals with type 1 diabetes may have reduced (impaired) awareness of hypoglycaemia. Symptoms can be experienced less intensely, or even be absent, despite blood glucose concentrations below 2.5 mmol/L (45 mg/dL). Such individuals are at an especially high risk of severe hypoglycaemia.

The prevalence of impaired awareness of hypoglycaemia increases with time; overall, it affects around 20–25% of people with type 1 diabetes and under 10% with insulin-treated type 2 diabetes.

Hypoglycaemia in diabetes: common causes and risk factors[1]

Causes of hypoglycaemia

- Missed, delayed or inadequate meal
- Unexpected or unusual exercise
- Alcohol
- Errors in oral anti-diabetic agent(s) or insulin dose/schedule/ administration
- Poorly designed insulin regimen, particularly if predisposing to nocturnal hyperinsulinaemia
- Lipohypertrophy at injection sites causing variable insulin absorption
- Gastroparesis due to autonomic neuropathy causing variable carbohydrate absorption
- Malabsorption, e.g. coeliac disease
- Unrecognised other endocrine disorder, e.g. Addison's disease
- Factitious (deliberately induced)
- Breastfeeding

Risk factors for severe hypoglycaemia

- Strict glycaemic control
- Impaired awareness of hypoglycaemia
- Age (very young and elderly)
- Long duration of diabetes
- Sleep
- C-peptide negativity (indicating complete insulin deficiency)
- History of previous severe hypoglycaemia
- Renal impairment
- Genetic, e.g. angiotensin-converting enzyme (ACE) genotype

Pathogenesis

In health, a number of mechanisms are in place to ensure that glucose homeostasis is maintained. If blood glucose falls, three primary physiological defence mechanisms operate:

1. Endogenous insulin release from pancreatic β cells is suppressed;
2. Release of glucagon from pancreatic α cells is increased; and
3. The autonomic nervous system is activated, with release of catecholamines both systemically and within the tissues.
   In addition, stress hormones, such as cortisol and growth hormone, are increased in the blood.

These actions reduce whole-body glucose uptake and increase hepatic glucose production, maintaining a glucose supply to the brain.

People with type 1 diabetes cannot regulate insulin once it is injected subcutaneously, and so it continues to act, despite developing hypoglycaemia. In addition, within 5 years of diagnosis, most patients will have lost their ability to release glucagon specifically during hypoglycaemia. This is thought to result mainly from loss of α-cell regulation by β cells. These two primary defects mean that hypoglycaemia occurs much more frequently in people with type 1 and longer duration type 2 diabetes.

Severity

The severity of hypoglycaemia is defined by the ability to self-treat;

1. 'mild' episodes are self-treated,
2. 'severe' episodes require assistance for recovery.

Clinical assessment

Symptoms of hypoglycaemia comprise two main groups:

1. those related to acute activation of the autonomic nervous system and
2. those secondary to glucose deprivation of the brain (neuroglycopenia).

Most common symptoms of hypoglycaemia[1]

Autonomic	
• Sweating	• Hunger
• Trembling	• Anxiety
• Pounding heart	
Neuroglycopenic	
• Confusion	• Inability to concentrate
• Drowsiness	• Incoordination
• Speech difficulty	• Irritability, anger
Non-specific	
• Nausea	• Headache
• Tiredness	

N.B. Symptoms differ with age; children exhibit behavioural changes (such as naughtiness or irritability), while elderly people experience more prominent neurological symptoms (such as visual disturbance and ataxia).

Symptoms of hypoglycaemia are idiosyncratic and differ with age and duration of diabetes. Hypoglycaemia also affects mood, inducing a state of increased tension and low energy.

Learning to recognise the early onset of hypoglycaemia is an important aspect of the education of diabetic patients treated with insulin.

