Chapter 1
The Pathobiology of Diabetes Mellitus

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Abbreviations

ACE	Angiotensin-converting enzyme
ADA	American Diabetes Association
AGEs	Advanced glycation end-products
ACTH	Adrenocorticotropic hormone
ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
CCK	Cholecystokinin
CGM	Continuous glucose monitoring
CKD	Chronic kidney disease

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CRF	Corticotropin-releasing factor (or hormone)
DCCT	Diabetes control and complications trial
DNA	Deoxyribonucleic acid
DIDMOAD	Diabetes insipidus, diabetes mellitus, optic atrophy, deafness
DKA	Diabetic ketoacidosis
DPP-4	Dipeptidyl peptidase-4
EGP	Endogenous glucose production
EDIC	Epidemiology of diabetes interventions and complications
GFR	Glomerular filtration rate
GH	Growth hormone
GHRF	Growth hormone-releasing factor
GHIH	Growth hormone inhibitory hormone
GIP-1	Glucose-dependent insulinotropic polypeptide-1
GLP-1	Glucagon-like peptide-1
GLUT	Glucose transporter
GSIS	Glucose-stimulated insulin secretion
GTP	Guanosine triphosphate
HIF	Hypoxia inducible factor
IAPP	Islet amyloid polypeptide
IV	Intravenous
LADA	Latent autoimmune diabetes of adulthood
MODY	Maturity-onset diabetes of the young
mRNA	Messenger ribonucleic acid
NADPH	Nicotinamide adenine dinucleotide phosphate
oGTT	Oral glucose tolerance test
PKC	Protein kinase C
PP	Pancreatic polypeptide
RER	Rough endoplasmic reticulum
RRP	Readily releasable pool
SD	Standard deviation
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
TNF	Tumor necrosis factor
TSH	Thyroid-stimulating hormone
UKPDS	United Kingdom Prospective Diabetes Study
VEGF	Vascular endothelial growth factor
VIP	Vasoactive intestinal peptide

This chapter is dedicated to Marie-Elise and Liam McCallum and to other people who live with type 1 diabetes, with the hope that results of ongoing and future medical research will lessen the impact of diabetes on their lives.

Introduction

Diabetes mellitus is an increasingly common chronic condition characterized by an absolute [as in type 1 diabetes (T1D)] or relative lack of insulin [as in type 2 diabetes (T2D)], hyperglycemia, dyslipidemia, and neurovascular damage that can affect every organ system in an individual. It is associated with both acute and chronic complications which can be life-threatening. Every 6 s today someone dies from diabetes (International Diabetes Federation 2013). Diabetes also impacts on the affected individual's family, friends, colleagues and the community, including the healthcare system, and the national and global economies (Jenkins 2015). In 2013, there were ≈382 million people with diabetes globally, most in low- to middle-income countries, predicted to rise to over 592 million in the next 25 years, the majority of whom have T2D (International Diabetes Federation 2013). Almost half of the many people with T2D are undiagnosed, particularly in less affluent regions.

The increasing incidence and prevalence of T2D are contributed to by non-modifiable factors such as population growth, increased longevity and better screening and therefore case ascertainment. Importantly though, the T2D epidemic parallels increasing rates of overweight and obesity associated with changing lifestyles (urbanization and increased sedentary behavior) that potentially are modifiable (Eckel et al. 2011). Gestational diabetes (GDM), which is glucose intolerance diagnosed in pregnancy, and T2D in pregnancy are also increasing in incidence for the same reasons (Nolan et al. 2011). The incidence of the autoimmune condition T1D, which very often starts in childhood, has been increasing at about 3 % per annum in Australia (Insulin-treated diabetes in Australia 2000–2007; Shaw and Tanamas 2012) and similarly overseas over the past 30–40 years (Gale 2002). This increase is most likely due to environmental rather than changing genotypes. The 'hygiene hypothesis' postulates that it relates to changing immune function as a consequence of reduced early life immune stimuli due to our more hygienic environment (Versini et al. 2015). Not mutually exclusive is the 'accelerator hypothesis' which postulates that insulin resistance, as a consequence of the obesogenic environment, accelerates development of T1D in people at risk (Fourlanos et al. 2008).

In spite of the availability of modern therapies for glucose, blood pressure and lipid control, which are often not available or affordable to all who may benefit (Jenkins 2015), optimal treatment targets are often not met, hence increasing the risk of both acute and chronic complications of diabetes. The predominant acute complications of diabetes include both hypoglycemic and hyperglycemic crises which relate to a mismatch between blood glucose and insulin (and other related glucose-modulating hormones and neurogenic stimuli). Chronic complications are a consequence of hyperglycemic and mixed nutrient-induced damage to tissues of the body, particularly via the vascular supply involving both the larger arteries (macrovascular), causing myocardial infarctions, strokes and peripheral vascular disease, and the small vessel (microvascular) networks, causing

diabetic eye disease (retinopathy), renal disease (nephropathy) and neuropathy. Peripheral neuropathy and/or peripheral vascular disease increase the risk of lower limb amputation. Acute and chronic complications of diabetes, many of which are life-threatening, cause even greater physical, emotional and socioeconomic demands on the person with diabetes. Furthermore, compared to persons with well-controlled complication-free diabetes, those with complications exponentially increase healthcare costs (Shaw and Tanamas 2012). Even 'pre-diabetes,' in which blood glucose levels are elevated above normal, but not to the level of those diagnostic of diabetes, is associated with accelerated atherosclerosis (Faerch et al. 2014), but not with renal, retinal or nerve damage. Better means to predict, detect, stage and prevent the various forms of diabetes and to predict, prevent and treat the short- and long-term complications of diabetes are highly desirable.

