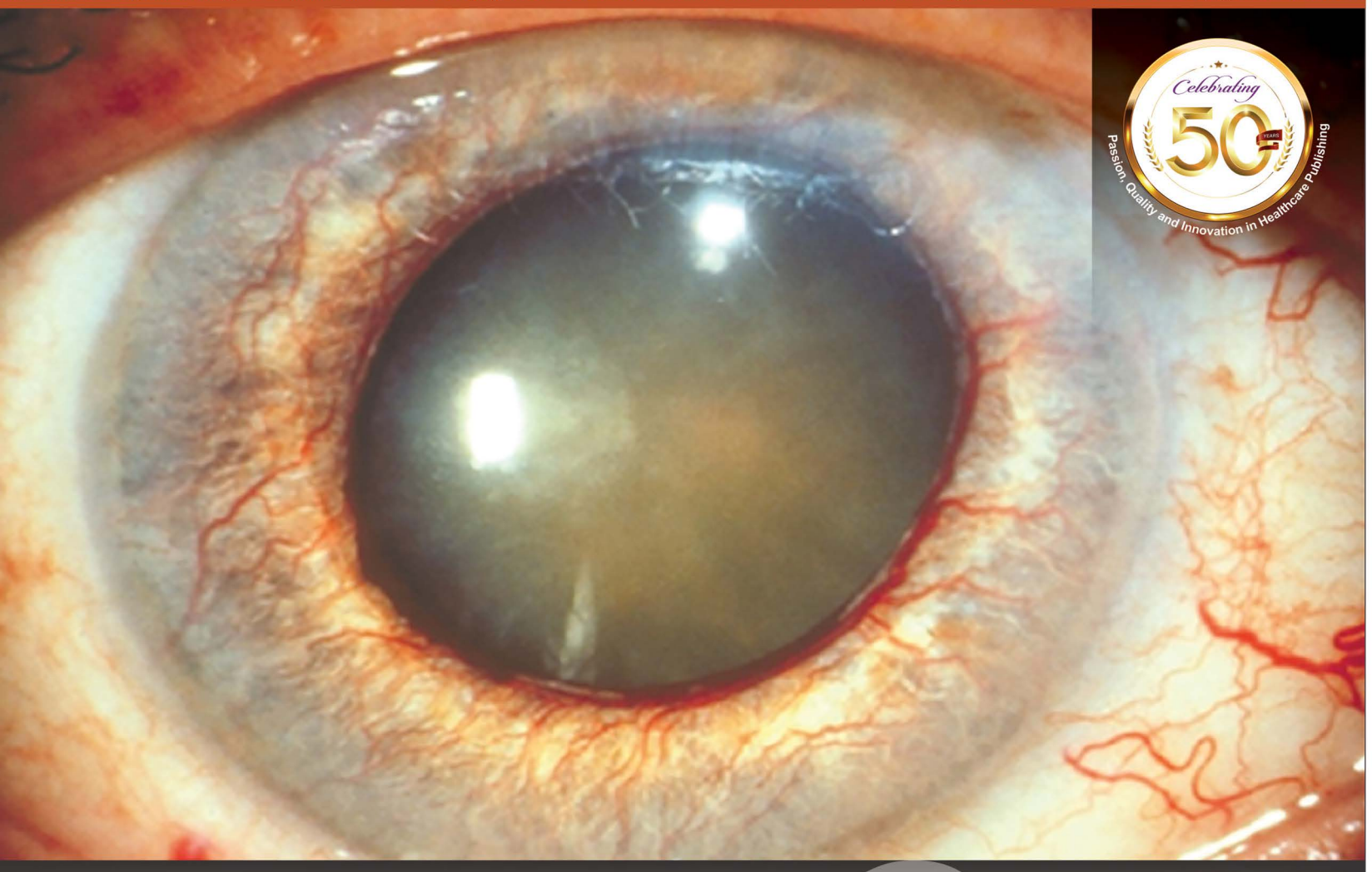
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Systemic & Ophthalmic

Management of Diabetes Mellitus

Chris Steele

JAYPEE

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Type 1 Diabetes Mellitus: Pathogenesis, Clinical Presentation and Management

CHAPTER 4

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is the main type of diabetes in young people comprising ~85% of all DM cases in patients less than 20 years of age. T1DM has arguably become a largely forgotten disease entity subsumed into the epidemic of type 2 diabetes mellitus (T2DM). Diabetes in young people was usually always T1DM and this still holds true for nearly all children diagnosed with DM under 10 years of age. However, among US teenage children (10–19 years) at diagnosis, 50% of African-American and Hispanic patients are now diagnosed with T2DM. For Asian, Pacific Islanders (e.g. Polynesia) and American Indians, well over half of these young people now present with T2DM.

In 2015, T1DM affected over 370,000 adults in the United Kingdom and continues to rise as in all other parts of the world; around 2–5% per year, according to the American Association of Clinical Endocrinologists (AACE) with prevalence in the United States of 1 in 300. What causes the initial fault in the immune system that causes T1DM is yet to be discovered, however, research suggests that the condition results from a combination of genetic predisposition with environmental factors.

In the past decade, life expectancy for adults living with T1DM has increased, but it remains significantly shorter than for people without diabetes, as there are still important deficiencies in care provision. In fact, most adults with T1DM have glycosylated hemoglobin (HbA1c) above target levels, and rates of diabetic ketoacidosis (DKA) (the acute complication of insulin deficiency) and renal failure have increased. In the updated National Institute for Health and Clinical Excellence (NICE) guideline NG17 regarding T1DM in adults: diagnosis and management (November 2015) recommendations on key priorities for implementation were published.

According to the AACE treatment goals for patients with T1DM are the same as those for patients with T2DM (*see* Chapter 5). These are discussed later in this chapter. In terms of HbA1c levels, these should be individualized with respect to:

- Age
- Residual life expectancy
- Duration of diabetes
- Presenting microvascular and macrovascular complications
- Cardiovascular disease (CVD) risk factors
- Risk for severe hypoglycemia
- Psychological, social and economic status.