Other circumstances

1. Severe hypoglycaemia can have serious morbidity (e.g. convulsions, coma, focal neurological lesions) and has a mortality of up to 4% in insulin-treated patients.
2. Rarely, sudden death during sleep occurs in otherwise healthy young patients with type 1 diabetes ('dead-in-bed syndrome') and may result from hypoglycaemia induced cardiac arrhythmia.
3. Severe hypoglycaemia is very disruptive and impinges on many aspects of the patient's life, including employment, driving, travel, sport and personal relationships.
4. Nocturnal hypoglycaemia in patients with type 1 diabetes is common but often undetected, as hypoglycaemia does not usually waken a person from sleep. Patients may describe poor quality of sleep, morning headaches and vivid dreams or nightmares, or a partner may observe profuse sweating, restlessness, twitching or even seizures. The only reliable way to identify this problem is to measure blood glucose during the night.
5. Exercise-induced hypoglycaemia occurs in people with well-controlled, insulin-treated diabetes because of hyperinsulinaemia. Suppression of endogenous insulin secretion to allow increased hepatic glucose production to meet the increased metabolic demand is key to the normal physiological response to exercise. In insulin-treated diabetes, insulin levels may actually increase with exercise because of improved blood flow at the site of injection and this increases the risk of hypoglycaemia.

Management

Acute treatment of hypoglycaemia

Treatment of hypoglycaemia depends on its severity and on whether the patient is conscious and able to swallow.

Oral carbohydrate usually suffices if hypoglycaemia is recognised early. If parenteral therapy is required, then as soon as the patient is able to swallow, glucose should be given orally. Full recovery may not occur immediately and reversal of cognitive impairment may not be complete until 60 minutes after normoglycaemia is restored.

When hypoglycaemia has occurred in a patient treated with a long- or intermediate-acting insulin or a long-acting sulphonylurea, such as glibenclamide, the possibility of recurrence should be anticipated; to prevent this, infusion of 10% dextrose, titrated to the patient's blood glucose, may

be necessary.

If the patient fails to regain consciousness after blood glucose is restored to normal, then cerebral oedema and other causes of impaired consciousness – such as

- alcohol intoxication,
- a post-ictal state or
- cerebral haemorrhage – should be considered.

Emergency treatment of hypoglycaemia [1]

Mild (self-treated)

- Oral fast-acting carbohydrate (10–15 g) is taken as glucose drink or tablets or confectionery
- This should be followed with a snack containing complex carbohydrate

Severe (external help required)

- If patient is semiconscious or unconscious, parenteral treatment is required:
  - IV 75 mL 20% dextrose (= 15 g; give 0.2 g/kg in children)*
  - Or
  - IM glucagon (1 mg; 0.5 mg in children)
- If patient is conscious and able to swallow:
  - Give oral refined glucose as drink or sweets (= 25 g)
  - Or
  - Apply glucose gel or jam or honey to buccal mucosa

*Use of 50% dextrose is no longer recommended.

Cerebral oedema has a high mortality and morbidity, and requires urgent treatment with mannitol and high-dose oxygen. Following recovery, it is important to try to identify a cause and make appropriate adjustments to the patient's therapy.

Unless the reason for a hypoglycaemic episode is clear, the patient should reduce the next dose of insulin by 10–20% and seek medical advice about further adjustments in dose.

Prevention of hypoglycaemia

Patient education is fundamental to the prevention of hypoglycaemia. Risk factors for, and treatment of hypoglycaemia should be discussed. The importance of regular blood glucose monitoring and the need to have glucose (and glucagon) readily available should be stressed. A review of insulin and carbohydrate management during exercise is particularly useful.

Advice for patients when travelling is summarised below -

Avoidance and treatment of hypoglycaemia during travel [1]

- Carry a supply of fast-acting carbohydrate (non-perishable, in suitable containers)
  - Screwtop plastic bottles for glucose drinks
  - Packets of powdered glucose (for use in hot, humid climates)
  - Confectionery (foil-wrapped in hot climates)
- Companions should carry additional oral carbohydrate, and glucagon
- Perform frequent blood glucose testing (carry spare meter and/or visually read strips)
- Use fast-acting insulin analogues for long-distance air travel

Relatives and friends also need to be familiar with the symptoms and signs of hypoglycaemia and should be instructed in how to help (including how to inject glucagon).