Clinical and basic science research has taught us much about diabetes, its etiologies, complications and treatments. Modern medicine has led to a wide range of oral and injectable glucose control agents, including insulin, first available for clinical use in 1922, but followed by improved engineered insulin analogues in recent years. Major advances have also been achieved in insulin delivery and blood glucose monitoring devices, including increasingly 'smarter' insulin pumps and subcutaneous continuous glucose monitors. In addition, today there are many other drugs and therapies to treat diabetes, risk factors and its complications, including islet cell, pancreas and kidney transplantation (which usually require immunosuppression). The challenges of living with diabetes have lessened, and its prognosis has improved substantially, at least in regions with access to modern diabetes care (Gregg et al. 2014). Nevertheless, much further work, including clinical and basic science research, biomedical engineering, population health, healthcare systems, policy and health economics research, is needed to lessen the major personal and economic burden of diabetes.

In this chapter, we describe the normal pancreas, islets of Langerhans, normal glucose homeostasis, with an emphasis on insulin, the types of diabetes and its complications, the underlying pathobiology of diabetes per se and its vascular and neurological complications, and current treatment modalities. We hope this chapter will complement other excellent chapters in this volume, which will inform and update the reader regarding many aspects of the pancreas, diabetes and its treatment.

The Pancreas

Located in the retroperitoneal space in the abdominal cavity, at the level of the first and second lumbar vertebrae, the pancreas is a J-shaped soft lobulated yellowish colored organ usually measuring about 15–20 cm long (in adults), 5 cm wide and with an average weight of about 90 g. The pancreas is usually described as consisting of a head, body and tail, the majority of which is located on the left side of

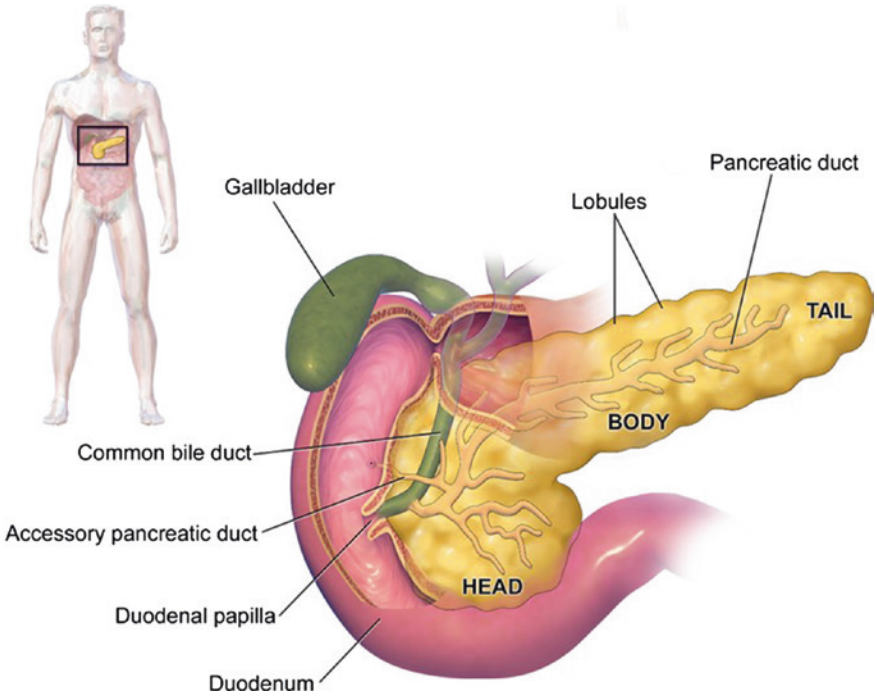

Fig. 1.1 Anatomy of the pancreas. Blausen.com staff. "Blausen gallery 2014". Wikiversity Journal of Medicine. doi:10.15347/wjm/2014.010. ISSN 20018762.—Own work. Licensed under CC BY 3.0 via Commons—https://commons.wikimedia.org/wiki/File:Blausen_0699_PancreasAnatomy2.png#/media/File:Blausen_0699_PancreasAnatomy2.png

the abdomen. The head of the pancreas is closely surrounded by the duodenum, and its tail abuts the spleen and left colic flexure (Fig. 1.1). In front of the pancreas are the stomach and loops of small intestine, and behind it is the left kidney and adrenal gland, inferior vena cava and aorta (Guyton and Hall 1996).

The *blood supply* to the pancreas is via the superior mesenteric and the common hepatic and splenic artery branches of the celiac trunk. Its venous drainage is via the superior mesenteric, portal and splenic veins. *Innervation* of the pancreas is by the vagal and spinal nerves. *Lymphatic drainage* is via the splenic, celiac and superior mesenteric lymph nodes.

In the pancreas parenchyma, stemming from many minor ducts in the pancreatic exocrine tissue, there is a major *pancreatic duct* (also called the duct of Wirsung) which drains the pancreatic exocrine secretions (bicarbonate and digestive enzymes) into the duodenum. A smaller, shorter and more anatomically variable accessory pancreatic duct often joins the main pancreatic duct in the head of the pancreas. The pancreas is a *dual-function gland*, having features of both exocrine and endocrine glands (Guyton and Hall 1996; Greenstein and Wood 2011).

The Exocrine Pancreas

The majority of the mass of the pancreas is dedicated to its exocrine function of producing (protein, fat and carbohydrate) digestive enzymes and bicarbonate, which are produced by cellular clusters (called acini) and secreted via the acinar lumen to intralobular ducts to the main pancreatic duct(s) and into the duodenum. The main digestive enzymes are secreted as inactive proenzymes or zymogens (to protect against pancreatic autodigestion) and are activated by enzymes and bile acids once in the small intestine.