For most relatively "normal or healthy" T1DM people an HbA1c ≤6.5% (48 mmol/mol) is the treatment goal (*see* later). For those that are considered "less healthy" a less stringent goal may be applied. The AACE recommend a fasting plasma glucose (FPG) <100 mg/dL and 2-h postprandial glucose (PPG) level of <140 mg/dL.

First, the pathogenesis of T1DM will be considered in order to understand how T1DM should be classified and managed according to the latest guidance.

PATHOGENESIS

Type 1 diabetes mellitus is a disease of insulin deficiency (Fig. 4.1) and belongs to a group of human leukocyte antigen (HLA)—associated immune mediated organ specific diseases. T1DM is commonly diagnosed in children aged 10–14 years, although the condition can develop at any age. As T1DM causes the loss of insulin production, it therefore requires regular insulin administration either by injection or via an insulin pump for a person's very survival. Insulin plays a key role in the regulation of carbohydrate, fat and protein metabolism.

Type 1a DM

In Western countries, nearly all patients have the immune-mediated form of the disease type 1a which includes:

- Typical human leukocyte antigen (HLA-DR3, 4 or 9)
- Slow progressing latent autoimmune diabetes of adults (LADA; *see* later)

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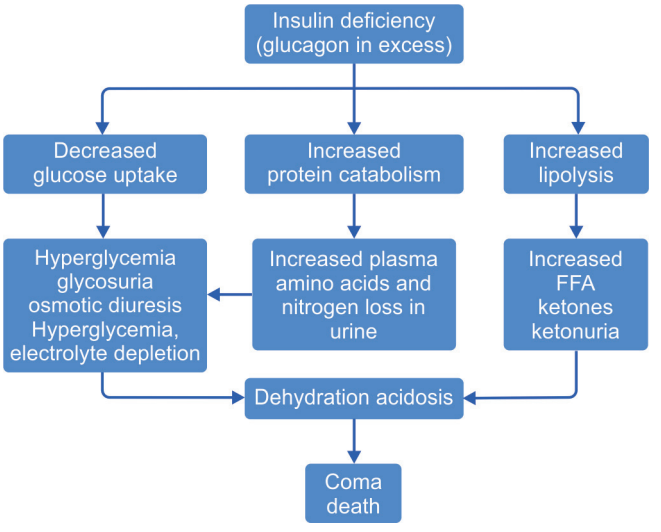


Fig. 4.1: Summary of insulin deficiency.

- Autoimmune polyendocrine syndromes
- Immunodeficiency, polyendocrinopathy enteropathy, X-linked syndrome.

This condition is currently irreversible and unpreventable, unlike T2DM, which is considered a lifestyle disease and eminently preventable with appropriate action.

Latent Autoimmune Disease in Adults

A "slow burning" variant with slower progression to insulin deficiency presents later in life, which has until recently been referred to as LADA. LADA is a disorder in which, despite the presence of islet antibodies at diagnosis of diabetes, the progression of autoimmune β-cell failure is slow. LADA patients may therefore not require insulin initially, although as the disease progresses insulin therapy will be needed. Among patients with phenotypic T2DM, LADA occurs in 10% of individuals older than 35 years and in 25% below that age. This may be easily confused with maturity onset diabetes in the young (MODY) and is sometimes referred to as type 1.5 DM. Differential diagnosis between these two clinical entities include: hyperglycemia, which fails to correct with diet and oral medication, and antibody tests indicating autoimmune disease. Prospective studies of β-cell function show that LADA patients with multiple islet antibodies develop β-cell failure within 5 years, whereas those with only glutamic acid decarboxylase autoantibodies or only islet cell antibodies mostly develop β-cell failure after 5 years. Even though it may take up to 12 years until β-cell failure occurs in some patients, impairments in the β-cell response to intravenous glucose and glucagon can be detected at diagnosis of diabetes. Consequently, LADA is not a latent disease and therefore, autoimmune diabetes in adults with slowly progressive β-cell failure has recently been suggested as a more accurate description of this condition.

Type 1b DM

There is also a non-immune-mediated idiopathic type 1b of unknown cause and is usually inherited. There is no immunological evidence for β-cell autoimmunity and no HLA association. Type 1b is most common in people of African or Asian ethnicity. They may have permanent insulin deficiency (insulinopenia) and are often disposed to DKA.

Fulminant Type 1b

Another category of type 1b is fulminant T1DM. This may present with extremely high glucose levels with DKA, with on average only 4 days of hyperglycemia and often normal or near-normal HbA1c levels. Onset may often be preceded by a viral infection, e.g. common cold-like and/or gastrointestinal symptoms. Occasionally, it may be seen in pregnancy and pancreatic enzymes are typically raised.

Genetic Predisposition

Genetic susceptibility is polygenic with the greatest contribution from the HLA region. Autoantibodies directed against pancreatic islet constituents appear in the circulation within the first few years of life and are often present long before any clinical signs or symptoms are evident. Autoantibodies are also found in older patients with LADA and these people have an increased risk of progression to requiring insulin therapy.

Through genome wide association studies, a number of genetic regions on human chromosomes have now been identified that are linked closely with T1DM. At least 18 different regions have been discovered and some of the genetic areas include an increased susceptibility for other autoimmune diseases. By far the greatest genetic contribution comes from the HLA region, but this is modulated by a large number of genes with small effects.

The HLA system is the locus of genes that encode for proteins on the surface of cells that are responsible for regulation of the immune system in humans. The *HLA* genes on chromosome 6 (with exception of β-2 microglobulin, which is located on chromosome 15) are highly

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polymorphic and modulate the immune defense system of the body. More than 90% of patients with T1DM carry HLA-DR3-DQ2, HLA-DR4-DQ8, or both compared with just 35% of the general population.

Even though genetics offers clues as to why some people are more susceptible to T1DM, genetic factors alone do not explain why some people with these genes develop T1DM and why others with these genes do not. For example, the identical twin of a patient with T1DM has a 30–50% chance of developing the disease, which implies other non-genetic factors must be involved. Interestingly, the risk of developing diabetes by age 20 years is slightly greater if the father is diabetic (3–7%) compared with if the mother is diabetic (2–3%).

In addition to a genetic predisposition to T1DM, there are a range of environmental factors that may play a key role in the initial development of T1DM in susceptible individuals.