It is important to recognise that all current insulin replacement regimens are suboptimal and do not accurately replicate normal physiological insulin profiles.

Understanding the pharmacokinetics and pharmacodynamics of the insulin regimen in use by the patient will help prevent further hypoglycaemia. For example, an individual experiencing regular nocturnal hypoglycaemia between midnight and 0200 hours may be found to be taking twice-daily soluble and intermediate-acting insulins before breakfast and before the main evening meal between 1700 and 1900 hours. In this case, the peak action of the isophane insulin will coincide with the period of maximum sensitivity to insulin – namely, 2300–0200 hours – and increase the risk of nocturnal hypoglycaemia. To address this, the evening dose of depot intermediate-acting insulin should be deferred until bedtime (after 2300 hours), shifting its peak action period to 0500–0700 hours. It is also a sensible precaution for patients to measure their blood glucose before they retire to bed and to have a carbohydrate snack if the reading is less than 6.0 mmol/L (approximately 110 mg/dL).

Hypoglycaemia in the Non-Diabetic Patient[5]

Hypoglycaemia develops when hepatic glucose output falls below the rate of glucose uptake by peripheral tissues. Hepatic glucose output may be reduced by:

- inhibition of hepatic glycogenolysis and gluconeogenesis by insulin
- depletion of hepatic glycogen reserves by malnutrition, fasting, exercise or advanced liver disease
- impaired gluconeogenesis (e.g. following alcohol ingestion).

In the first of these categories, insulin levels are raised, the liver contains adequate glycogen stores and the hypoglycaemia can be reversed by injection of glucagon. In the other two situations, insulin levels are low and glucagon is ineffective. Peripheral glucose uptake is accelerated by high insulin levels and by exercise, but these conditions are normally balanced by increased hepatic glucose output.

The most common symptoms and signs of hypoglycaemia are neurological. The brain consumes about 50% of the total glucose produced by the liver. This high energy requirement is needed to generate ATP, used to maintain the potential difference across axonal membranes.

Insulinomas

Insulinomas are pancreatic islet cell tumours that secrete insulin. Most are sporadic but some patients have multiple tumours arising from neural crest tissue (multiple endocrine neoplasia). Some 95% of these tumours are benign. The classic presentation is with fasting hypoglycaemia, but early symptoms may also develop in the late morning or afternoon. Recurrent hypoglycaemia is often present for months or years before the diagnosis is made, and the symptoms may be atypical or even bizarre. Common misdiagnoses include psychiatric disorders, particularly pseudodementia in elderly people, epilepsy and cerebrovascular disease. Whipple's triad remains the basis of clinical diagnosis. This is satisfied when:

- symptoms are associated with fasting or exercise
- hypoglycaemia is confirmed during these episodes
- glucose relieves the symptoms.

Presenting features of insulinoma

- Diplopia
- Sweating, palpitations, weakness
- Confusion or abnormal behaviour
- Loss of consciousness
- Grand mal seizures

A fourth criterion – demonstration of inappropriately high insulin levels during hypoglycaemia – may usefully be added. The diagnosis is confirmed by the demonstration of hypoglycaemia in association with inappropriate and excessive insulin secretion.

Hypoglycaemia is demonstrated by:

- Measurement of overnight fasting (16 h) glucose and insulin levels on three occasions. About 90% of patients with insulinomas will have low glucose and non-suppressed (normal or elevated) insulin levels.
- A prolonged 72-h supervised fast if overnight testing is inconclusive and symptoms persist.

Autonomous insulin secretion is demonstrated by lack of the normal feedback suppression during hypoglycaemia. This may be shown by measuring insulin, C-peptide or proinsulin during a spontaneous episode of hypoglycaemia.