The *digestive enzymes* are:

(i) trypsin, chymotrypsin, carboxypeptidases and elastase, which digest proteins;
(ii) lipase, phospholipase, lysophospholipase and cholesterol esterase, which digest lipids;
(iii) α-amylase, which (in conjunction with polysaccharidases produced by the intestinal mucosa) digests carbohydrates; and
(iv) ribonuclease and deoxyribonuclease, which digest nucleic acids.

These pancreatic secretions (including that of bicarbonate, which neutralizes acidic contents from the stomach) are stimulated via food in and distension of the stomach and duodenum, modulated by gut hormones (including secretin, cholecystokinin (CCK) and gastrin) and the autonomic nervous system.

The Endocrine Pancreas

The major role of the endocrine pancreas is the tight regulation of blood glucose levels and related energy sources, such as glycogen stores in liver and muscle. Representing only 1–1.5 g (<2 %) of the pancreas mass and scattered throughout the pancreas, with a higher concentration in the tail, are approximately a million clusters of endocrine, called the islets of Langerhans (after the German anatomical pathologist, Paul Langerhans, who discovered them in 1869) (Sakula 1988). Each islet is around 0.2 mm or 200 μm in diameter and encapsulated in a thin connective tissue capsule and is surrounded and infiltrated by a capillary network. This vascular network is particularly dense and contains highly fenestrated capillaries, such that islets have tenfold the blood flow than the exocrine pancreas and are able to respond rapidly to circulating nutrient levels, and similarly for the secreted hormones, importantly including insulin, to diffuse into the circulation (Guyton and Hall 1996; Greenstein and Wood 2011). It is these islets, isolated from human cadaver donors, that now form the basis of islet cell transplantation for a very small subset of adults with T1D, usually those with life-threatening recurrent severe hypoglycemia.

There are five known endocrine cell types in human islets of Langerhans:

(i) *β-cells*, which produce insulin and amylin and account for ~60 % of islet cells;
(ii) *α-cells*, which produce glucagon and account for ~30 % of islet cells;
(iii) *δ-cells*, about 5 % of islet cells, which produce somatostatin;
(iv) *γ-cells (also known as PP cells)*, about 5 % of islet cells, which produce pancreatic polypeptide; and
(v) *ε-cells*, <1 % of islet cells, which produce ghrelin (Eissa and Ghia 2015; Granata and Ghigo 2013; Horner and Lee 2015; Zigman et al. 2015).

The proportion as well as the architecture of islet cells is known to be different in mice (discussed by Manami Hara and colleagues in Chap. 2 of this volume). Mouse islets contain ~80 % β-cells that form a central core of the islet and are surrounded by non-β-islet cells, including ~10 % α-cells (Cabrera et al. 2006; Kilimnik et al. 2012; Kim et al. 2009). The function of each of these hormones is briefly described later.

Normal Glucose Homeostasis and the Importance of Hormonal Regulation

In non-diabetic subjects, blood glucose levels are tightly maintained within narrow limits, usually between 3.5 and 5.5 mmol/L in the fasted state and 5.0–7.5 mmol/L after meals. The body utilizes 180–260 g of glucose/day, of which about 50 % is taken up by the brain. Some tissues, such as the brain, red blood cells and the renal medulla, rely entirely on glucose for energy. Other tissues can additionally metabolize alternate substrates for their energy needs such as ketone bodies and fatty acids (Guyton and Hall 1996).

Glucose levels are controlled by the following hormones:

(i) insulin;
(ii) glucagon;
(iii) somatostatin (with i–iii arising from pancreatic islets);
(iv) incretin hormones [e.g., glucagon-like peptide-1 (GLP-1)] from the gut;
(v) catecholamines [e.g., adrenaline (epinephrine)] from the adrenal medulla;
(vi) cortisol from the adrenal cortex; and
(vii) growth hormone (GH) from the pituitary gland.

Fasting blood glucose is determined by the balance between the rate of endogenous glucose production (EGP), mainly from hepatic glycogenolysis and gluconeogenesis, and its utilization by tissues, in particular essential use by the brain, which is insulin independent. EGP prevents hypoglycemia and is supported by a low plasma insulin/glucagon ratio. Some insulin is required to maintain normoglycemia during fasting, as EGP, by default, is high in its absence. Glucose is spared for brain use during fasting through the provision of non-glucose nutrients (e.g., free fatty acids from adipose tissue lipolysis) to other tissues such as heart and skeletal muscle (Fig. 1.2) (Nolan et al. 2011; Guyton and Hall 1996).