Viral Infections

Associations have been found between T1DM and a number of different viruses. Of these, enteroviruses have attracted the most interest as research studies have shown that pregnant mothers with higher than normal levels of enterovirus antibodies often produce children who then develop T1DM later. Higher frequencies of enterovirus infections have also been detected in children that develop T1DM when compared with siblings that have not developed the condition. Other studies have also implicated coxsackie B virus, rubella virus and cytomegalovirus in the etiology of diabetes in that:

- IgM antibodies to coxsackie B virus are found in between 25 and 35% of newly diagnosed diabetics
- There is an increased incidence of T1DM in those with congenital rubella
- Cytomegalovirus DNA sequences are found to be incorporated into 22% of newly diagnosed diabetics compared with only 2.6% of controls

Childhood Vaccinations

Childhood vaccinations may increase the chances of developing T1DM in certain individuals. Recent research suggests there could be a link between T1DM and childhood vaccinations such as smallpox, tuberculosis and Hib vaccines. Interestingly, the tuberculosis vaccine, also known as the BCG vaccine, has also been suggested as a possible vaccination against T1DM.

Vitamin D

Researchers have noted that countries with the highest incidences of T1DM tend to be located further from the equator. Countries such as the United Kingdom, Canada, Australia and the countries of Scandinavia all have notably high rates of T1DM. Studies have also shown that people with lower levels of vitamin D had a higher incidence rate of developing T1DM. A number of studies, including the EURODIAB Sub-study 2, have shown that supplementation of vitamin D appears to lower the risk of developing T1DM.

Cow's Milk

Theoretically at least it has also been proposed that cow's milk could be a factor linked with development of T1DM. Research studies suggest that earlier introduction of cow's milk to be associated with a higher risk of T1DM. It is thought that bovine insulin within cow's milk could be a risk raising factor.

A Finnish study published in 2012, showed that using insulin free cow's milk resulted in a reduced number of autoantibodies in children at 3 years, corresponding to a lower risk of T1DM.

Increased Insulin Demand

Increased demand on insulin has also been put forward as a contributing factor. A study, carried out by the University of Colorado and published in 2008, showed that a diet with high glycemic index (GI) foods could speed up the progression to T1DM in children with signs of islet autoimmunity. Consumption of high GI foods results in large postprandial spikes in blood glucose and a subsequent larger production of insulin. The Colorado study hypothesized that diets high in GI and/or glycemic load would stress β-cells, thus increasing β-cell apoptosis and β-cell vulnerability to the immune system. Therefore, such diets may be associated with islet autoimmunity development and more rapid progression to T1DM.

The growth phase that children go through in teenage years increases the amount of insulin released and could lead to extra stress on beta cells (*see* later), raising the risk of the immune system attacking the insulin producing cells.

Insulin Structure and Secretion

Insulin is the key hormone involved in the storage and controlled release within the body of the chemical energy available from food. Insulin is synthesized in the β-cells

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of the islets of Langerhans of the pancreas from a single amino acid precursor molecule called proinsulin. The ribosomes manufacture preproinsulin from mRNA. The hydrophobic "pre" portion of preproinsulin allows it to be transferred to the Golgi apparatus where protease enzymatic activity cleaves off the "pre" portion to give rise to the synthesis proinsulin. The gene for preproinsulin is located on chromosome 11. Proinsulin is stored in vesicles within the Golgi apparatus of the B cells. From these, secretory granules are matured as they move toward the cell membrane where they are stored before release. As these matured proinsulin granules are finally released and break away from the cell membrane surface, 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. Equimolar quantities of insulin and C peptide are released into circulation. A small amount of insulin is secreted by the beta cell directly via the "constitutive pathway," which bypasses the secretory granules (Fig. 4.2).

The islets of Langerhans secrete at least four peptides with hormonal activity. Two of these, insulin and glucagon, have important functions in the metabolism of carbohydrates, proteins and fats. The third hormone, somatostatin, plays a role in islet cell secretion while the fourth, pancreatic polypeptide, is mainly concerned with gastrointestinal function.

Insulin is a major regulator of intermediary metabolism, although its actions are modified by many other hormones. Glucose is of course ultimately the human body's fuel; excess glucose unused by activity is stored predominantly as fat. All carbohydrate is converted to glucose by the action of insulin. In the fasting state, insulin concentrations are low and it acts as a hepatic hormone, modulating glucose production via glycogenolysis and gluconeogenesis from the liver. Hepatic glucose production rises as insulin levels fall. In the post prandial state, insulin concentrations are high and it then suppresses glucose production from the liver and promotes the entry of glucose into peripheral tissues enabling increased glucose utilization for energy. The brain is the major consumer of glucose in the fasted state and its uptake of glucose is obligatory and not dependent on insulin, with the glucose consumed converted to carbon dioxide and water. Other body tissues, e.g. muscle and fat, are, however, facultative glucose consumers. The effect of insulin peaks with associated meals is to lower the threshold for glucose entry into cells, whereas at other times energy requirements are mainly met by oxidation of fatty acids. Glucose taken up by muscle is stored as glycogen or broken down to lactate, which re-enters the circulation and becomes a major substrate for hepatic gluconeogenesis.

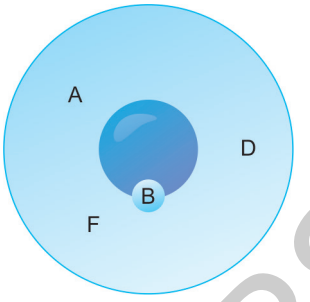


Fig. 4.2: Structure of the islets.

Insulin is anabolic in that it stimulates the storage of glucose as well as fatty acids and amino acids. Glucagon, on the other hand, is catabolic, mobilizing glucose, fatty acids and amino acids from their stores. Thus the two hormones are reciprocal in their overall actions and are normally secreted alternately. Insulin excess causes hypoglycemia (low blood sugar), while insulin deficiency, either absolute or relative, causes DM.