Management

The most effective therapy is surgical excision of the tumour but insulinomas are often very small and difficult to localize. Many techniques can be used to attempt to localize insulinomas. Sensitivity and specificity vary between centres and between operators. These include highly selective angiography, contrast-enhanced high-resolution computed tomography scanning, scanning with radiolabelled somatostatin (some insulinomas express somatostatin receptors), and endoscopic and intraoperative ultrasound scanning. Venous sampling for the detection of 'hot spots' of high insulin concentration in the various intra-abdominal veins is still used occasionally.

Medical treatment with diazoxide is useful when the insulinoma is malignant, when a tumour cannot be located and when elderly patients have mild symptoms. Symptoms may also remit on treatment with a somatostatin analogue (octreotide or lanreotide).

Hypoglycaemia with other tumours

Hypoglycaemia may develop in the course of advanced neoplasia and cachexia, and has been described in association with many tumour types. Certain massive tumours, especially sarcomas, may produce hypoglycaemia owing to the secretion of insulin-like growth factor-1. True ectopic insulin secretion is extremely rare.

Postprandial hypoglycaemia

If frequent venous blood glucose samples are taken following a prolonged glucose tolerance test, about 1 in 4 subjects will have at least one value below 3 mmol/L. The arteriovenous glucose difference is quite marked during this phase, so that very few are truly hypoglycaemic in terms of arterial (or capillary) blood glucose content. Failure to appreciate this simple fact led some authorities to believe that postprandial (or reactive) hypoglycaemia was a potential 'organic' explanation for a variety of complaints that might otherwise have been considered psychosomatic. An epidemic of false 'hypoglycaemia' followed, particularly in the USA. Later work showed a poor correlation between symptoms and biochemical hypoglycaemia. Even so, a number of otherwise normal people occasionally become pale, weak and sweaty at times when meals are due, and report benefit from advice to take regular snacks between meals.

True postprandial hypoglycaemia may develop in the presence of alcohol, which 'primes' the cells to produce an exaggerated insulin response to carbohydrate. The person who substitutes alcoholic beverages for lunch is particularly at risk. Postprandial hypoglycaemia sometimes occurs after gastric surgery, owing to rapid gastric emptying and mismatching of nutrient absorption and insulin secretion. This is referred to as 'dumping' but it is now rarely encountered.

Hepatic and renal causes of hypoglycaemia

The liver can maintain a normal glucose output despite extensive damage, and hepatic hypoglycaemia is uncommon. It is, however, a particular problem with acute hepatic failure.

The kidney has a subsidiary role in glucose production (via gluconeogenesis in the renal cortex), and hypoglycaemia is sometimes a problem in terminal renal failure.

Hereditary fructose intolerance occurs in 1 in 20 000 live births and can cause hypoglycaemia.

Endocrine causes of hypoglycaemia

Deficiencies of hormones antagonistic to insulin are rare but well-recognized causes of hypoglycaemia. These include hypopituitarism, isolated adrenocorticotrophic hormone (ACTH) deficiency and Addison's disease.

Drug-induced hypoglycaemia

Many drugs have been reported to produce isolated cases of hypoglycaemia, but usually only when other predisposing factors are present:

- Sulphonylureas may be used in the treatment of diabetes or may be taken by non-diabetics in suicide attempts.
- Quinine may produce severe hypoglycaemia in the course of treatment for falciparum malaria.
- Salicylates may cause hypoglycaemia, usually after accidental ingestion by children.
- Propranolol can induce hypoglycaemia in the presence of strenuous exercise or starvation.
- Pentamidine, used in the treatment of resistant Pneumocystis pneumonia, may produce hypoglycaemia.

Alcohol-induced hypoglycaemia

Alcohol inhibits gluconeogenesis. Alcohol-induced hypoglycaemia occurs in poorly nourished chronic alcohol users, binge drinkers, and children who have taken relatively small amounts of alcohol, since they have a diminished hepatic glycogen reserve. They present with coma and hypothermia (hypothermia is a feature of hypoglycaemia, due to the suppression of central thermoregulation, particularly the shivering response; children manifest hypothermia more frequently due to their high ratio of surface area to body mass).