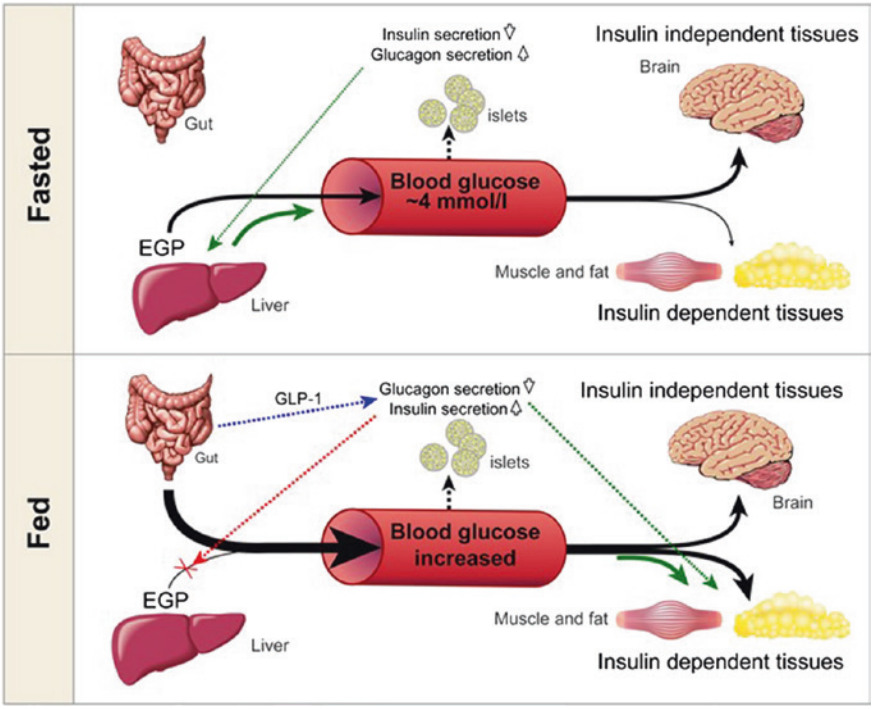

Fig. 1.2 Overview of normal glucose homoeostasis. In the fasting state, blood glucose concentration is determined by the balance between EGP production, mainly through hepatic glycogenolysis and gluconeogenesis, and use by insulin-independent tissues, such as the brain. EGP prevents hypoglycemia and is supported by a low insulin-to-glucagon ratio in plasma. In the fed state (meal with carbohydrate), glucose concentrations in the blood rise because of absorption in the gut, which stimulates insulin secretion by islet β-cells and suppresses glucagon secretion from α-cells. EGP is suppressed (which helps to curtail total glucose input into blood), and uptake into insulin-sensitive peripheral tissues, such as the heart, skeletal muscle, and adipose tissue, is activated (which increases the rate of glucose disposal). Neurohormonal processes include the release of the incretin hormones, such as GLP-1, which increases glucose-stimulated insulin secretion and glucose suppression of glucagon secretion. *GLP-1* glucagon-like peptide-1, *EGP* endogenous glucose production (Nolan et al. 2011)

In the fed state (e.g., meal with carbohydrate), the rate of glucose appearance into the blood increases due to gut glucose absorption. An elevation in blood glucose stimulates insulin secretion and suppresses glucagon secretion from, respectively, pancreatic islet β- and α-cells. This results in the suppression of EGP (helps to curtail the total rate of glucose appearance) and the activation of glucose uptake into insulin-sensitive peripheral tissues such as heart, skeletal muscle and adipose tissue (increases the rate of glucose disposal) (Fig. 1.2) (Nolan et al. 2011; Guyton and Hall 1996).

Other complex neurohormonal processes are also involved, including the release of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent

insulinotropic peptide (GIP). Incretin hormones enhance both glucose-stimulated insulin secretion (GSIS) and glucose suppression of glucagon secretion (discussed in more detail below). These normal physiological responses prevent excessive rises in plasma glucose after meals and, in most circumstances, return plasma glucose levels close to the fasting level within 2 h. At the same time, the fed-state neurohormonal and metabolite mix suppresses adipose tissue lipolysis and promotes a general state of anabolic metabolism (Fig. 1.2) (Nolan et al. 2011; Guyton and Hall 1996; Steele et al. 2004; Vega-Monroy and Fernandez-Mejia 2011).

We now provide an overview of each of the major glucose-influencing hormones, with an emphasis on those produced by the pancreas.

Insulin

Insulin Structure and Synthesis

The structure of insulin is shown in Fig. 1.3. Mature, active insulin is a 5.8-kDa, 51-amino acid polypeptide with two (A and B) chains of 21 and 30 amino acid residues, respectively, joined by disulfide bridges and another disulfide bridge within the A chain, all between cysteine residues. There are two inactive precursors, pre-proinsulin (of 110 amino acids) and proinsulin (of 86 amino acids) (Fu et al. 2013).

Insulin synthesis is regulated at both transcriptional and translational levels. In the β-cell nucleus insulin coding (*pro*-ins) gene is transcribed to mRNA, which is then transferred into the cytoplasm, where translation occurs on ribosomes. Pre-proinsulin contains a hydrophobic N-terminal signal peptide, which interacts with cytosolic ribonucleoprotein signal recognition particles that facilitate translocation of the signal sequence, mRNA and ribosomes to the rough endoplasmic reticulum (RER) in the cytoplasm, which is responsible for protein assembly (Fu et al. 2013). The N-terminal signal sequence translocated to the RER membrane is elongated, to form pre-proinsulin. With removal of the N-terminal signal sequence, proinsulin is formed, folded and stabilized by the formation of the three disulfide bonds within the RER lumen and is then transported to the cytosolic Golgi complex. In the Golgi apparatus, the proinsulin enters immature secretory granules inside of which C-peptide is cleaved from the proinsulin (Fu et al. 2013). The insulin and C-peptide are then stored within secretory granules, along with amylin and other products including zinc, until their release by fusion with the plasma membrane and exocytosis in response to a range of stimuli (discussed below), with the most potent stimulus being rising glucose levels. Glucose metabolism activates insulin gene transcription and mRNA translation, having a particularly important role in stabilizing pre-proinsulin mRNA (Fu et al. 2013).

Insulin has a half-life in the circulation of about 6 min, while that of C-peptide is approximately 30 min. Circulating insulin is predominantly removed by the liver, and C-peptide is excreted by the kidneys (Gale 2015).