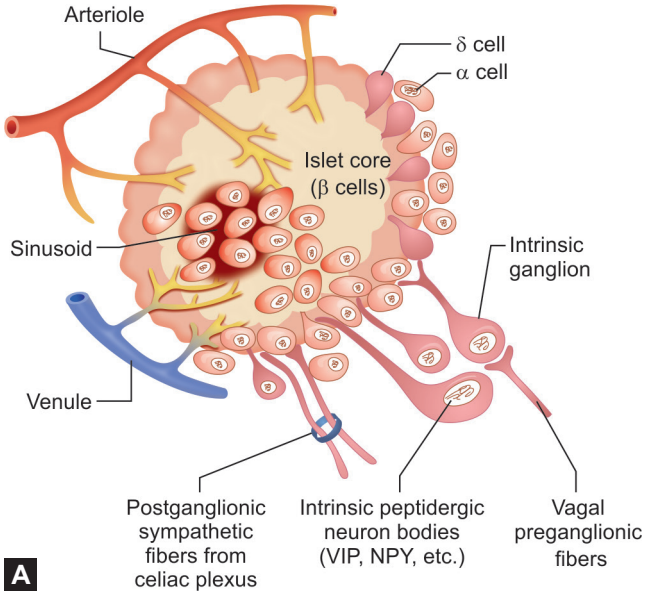
Islets of Langerhans

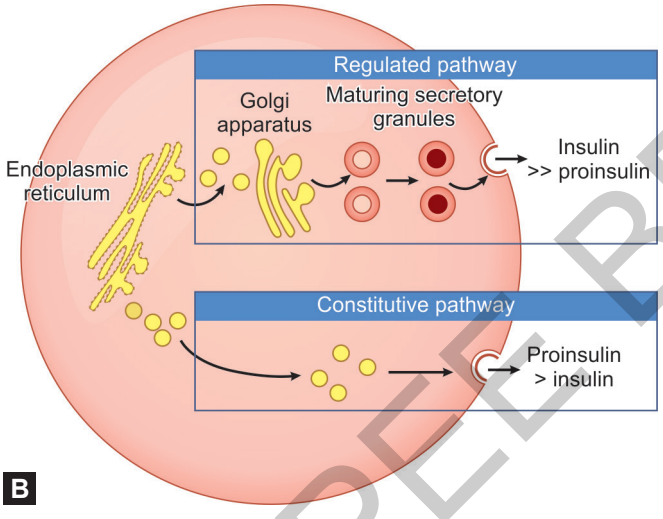
These are located in the pancreas (Fig. 4.3A). In humans they number 250,000–500,000. Each has a copious blood supply which drains directly into the portal vein. The blood flow within the islets flows centrifugally so that the different cells are supplied in a particular order. The islets are made up of four types of cells named A, B, D and F. The blood is supplied from B to A and to D then F. The structure of the islets is shown diagrammatically (Figs. 4.2 and 4.3A). A single islet is about 0.2 mm in diameter. The secretions of the islet cells are:

- A cells—glucagon
- B cells—insulin
- D cells—somatostatin
- F cells—pancreatic polypeptide.

The different cell types can be identified by various techniques including immunostaining techniques and electron microscope appearance of the secretory granules. The B cells are the most common and are located in the core of the islet, while A and F cells are located peripherally. B cells are programmed to synthesize insulin and have a very sophisticated mechanism to regulate its secretion (Fig. 4.3B). The islets are densely innervated with autonomic and peptidergic nerves. Parasympathetic innervation is supplied via the vagus nerve which stimulates insulin

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Figs. 4.3A and B: (A) Diagrammatic illustration of the structure of the islets of Langerhans. (B) Diagrammatic representation of the intracellular production of insulin.

release. Conversely adrenergic sympathetic nerves inhibit insulin and stimulate glucagon secretion. Other nerves that originate in the pancreas contain peptides such as vasoactive intestinal peptide. This is responsible for the stimulation and release of all islet hormones and neuropeptide Y which inhibits insulin secretion. Exactly how all these different neuropeptides interact is still not fully understood.

Regulation of Insulin Secretion

The most influential factor in the regulation of insulin secretion is the change in blood glucose concentrations.

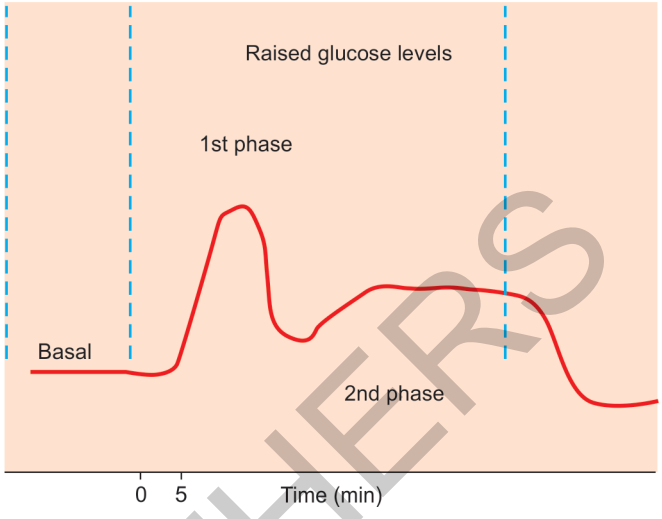


Fig. 4.4: Biphasic half-life of insulin released from islet cells.

The responses to these changes are both sensitive and rapid—usually within 30 seconds of the arrival of a glucose stimulus.

Glucose-stimulated insulin release is biphasic—a rapid first phase lasting some 5–10 minutes followed by a more prolonged second phase which continues for as long as the duration of the stimulus (Fig. 4.4). The half-life of insulin in the circulation in humans is about 5 minutes.

Effects of Insulin

Insulin's physiological effects are extensive and comprehensive, affecting the metabolism of carbohydrates, fats and proteins. They can conveniently be divided into rapid, intermediate and delayed. These are shown in Box 4.1.

The effects of insulin on adipose tissue, muscle and liver are detailed in Box 4.2.

Thus all the effects are anabolic. It encourages the storage of carbohydrate as glycogen and the building up of lipid and protein stores.