Factitious hypoglycaemia

This is a relatively common variant of self-induced disease and is more common than an insulinoma. Hypoglycaemia is produced by surreptitious self-administration of insulin or sulphonylureas. Many patients in this category have been extensively investigated for an insulinoma. Measurement of C-peptide levels during hypoglycaemia should identify patients who are injecting insulin; sulphonylurea abuse can be detected by chromatography of plasma or urine.

References

1. Walker, B.R. et al. *Davidson's Principles and Practice of Medicine*. Churchill Livingstone/Elsevier, 2014.

2. Hall, J.E. *Guyton and Hall Textbook of Medical Physiology*. Elsevier Health Sciences, 2015.

3. Barrett, K.E. et al. *Ganong's Review of Medical Physiology*. McGraw-Hill Education, 2016.

4. Longmore, M. et al. *Oxford Handbook of Clinical Medicine*. OUP Oxford, 2014.

5. Kumar, P. and M.L. Clark. *Kumar and Clark's Clinical Medicine*. Elsevier Health Sciences, 2016.

6. "Diagnosis and Classification of Diabetes Mellitus." *Diabetes Care*, vol. 33, no. Supplement 1, 2010, pp. S62-S69, doi:10.2337/dc10-S062.

7. International Diabetes Federation. "IDF Consensus Worldwide Definition of the Metabolic Syndrome." 2006, https://www.idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definitionof-the-metabolic-syndrome.html

8. International Diabetes Federation. *IDF Diabetes Atlas*. 7th edition, Brussels, Belgium: International Diabetes Federation, 2015. http://www.diabetesatlas.org/

9. Kasper, D.L. et al. *Harrison's Principles of Internal Medicine 19/E (Vol.1 & Vol.2)*. McGraw-Hill Education, 2015.

10. "Introduction." *Diabetes Care*, vol. 40, no. Supplement 1, 2017, pp. S1-S2, doi:10.2337/dc17-S001.

11. World Health Organization. "Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia: Report of a WHO/IDF Consultation." edited by WHO and IDF, 2006.

12. World Health Organization. "Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy." 2013, http://www.who.int/diabetes/publications/Hyperglycaemia_In_Pregnancy/en/http://www.who.int/diabetes/publications/Hyperglycaemia_In_Pregnancy/en/

13. World Health Organization. "Global Report on Diabetes." 2016. http://www.who.int/diabetes/global-report/en/http://www.who.int/diabetes/global-report/en/, 1 March 2017.

14. Katzung, B.G. and A.J. Trevor. *Basic & Clinical Pharmacology*, Thirteenth Edition, Smartbooktm. McGraw-Hill Education, 2014.

15. Murtagh, J. *John Murtagh's General Practice*. McGraw-Hill Education, 2015.

16. Goldman, L. and A.I. Schafer. *Goldman's Cecil Medicine*. Elsevier Health Sciences, 2011.

17. "Standards of Medical Care in Diabetes." *Diabetes Care*, vol. 27, no. suppl 1, 2004, pp. s15-s35, doi:10.2337/diacare.27.2007.S15.

18. Joint British Diabetes Societies Inpatient Care Group. *The Management of Diabetic Ketoacidosis in Adults*. 2nd edition, September 2013.

19. Gosmanov AR, Gosmanova EO, Kitabchi AE. *Hyperglycemic Crises: Diabetic Ketoacidosis (DKA), And Hyperglycemic Hyperosmolar State (HHS)* [Updated 2015 May 19]. In: De Groot LJ, Chrousos G, Dungan K, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279052/

20. Kitabchi, Abbas E. et al. "Hyperglycemic Crises in Adult Patients with Diabetes." *Diabetes Care*, vol. 32, no. 7, 2009, pp. 1335-1343, doi:10.2337/dc09-9032.

21. Netter, F.H. *Atlas of Human Anatomy*. Saunders/Elsevier, 2014.

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