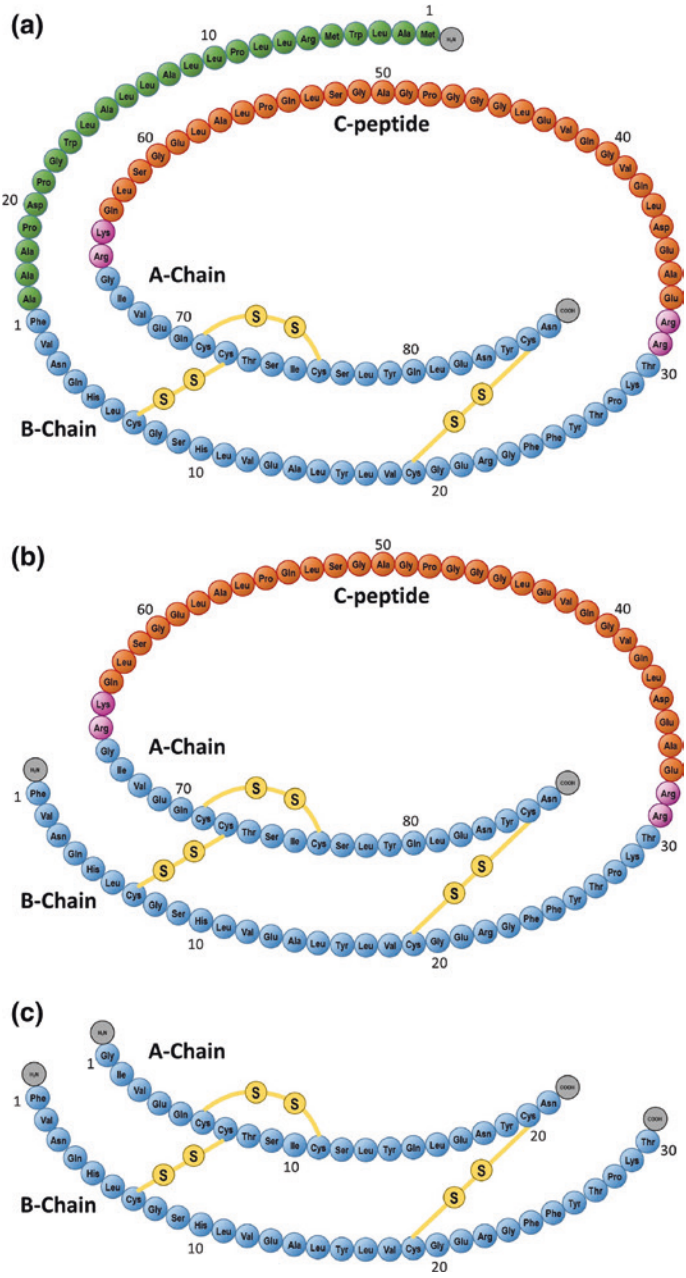

Fig. 1.3 Amino acid structures of pre-proinsulin (**a**), proinsulin (**b**) and insulin (**c**)

Signaling of Insulin Secretion

The islet β-cell senses multiple nutrient and neurohormonal inputs and accordingly secretes an appropriate amount of insulin for the requirements of the body at that time. Essential for insulin secretion is β-cell metabolic activation in response to an increased mixed nutrient supply, of which glucose is the most important (Fig. 1.4) (Nolan and Prentki 2008; Prentki et al. 2013).

In order to couple glucose sensing to insulin release, islet β-cell glucose metabolism is essential, and this is via three pathways with the production of metabolic coupling factors:

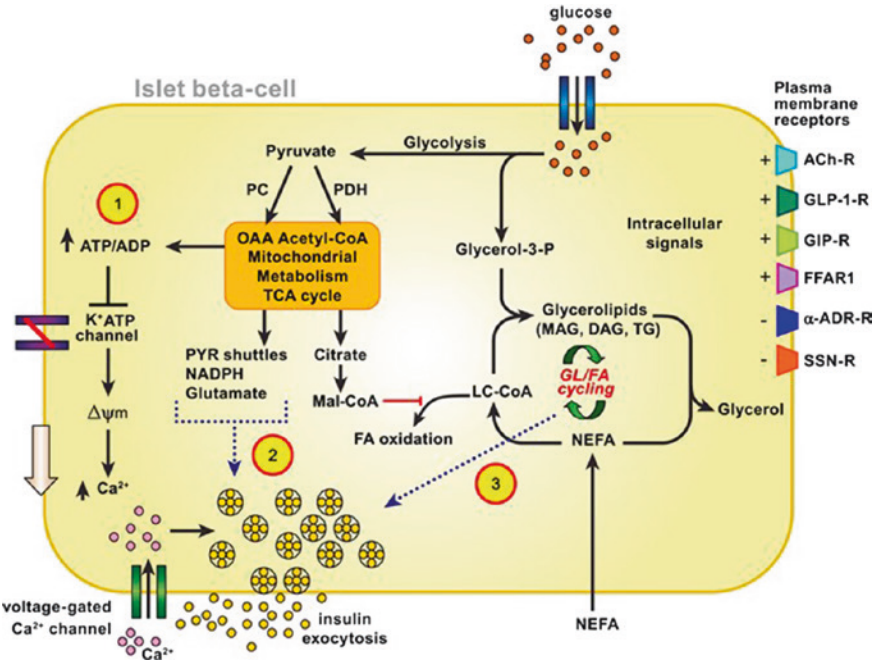

Fig. 1.4 Role of islet β-cell metabolic activation by fuels and neurohormonal agonists in insulin secretion. Islet β-cell glucose metabolism is essential for glucose to stimulate insulin secretion via three key pathways that produce metabolic coupling factors: *1* the K_{ATP}^{+} channel-dependent pathway of GSIS. *2* The anaplerosis amplification pathway of GSIS. *3* The glycerolipid/fatty acid cycling amplification pathway (refer to text for details). Amino acids, such as glutamine and leucine, also interact with the glucose metabolism pathways to increase the coupling signals produced by glucose alone. The β-cell also responds to other neurohormonal and metabolic extracellular signals via various plasma membrane receptors. *PC* pyruvate carboxylase, *PDH* pyruvate dehydrogenase. *Ach-R* acetylcholine receptor, *FA* fatty acid, *GIP-R* gastric inhibitory polypeptide receptor, *GLP-1-R* glucagon-like peptide-1 receptor, *FFAR1* free fatty acid receptor-1, *α-ADR-R* α2-adrenergic receptor, *SSN-R* somatostatin receptor. OAA, oxaloacetate, *CoA* coenzyme A, *MAG* monoacylglycerides, *DAG* diacylglycerides, *TG* triacylglycerides, *Δψm* change in plasma membrane potential, *Mal-CoA* malonyl-CoA, *LC-CoA* long-chain acyl-CoA, *GL* glycerolipid, *FA* fatty acid, *NEFA* non-esterified fatty acids (Nolan et al. 2011)

(i) *The K_{ATP}^+ channel-dependent pathway of GSIS.* Glucose is metabolized via glycolysis to pyruvate and then acetyl-CoA via pyruvate dehydrogenase with subsequent oxidation in the tricarboxylic acid cycle. This gives rise to an increased cytosolic ATP/ADP ratio, which closes ATP-sensitive K^+ channels, depolarizes the plasma membrane potential, opens voltage-gated Ca^{2+} channels, and Ca^{2+} influx activates insulin granule exocytosis (Fig. 1.4) (Nolan and Prentki 2008; Prentki et al. 2013).

(ii) *The anaplerosis amplification pathway of GSIS.* Pyruvate from glucose can also be metabolized via pyruvate carboxylase into the anaplerosis/cataplerosis pathway, which can impact on insulin secretion by increasing levels of cataplerosis-derived metabolic coupling molecules such as NADPH from the malate-, citrate- and isocitrate/α-ketoglutarate-pyruvate shuttles, as well as malonyl-CoA and glutamate (Fig. 1.4) (Nolan and Prentki 2008; Prentki et al. 2013).

(iii) *The glycerolipid/fatty acid cycling amplification pathway.* Glucose interacts with non-esterified fatty acids by promoting activity in an islet glycerolipid fatty acid cycle by elevating malonyl-CoA, via the anaplerosis pathway, which inhibits partitioning of long-chain acyl-CoA to the mitochondrion for fatty acid oxidation (via carnitine palmitoyltransferase-1 inhibition), such that the long-chain acyl-CoA are then more available for esterification processes. Glycerolipids formed are rapidly hydrolyzed by lipases back to fatty acids and glycerol creating a cycle of newly formed lipids. This cycle produces lipid signaling molecules such as monoacylglycerols and diacylglycerols that are able to enhance GSIS (Nolan and Prentki 2008; Prentki et al. 2013; Zhao et al. 2014) (Fig. 1.4).

Amino acids, such as glutamine and leucine, also interact with the glucose metabolism pathways to enhance the coupling signals produced by glucose alone. The β-cell also responds to other neurohormonal/metabolic extracellular signals by various plasma membrane receptors and their signal transduction pathways (e.g., G-protein-coupled signaling for example by cyclic AMP). Relevant to nutrient-induced insulin secretion, islet β-cells have cell surface receptors for fatty acids (e.g., FFAR1) that can modulate GSIS. Effector metabolic coupling factors interact with the insulin granule exocytosis machinery to cause insulin secretion (Nolan and Prentki 2008; Prentki et al. 2013) (Fig. 1.4).

Phases of Insulin Secretion

In healthy people, about half of the total daily insulin secretion is in the basal state, with pulses about every 10–15 min, and the remainder is postprandial (Lang et al. 1979). Postprandial Insulin secretion in healthy humans follows a biphasic response, shown in Fig. 1.5 (Curry et al. 1968; Henquin 2009; Seino et al. 2011).

First-phase insulin release starts in humans as plasma glucose levels rise above fasting levels about 2 min after food ingestion and lasts for about 10 min. This secretion is due to release of about 1 % of all insulin granules that are 'readily releasable,' called the readily releasable pool (RRP). Once the RRP is depleted, it is replaced by insulin from the 'reserve pool' (RP). While it was generally believed that the RRP consisted predominantly of docked granules, this has been questioned with the use of new methods of studying the exocytosis, which suggest that insulin granules released from the RRP in first-phase insulin release are mostly recruited to the plasma membrane (i.e., restless newcomers) (Seino et al. 2011). Recent studies have identified novel regulatory factors for first-phase insulin secretion and glucose homeostasis, including hypoxia inducible factor (HIF) 1α, von Hippel-Lindau, factor inhibiting HIF, nicotinamide phosphoribosyltransferase, and sirtuins (Cheng et al. 2013).

This first phase is followed by a longer second phase, utilizing the RP of insulin granules, that lasts for one to 2 h until the blood glucose level is returned to baseline (Fig. 1.5). While first-phase insulin secretion was believed to be a consequence of triggering of secretion by the K_{ATP}^{+}channel-dependent pathway of GSIS and the second phase a consequence of metabolic and neurohormonal amplification, it is now generally accepted that both first and second phases of insulin secretion are regulated by triggering (mostly via increasing intracellular Ca^{++}) and amplification processes (Prentki et al. 2013; Henquin 2009). This is why glucose control treatments that amplify secretory responses to glucose, such as the incretin-related agents, can partly restore first-phase insulin release; hence, this potentially reversible feature of insulin secretion is a worthwhile therapeutic target.