Glucagon

The actions of glycogen are exactly the opposite to that of insulin, that is, they are all catabolic. Its main target organ is the liver where it stimulates hepatic glucose output by breaking down glycogen stores (glycogenolysis) and by stimulating glucose synthesis by increasing the conversion of gluconeogenic amino acids into glucose (gluconeogenesis). It also stimulates the uptake of amino acids for the process of gluconeogenesis and stimulates fatty acid

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Box 4.1: Principal actions of insulin.

Rapid (seconds)
Increased transport of glucose, amino acids and potassium into insulin-sensitive cells

Intermediate (minutes)
Stimulation of protein synthesis
Inhibition of protein breakdown
Activation of glycolytic pathway enzymes and glycogen synthase
Inhibition of gluconeogenic enzymes

Delayed (hours)
Increase in the production of lipogenic enzymes

Box 4.2: Effects of insulin on adipose tissue, muscle, and liver.

Adipose tissue
Increased glucose entry
Increased fatty acid synthesis
Increased glycerol phosphate synthesis
Increased triglyceride deposition
Activation of lipoprotein lipase
Inhibition of hormone-sensitive lipase
Increased potassium uptake

Muscle
Increased glucose entry
Increased glycogen synthesis
Increased amino acid uptake
Increased protein synthesis
Decreased protein catabolism
Decreased release of gluconeogenic amino acids
Increased ketone uptake
Increased potassium uptake
Cell growth

Liver
Decreased ketogenesis
Increased protein synthesis
Increased lipid synthesis
Decreased glucose output due to decreased gluconeogenesis and increased glycogen synthesis

oxidation and ketone formation, alternative sources of fuel for muscle and adipose tissue in the fasted state, preserving glucose for utilization by the brain.

Insulin Receptors

Cells which are insulin sensitive have a specific insulin receptor on their outer cell surface. Insulin binds to this and then triggers its effects. Not all tissues are insulin sensitive. The brain is the most unresponsive; other non-responsive organs are the intestine and kidney.

Glucose Transport

Glucose enters cells by a process of facilitated diffusion, or in the kidneys and intestine, by secondary active transport with sodium. Insulin facilitates glucose entry by increasing the number of glucose transporters in the cell membrane. Clearly any interference with insulin receptors and/or glucose transport could impair the action on insulin.

Other Influences on Blood Glucose Regulation

Insulin is the principle hormone that lowers blood glucose concentrations. Corticosteroids, adrenaline, growth hormone and glucagon can all increase blood glucose levels. Thus glucose homeostasis is dependent on striking a right balance between the effects of insulin and the effects of the hormones which raise blood glucose levels. A severe deficiency of insulin will impact on carbohydrate, fat and protein metabolism with far reaching consequences (Fig. 4.1).

Carbohydrate Metabolism

Owing to the absence of insulin, the blood sugar lowering effect is lost and blood sugar levels rise. In the absence of insulin, there is no inhibition of gluconeogenesis in the liver, and an unopposed glucagon effect on increasing glycogen breakdown to glucose, both of which add to rising blood glucose levels—hyperglycemia.

The hyperglycemia is followed by glycosuria because the capacity of the renal tubules to reabsorb glucose is greatly exceeded. Rising glucose levels increase the osmolarity of the blood, and excretion of the osmotically active glucose molecules involves the loss of large volumes of water, leading to a state of dehydration. This in turn activates the mechanisms in regulating water intake resulting in polydipsia.

In addition to losing water, there is also an appreciable loss of sodium and potassium in the osmotic diuresis caused by the high blood glucose levels. Although people with T1DM tend to have enhanced appetite, this only serves to raise blood glucose levels. While there is an extracellular excess of glucose, there is an intracellular glucose deficiency so that cells are deprived of their major source of energy.

Effects of Intracellular Glucose Deficiency

In the absence of glucose, the major source of energy, alternative sources have to be found. This means drawing on reserves of energy in protein and fat stores under the influence of glucagon. Protein and fat are broken down (catabolized) to

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provide energy. This contributes to the weight loss and muscle wasting which is a clinical feature of T1DM.

Effects of Insulin Deficiency on Protein Metabolism

The inhibitory effect of insulin on protein breakdown (catabolism) is lost. The unopposed action of glucagon increases the rate of protein catabolism and further contributes to the weight loss and wasting seen in T1DM.

In T1DM, the net effect of accelerated protein catabolism to produce carbon dioxide, water and glucose under the influence of glucagon is not matched by an increase in protein synthesis because of the deficiency of insulin. The result is a negative nitrogen balance.

Effects of Insulin Deficiency on Fat Metabolism

The deficiency of insulin means that the enzyme hormone sensitive lipase is not inhibited. In addition, the catabolic effect of glucagon is not opposed by insulin so that the net effect is the release of free fatty acids and plasma levels can double.

Under the influence of insulin, 50% of ingested glucose is normally burned to carbon dioxide and water, 5% converted to glycogen and 45% converted to fat to be stored in fat deposits. In untreated T1DM, less than 5% of ingested glucose is converted to fat which further increases blood glucose levels.

Ketosis

As a result of the increased fat catabolism due to insulin deficiency, and the action of glucagon being unopposed, the liver is bombarded with their breakdown products. These are converted in the liver to ketones: acetoacetate and its derivatives acetone and β-hydroxybutyrate, which then enter the circulation in large quantities and are important sources of energy. However, in untreated T1DM production exceeds utilization so that a state of ketosis occurs.

Acidosis

Although some of the hydrogen ions liberated from the breakdown of ketones are buffered, a state of acidosis still develops. The resulting low plasma pH stimulates the respiratory center resulting in the rapid deep respiration known as Kussmaul's breathing. The loss of water and electrolytes produces a state of dehydration and hypovolemia and hypotension. If untreated, the state of dehydration and acidosis can depress consciousness to the point of coma and even death. Diabetic DKA is a serious medical emergency (*see* Chapter 6) requiring urgent fluid and electrolytic replacement and treatment with exogenous insulin.

T1DM SYMPTOMS AND PRESENTATION

Even though the major symptoms of diabetes are similar for type 1 and type 2, it is important to be able to recognize the specific symptoms of T1DM in addition to the more general symptoms of diabetes.

The clinical features of T1DM tend to present more acutely than those of T2DM. Young patients typically have a short history (a few days or weeks) of the classic symptoms which are as follows.

Diabetic Ketoacidosis

This may often be the first manifestation of T1DM in many patients, especially young children and teenagers. This may be caused by infection or environmental triggers (*see* earlier) or a rapid change from modest fasting hyperglycemia to severe hyperglycemia. According to the American Diabetic Association in some patients (especially adults), residual β-cell function may prevent ketoacidosis for many years. Once patients become insulin dependent (with low or undetectable plasma C-peptide), they are at risk for DKA. Even though a small proportion may be present with severe DKA (pH <7.1), this mostly presents within a range of pH 7.1–7.3.

Thirst

This is owing to the resulting loss of fluid and electrolytes. This is often intense and signs of unusual thirst may include:

- Regularly getting up to drink during the night
- Drinking a full glass or bottle of liquid and still being very thirsty
- Having only short gaps between bouts of thirst
- Usually associated with temporary or pronged dryness of the mouth.

Polyuria

This is the passage of large amounts of urine (perhaps several liters (>5 liters) per day owing to the osmotic diuresis caused by high glucose levels that exceed the renal threshold. Needing to visit the toilet more often than usual, going during the night (nocturia) also affecting

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sleep patterns, or having very short breaks between going to the toilet are all part of one of the main symptoms of T1DM. If a child starts to regularly wet the bed (enuresis), having not wet the bed for some time, it could also indicate a sign of diabetes. Polyuria is present in over 95% of cases.

Exaggerated and/or Unexplained Loss of Body Weight

Rapid weight loss owing to fluid depletion (dehydration) and the accelerated breakdown (catabolism) of fat and muscle, which is a secondary to insulin deficiency. Patients may notice an increased appetite (polyphagia). A lack of insulin means the body cannot get enough glucose from the blood into cells and so the body starts to break down fat and muscle into ketones to use as an alternative source of energy. Weight loss is noted in approximately two thirds of cases.

Tiredness

When the body lacks insulin, as happens in T1DM, cells of the body cannot take in glucose from the blood for energy, which can leave the body tired and under nourished. Tiredness in T1DM may be spotted if someone who is usually active starts finding physical activity particularly difficult to carry out.

The symptoms of thirst, polyuria and weight loss should always point to a diagnosis of T1DM until proven otherwise. In children, these symptoms in combination with a positive urine test for glucose demand immediate referral to a pediatrician. Fatigue is reported in approximately half of all cases.

Genital Itching

This is caused by Candida fungal infections such as pruritus vulvae or balanitis.

Obesity

Although T1DM patients are rarely obese, this can be a presenting sign, as obesity is not incompatible with T1DM.

Susceptibility to Other Autoimmune Diseases

Some people with T1DM are at increased risk of developing any of the following autoimmune conditions:

- Addison's disease
- Autoimmune hepatitis
- Celiac sprue
- Graves' disease
- Hashimoto's thyroiditis
- Myasthenia gravis
- Pernicious anemia
- Vitiligo.

MANAGEMENT OF T1DM

Loss of insulin secretion results in high blood glucose and other metabolic as well as hematological abnormalities, which has both short-term and long-term adverse effects on health. Over a number of years, T1DM causes tissue damage, which, if not detected and managed early, can result in disability including blindness, kidney failure and foot ulceration leading to amputation, as well as premature heart disease, stroke and death. The risk of all of these complications is greatly reduced by the treatment that keeps circulating glucose levels to as near normal as possible, thus reducing tissue damage. T1DM is treated by insulin replacement and supported by active management of other cardiovascular risk factors, such as hypertension and high circulating lipids.

Diagnosis and Initial Management Plan

Type 1 diabetes mellitus is diagnosed on clinical grounds in adults presenting with hyperglycemia and typically (but not always) also having one or more of the following present:

- Ketosis
- Rapid weight loss
- Age of onset below 50 years
- Body mass index (BMI) below 25 kg/m^2 (BMI was once thought to be suggestive of diabetes type, but as obesity rates have risen, patients' physical characteristics are no longer reliable diagnostic indicators)
- Personal and/or family history of autoimmune disease.
- A diagnosis of T1DM should not be discounted if an adult presents with a BMI of 25 kg/m^2 or above or is aged 50 years or above.

Type 1 diabetes mellitus should always be suspected in pediatric patients with hyperglycemia, particularly, if they are younger than 10 years, as nearly all these patients will have T1DM, regardless of race or ethnicity.

According to AACE guidance, T1DM is typified by absolute insulin deficiency and may be confirmed by the presence of autoantibodies to glutamic acid decarboxylase, pancreatic islet β cells (tyrosine phosphatase IA-2), zinc transporter (ZnT8) and/or insulin. At least 1 type

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of antibody is present in 85–95% of people newly diagnosed with T1DM. This varies depending on patient's age, the number and quality of the assays used and ethnicity according to Rewers et al. (2012).

Type 1b (idiopathic) diabetes (T1bD) is characterized by permanent insulinopenia and a tendency to present with ketoacidosis without evidence of autoimmunity. Only a small proportion of people with T1DM fall into this category of which, most are of African or Asian ethnicity.

According to NICE, C-peptide and/or diabetes-specific autoantibody titers are not routinely be used to confirm T1DM in adults. However, many diabetologists would disagree with this statement from NICE, especially those with experience of identifying MODY. Further, investigation in adults that involve measurement of C-peptide and/or diabetes-specific autoantibody titers are indicated if:

- T1DM is suspected but the clinical presentation includes some atypical features (e.g. age 50 years or above, BMI of 25 kg/m^2 or above, slow evolution of hyperglycemia or long running signs and symptoms—prodrome) or
- T1DM has been diagnosed and the treatment started but there is a clinical suspicion that the person may have a monogenic form of diabetes (MODY), and C-peptide and/or autoantibody testing may guide the use of genetic testing or where classification is uncertain, and confirming T1DM would have implications for availability of therapy [e.g. continuous subcutaneous insulin infusion (CSII or "insulin pump") therapy].

When measuring C-peptide and/or diabetes-specific autoantibody titers, it is important to consider that:

- Autoantibody tests have their lowest false negative rate at the time of diagnosis, and that the false negative rate rises thereafter.
- C-peptide has better discriminative value, the longer the test is done after diagnosis with autoantibody testing, carrying out tests for two different diabetes-specific autoantibodies, with at least one being positive, reduces the false negative rate.