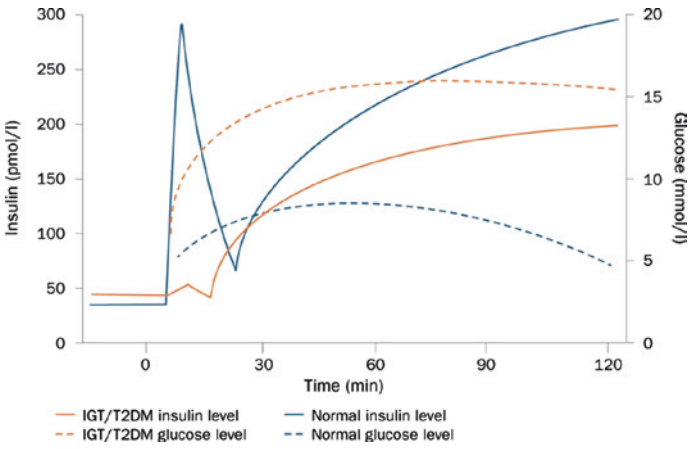

Fig. 1.5 First- and second-phase insulin release and corresponding glycemia after an intravenous glucose challenge in normal and impaired glucose tolerance/type 2 diabetic subjects (Jenssen and Hartmann 2015)

Non-nutrient Modulators of Insulin Secretion

Islet β-cells sense multiple neurohormonal stimuli that can modulate nutrient-stimulated secretion. These can be via endocrine and neural inputs from distant sites or can occur locally by paracrine and autocrine mechanisms, as well as at the cell-to-cell level through gap junctions and electrical activity. Of particular interest is the positive effect of the incretin hormones GLP-1 and GIP on insulin secretion. The autonomic nervous system can also modulate secretion, with the parasympathetic system being stimulatory and the sympathetic system being inhibitory (Wilcox 2005). Somatostatin and glucagon act in a paracrine fashion and are inhibitory (Fig. 1.4) (Wilcox 2005). Cortisol is also known to inhibit insulin secretion. In pregnancy, function and proliferation of islet β-cells can be modulated by gestational hormones such as prolactin, human placental lactogen and estrogen (Weinhaus et al. 2007; Tiano et al. 2011).

The Incretin Effect

The incretin effect refers to the phenomenon by which an oral glucose load induces a greater insulin response than the same amount of glucose delivered intravenously. The augmented insulin response with an oral glucose stimulus, shown in Fig. 1.6, is due to release of gut hormones (called incretins), including GLP-1 and GIP. Loss of the incretin effect occurs in T2D and is ameliorated by use of therapeutic drugs such as the dipeptidyl peptidase-4 (DPP-4) inhibitors and incretin mimetics (Holst et al. 2009) (Fig. 1.6).

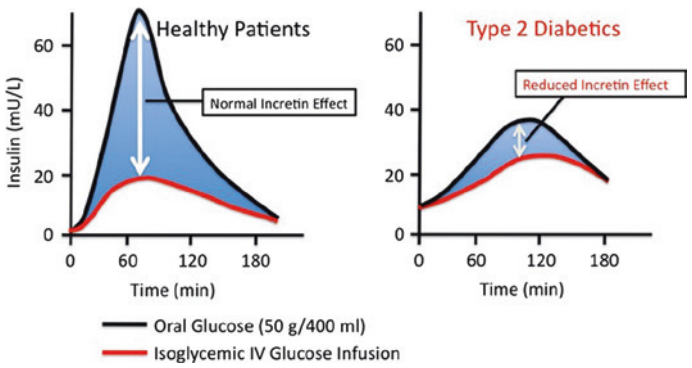

Fig. 1.6 Incretin effect on insulin release in normal and type 2 diabetic subjects (Nauck et al. 1986)

Altered Insulin Secretion in Obesity and in Diabetes

In *obesity*, a common risk factor for T2D, in the absence of abnormal glucose tolerance, β-cell mass and function is increased relative to lean non-diabetic subjects and insulin release (in both phases 1 and 2) is heightened (Polonsky 2000). In pre-diabetes and T2D, substantial β-cell mass has been lost, and both phases of insulin release are suppressed relative to lean (and obese) non-diabetic subjects (Fonseca 2009).

Type 2 diabetes: As shown in Fig. 1.5, in people with T2D, the first phase of insulin release is particularly low, with lower second-phase insulin release also. The first phase of insulin release is also blunted in people with pre-diabetes, in non-diabetic relatives of people with T2D, in gestational diabetes and in non-pregnant women with normal glucose tolerance but previous gestational diabetes. The incretin effect is also blunted in T2D (Seino et al. 2011; Holst et al. 2009).

Type 1 diabetes: By the time when T1D is clinically diagnosed, there has been substantial (but usually not total) β-cell loss. Abnormalities of insulin secretion occur prior to and at T1D diagnosis. This has been discerned by evaluation of subjects with autoantibodies, which place them at high risk of developing T1D, and of newly diagnosed T1D patients. Steele et al. (Steele et al. 2004) evaluated 42 newly diagnosed subjects. Basal insulin secretion was approximately half that of non-diabetic subjects and, in response to a mixed meal test, the first-phase insulin peak was markedly reduced and delayed. The second-phase insulin secretion was prolonged and failed to return blood glucose to baseline in many (Steele et al. 2004). On 1-year follow-up of the T1D subjects, C-peptide levels fell below the detectable in 47 % of the subjects. Over the 2-year follow-up, the insulin response to the mixed meal test predicted residual insulin secretion.