Patient Education and Training

Education and information are vital for T1DM to understand how to manage their condition properly. At ~6–12 months post diagnosis, all adults with T1DM should now be encouraged to undertake a structured evidence-based education program of audited, proven benefit, for example, the Dose Adjustment For Normal Eating (DAFNE) program. It should be stressed that structured education is an essential part of their overall care. Furthermore, a Blood Glucose Awareness Training program for adults with T1DM should be offered to those who are having recurrent episodes of hypoglycemia.

According to the National Diabetes Audit, only a fraction of people with T1DM has attended or been offered DAFNE or an equivalent course. T1DM is often unpredictable, and effective training in matching carbohydrates to insulin doses, food and insulin absorption profiles, corrections, exercise, hormones, alcohol and sick-day rules are essential in balancing the many variables that go into managing blood glucose results. This applies to everyone with T1DM, whether diagnosed for a matter of months or 20 years, whether they have heard of DAFNE or not, and whether they think they need it or not. T1DM can be a very isolating condition and many who attend these courses will be meeting others facing the same daily struggles for the very first time. The value of this peer interaction should not be underestimated.

Adults with T1DM should be advised to aim for a target HbA1c level of 48 mmol/mol (6.5%) or lower in order to minimize the risk of long-term vascular complications. This target HbA1c may need to be individualized for many adults with T1DM, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycemia.

Adults with T1DM should test their blood sugars at least four times a day, and up to 10 times a day if any of the following apply:

1. The desired blood glucose control target (measured by HbA1c level) is not being adequately met.
2. Increases in frequency of hypoglycemic episodes.
3. If the patient intends to drive, as per Driving and Vehicle Licensing Agency regulations on fitness to drive.
4. During periods of illness.
5. Before, during and after sporting activities.
6. If planning a pregnancy, during pregnancy or while breastfeeding.
7. Where there is a need to know blood glucose levels more than four times a day for other reasons (e.g. impaired awareness of hypoglycemia or high-risk activities).

Importance of the Early Care Plan for T1DM

At the time of diagnosis, the diabetes professional team should carefully explain the importance of an early care plan with T1DM patients. This must first ensure that the exact type of diabetes has been correctly diagnosed and to ensure appropriate acute care is given as and when

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required. NICE guidelines 2015 recommends that any other potentially confounding disease should be detected and appropriate medicines reviewed, with particular emphasis on identifying any adverse vascular risk factors. Other important considerations include:

- Social, home, work and recreational circumstances of the person and caregiver.
- Their nutritional preferences.
- Attitudes toward and participation levels in physical activity.
- Other relevant factors, such as substance use and their general emotional state.
- Cultural and educational assessment to identify prior knowledge and to enable optimal advice and planning about treatment modalities and diabetes education programs.

The results of this assessment should be used to agree a future care plan and appropriate pace of education. The initial diabetes assessment should always include:

- Acute medical history
- Social, cultural and educational history/lifestyle review complications history/symptoms
- Long-term/recent diabetes history
- Other medical history/systems
- Family history of diabetes/CVD medication history/current medicines
- Vascular risk factors
- Smoking: this should be strongly discouraged as it is a major risk factor for CVD and lung cancer. Stopping smoking is as effective as lowering cholesterol and treating hypertension in reducing CVD
- General examination
- Weight/BMI
- Exercise: regular exercise should be encouraged as it improves glycemic control and lowers long-term morbidity and mortality. Patients should carry measures to combat hypoglycemia which should occur
- Foot/eye/vision examination
- Urine albumin excretion/urine protein/serum creatinine
- Psychological well-being
- Attitudes to medicine and self-care
- Immediate family and social relationships and availability of informal support.

Dietary Advice for Patients with T1DM

Carbohydrate-counting training to adults with T1DM should be provided as part of structured education programs for self-management. The new NICE guidelines recommend DAFNE as an education protocol. People with diabetes need to know what normal eating is.

Adults with T1DM are now not advised to follow a low-glycemic index (GI) diet for blood glucose control as once recommended. Low-GI foods, however, include whole foods such as meat, fish, dairy produce, fruit, vegetables, nuts and pulses. Fats and oils are also a key in promoting good health and well-being. Interestingly, the NICE guidelines, however, do not actually suggest an alternative diet.

Adults with T1DM should also be given advice about issues other than blood glucose control, such as weight control and cardiovascular risk management as clinically indicated. Information regarding the hyperglycemic effects of different foods should be readily available to adults with T1DM, so that they can make informed decisions about what foods to eat in the context of the insulin preparations chosen to match their food and activity level choices. The benefits of healthy eating should be emphasized, particularly in reducing cardiovascular risk. This should include information about fruit and vegetables, types and amounts of fat and ways of making appropriate nutritional changes.

Blood Glucose Management

HbA1c is a form of hemoglobin that is measured primarily to identify the 3-month average plasma glucose concentration (*see* Chapter 3). The test is limited to a 3-month average because the lifespan of a red blood cell is 3 months.

HbA1c levels should be measured every 3–6 months in adults with T1DM.

HbA1c levels should be measured more often in adults with T1DM if the person's blood glucose control is suspected to be changing rapidly, for example, if the HbA1c level has risen unexpectedly above a previously sustained target.

Methods to measure HbA1c level that have been calibrated according to International Federation of Clinical Chemistry (IFCC) standardization should only be used.

Informing adults with T1DM of their HbA1c results after each measurement is very important thus ensuring that their most recent result is available at the time of their consultation. The principles in the NICE guideline on the patient experience in adult National Health Services about communication should always be followed.

Having a very supportive general practitioner, who can ensure ready access to as many test strips as needed, is

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really important for people living with T1DM and is a huge help in self managing their condition. T1DM cannot be relied upon to behave itself from one week to the next. The same food and doses can sometimes lead to frustratingly varied results, and the ability to monitor and adjust on an ongoing basis is crucial when playing at being your own pancreas. The new test strip recommendations reflect evidence showing that increased testing frequency correlates with improved outcomes, and still remains cost-effective even at intensive levels.

Targets

Adults with T1DM should ideally aim for a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimize the risk of long-term vascular complications.

However, an individualized HbA1c target may be more realistically achieved by taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation, history of hypoglycemia and age. From a patient perspective, it is vital that the HbA1c target of 48 mmol/mol (6.5%) "to avoid long-term complications" is read alongside the recommendation to establish an individual target for each person. This new target is aspirational, with genuine benefits for the avoidance of complications, but for some it will sound like an impossible dream. Far from being a "failure stick" to beat healthcare professionals with, this recommendation becomes a source of support for anyone who has the time, skill, good fortune and technology to aim for a sub-7.0 HbA1c.

Current diabetes NICE guidelines promote a tailored program of support, including management strategies and treatment options for everyone to achieve their own personal balance between diabetes optimal control and still having a life.

When aiming for a particular HbA1c target, care must be taken to ensure this does not cause problematic hypoglycemic episodes. Diabetes services, nowadays, should also document the proportion of adults with T1DM who are being cared for who achieve an HbA1c level of 53 mmol/mol (7%) or lower.

According to NICE guidelines, adults with T1DM should be aiming for a FPG level of 5–7 mmol/L on waking and a plasma glucose level of 4–7 mmol/L before meals at other times of the day. Bedtime target plasma glucose levels that take into account timing of the last meal and its related insulin dose should be consistent with the recommended fasting level on waking.

For adults with T1DM who are capable of abiding by the requirements of real-time continuous glucose monitoring, flexible insulin therapy is now recommended with either a multiple daily injection insulin regimen or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy.

For real-time continuous glucose monitoring, this should only be provided by a center with expertise in its use, as part of strategies to optimize a person's HbA1c levels and reduce the frequency of hypoglycemic episodes. Some hypoglycemic episodes are an inevitable consequence of insulin therapy in most people using any insulin regimen. However, it is advisable that they should use a regimen that avoids or reduces the frequency of hypoglycemic episodes, while maintaining as optimal a level of blood glucose control as is feasible.

Insulin Regimes for Adults with T1DM

Insulin is a polypeptide hormone of complex structure. There are differences in the amino-acid sequence of animal insulins, human insulins and the human insulin analogs. Insulin may be extracted from pork pancreas and purified by crystallization. In the past, it has also been extracted from beef pancreas, but this source is rarely used nowadays. Human sequence insulin may be produced semisynthetically by enzymatic modification of porcine insulin, or biosynthetically by recombinant DNA technology using bacteria or yeast.

All insulin preparations are to a greater or lesser extent immunogenic in man but immunological resistance is uncommon. Preparations of human sequence should theoretically be less immunogenic but no significant difference has been demonstrated in clinical trials.

Type 1 diabetes mellitus is a disease of insulin deficiency and insulin replacement is necessary for survival. Insulin is inactivated by gastrointestinal enzymes and must therefore be given by injection. Ideally, insulin is normally given by a subcutaneous injection. These most common injection sites include the:

- Upper arms
- Abdomen
- Outer aspect of the thigh
- Upper outer buttock.

There are a range of injection devices all designed to make giving the injection easier and less painful. Insulin absorption from a limb site is increased if the limb is used in strenuous exercise after the injection.

In non-diabetic people, blood glucose levels are maintained within a fairly narrow range by a combination

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Table 4.1: Some commonly used insulin preparations.

Insulin class	Administration	Onset (h)	Peak (h)	Duration (h)	Origin
Rapid acting					
Novorapid, Humulin S, Apidra	Just before meals	0–0.25	1–3	3–5	
Short acting					
Insulin aspart (Novorapid) Insulin Lispro (Humalog) Insulin glulisine	Immediately before meals or as required shortly after meals	0.50	1–5	6–8	Synthetic recombinant human insulin analog
Intermediate acting					
Biphasic aspart (Novomix) 30 Biphasic Lispro (Humalog mix 25/50) Biphasic isophane (NPH) (Humulin M3) (Insuman comb15/25/50)	Usually10–15 minutes before meal or as soon after depending on requirements	0.5–1.0	2–10	12–18	
Long acting					
Insulin glargine Insulin detemir Insulin degludec	According to requirements	0.5–1.0	Peakless	18–24	Synthetic recombinant human insulin analogs

of endogenous insulin and regulatory hormones. The current approach to the use of insulin in people with T1DM is to recreate this physiological state as closely as possible. To do this, there are a plethora of insulin preparations available but basically they can be divided into three types, based on their rapidity and duration of action, that is, short, intermediate and long acting (Table 4.1).

Modern insulin replacement therapy aims to recreate normal fluctuations in circulating insulin concentrations. This supports a flexible lifestyle with minimal restrictions and, properly done, can improve blood glucose levels, reducing the risk of both structural complications and episodes of hypoglycemia. Flexible insulin therapy usually involves self-injecting multiple daily doses of insulin, with doses adjusted based on taken or planned exercise, intended food intake and other factors, including current blood glucose, which the insulin user needs to test on a regular basis. This self-management needs the insulin user to have the skills and confidence to manage the regimen. One of the most important roles of healthcare professionals providing diabetes care to adults with T1DM is to ensure that systems are in place to provide informed, expert support, education and training for insulin users as well as a range of other more conventional biomedical services and interventions.

Analog insulins have been modified to make them closely resemble naturally occurring human insulin and to make achieving glucose control closely resemble the normal physiological state. The word "analog" conveys the meaning of similar to, in this case similar to human insulin, but not an exact replicate. Like human insulin, they are genetically engineered. There are rapid and long-acting analog insulins and there are mixtures of the two.

The rapid-acting analog insulins take effect quicker than human or animal short-acting insulins. The latter are usually taken 15–30 minutes before a meal, whereas the analogs can be taken just before or during a meal. This is very useful if a person wants to have greater flexibility in choosing meal times.

Long-acting analogs are generally taken once a day, usually at bedtime and tend to have a relatively smooth action lasting between 16 and 24 h. Both rapid- and long-acting analog insulins are well suited for basal bolus regimens of insulin delivery (*see* later). Analog insulins are not superior to other forms of insulin but their benefit is that they offer greater flexibility and reduced frequency of hypoglycemia.

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