Insulin Actions

Insulin is an anabolic hormone with widespread actions encompassing carbohydrate, lipid and protein metabolism, but also affects on other cellular functions, such as cell proliferation and differentiation. Insulin signals via the insulin receptor, insulin receptor substrates and then the phosphoinositide 3-kinase-AKT/protein kinase B (PKB) pathway (responsible for most of the metabolic effects) or the mitogen-activated protein kinase (MAPK) pathway (responsible for the cell proliferation effects) (Taniguchi et al. 2006). The major sites of insulin action on glucose homeostasis are liver, muscle (skeletal and cardiac) and adipose tissue (the 'insulin-responsive' tissues). Tissues unresponsive to insulin for glucose uptake include renal tissue, the cornea, lens, red and white blood cells, the choroid plexus and gut epithelium. Insulin is essential for the transport of glucose into the insulin-responsive tissues. The various tissues of the body have different glucose transporter proteins (the GLUT proteins) that have different chromosome locations

of their genes and varying affinity for glucose (Wilcox 2005). The insulin-responsive tissues express GLUT4 which is translocated from intracellular vesicles to the plasma membrane in response to insulin stimulation to promote glucose uptake (Wilcox 2005; Bryant et al. 2002). Insulin-stimulated glucose uptake is accompanied by tissue uptake of ions such as potassium and phosphate. Insulin promotes glycogen synthesis in the liver and in muscle, as well as protein and lipid synthesis, and inhibits protein breakdown, lipolysis and ketogenesis. Insulin suppresses gluconeogenesis and glycogenolysis and, therefore EGP, via direct and less well-understood indirect mechanisms in the periphery (e.g., reducing supply of gluconeogenic substrate by inhibiting lipolysis and protein catabolism) (Wilcox 2005; Gaw et al. 1999) and via the brain (Rojas and Schwartz 2014).

History of Exogenous Insulin Therapy

In 1921 and 1922, an orthopedic surgeon Frederick Banting, a medical student Charles Best, a professor of physiology John Macleod, and biochemist James Collip isolated insulin from dogs and tested it in pancreatectomized dogs. They then (in January 1922) tested it in severely ill people with T1D, a previously universally fatal condition, and showed it to be effective. Banting and Macleod were awarded the 1923 Nobel Prize in Physiology or Medicine 'for the discovery of insulin.' An excellent account of the history of the discovery of insulin and this award is that by medical historian Bliss (2007). Their work complemented and built upon that of other researchers, including Nicolae Paulescu, a Romanian professor who isolated insulin (which he called pancreatine) about the same time as the Canadian group (Bliss 2007). The pharmaceutical company, Lilly, which is still a major producer of insulin today, rapidly partnered with the University of Toronto to improve and scale up the production and bring to market bovine, followed by porcine insulin. Lilly and other companies now use recombinant DNA technology to produce human insulin to save, ease and prolong the lives of people around the world with T1D. Bovine and porcine insulin differ from human insulin by three and one amino acid, respectively. Since the 1980s, an increasing range of rapid-, short-, intermediate- and long-acting genetically engineered human analogue insulins have become available for the treatment of T1D and insulin-requiring T2D patients. Tragically, even today, over 90 years after Banting and Best's discovery and the development of insulin for human use, many people in less affluent countries, particularly those with T1D, develop early severe complications and die prematurely due to lack of access to affordable insulin. On the cover of *The Lancet* in 2006, UK Diabetologist Edwin Gale quoted, 'What is the commonest cause of death in a child with diabetes? The answer—from a global perspective—is lack of access to insulin' (Gale 2006).

Amylin

Amylin, also known as islet amyloid polypeptide (IAPP) was only discovered as a hormone in 1987. It is a 37-amino acid peptide that is co-secreted with insulin (as a 67-amino acid prohormone) from the β-cells of the islets of Langerhans at a ratio of approximately 1–25 (Westermark et al. 1987a, b, 2011). Amylin is broken down by peptidases in the kidney, but is not detected in urine. Amylin deposits are commonly found in the islets of people with T2D or insulinoma pancreatic tumors, where it is thought to modulate β-cell apoptosis; however, it is as yet unclear if this is causative or an epiphenomenon (Tomita 2011). Amylin is thought to modulate glycemia via slowing gastric emptying, increasing production of gastric acid, bile from the liver, and pancreatic enzymes and increasing satiety. Amylin release is controlled by the same factors as control insulin production and secretion and, in addition, is also activated by TNFα and by fatty acids (Westwell-Roper et al. 2014; Miegueu et al. 2013). A synthetic modified form of amylin (pramlintide) is in clinical use for pre-meal injection in people with T1D or T2D to reduce postprandial hyperglycemia (Riddle et al. 2015; Tran et al. 2015).

Glucagon

Glucagon, a 29-amino acid peptide hormone produced in and secreted by the α-cells of the islets of Langerhans is initially produced as proglucagon, which is then cleaved by pro-hormone convertase-2 in the α-cells. Glucagon has a counter-regulatory effect on blood glucose compared to insulin, important in the prevention of hypoglycemia. Glucagon has a circulating half-life of 3–6 min (Greenstein and Wood 2011; Lebovitz and American Diabetes Association 2009).

Glucagon's main site of action is the liver, where it acts against insulin to:

- ↑ Glycogenolysis (the breakdown of glycogen, which is predominantly stored in liver and skeletal muscle).
- ↑ Gluconeogenesis (the synthesis of glucose from non-carbohydrate sources such as lactate, glycerol and amino acids). (Gluconeogenesis can also occur to a lesser extent in the kidney.)
- ↑ Ketogenesis. Ketone bodies can be used by some tissues as an alternate energy source (Valente-Silva et al. 2015).

Secretion of glucagon is *increased* by low glucose levels (in a non-diabetic person, and this release is impaired in people with diabetes), increased levels of amino acids (in particular alanine and arginine), increased gastrointestinal hormones (e.g., CCK), increased 'stress' hormones (catecholamines and glucocorticoids) and sympathetic and parasympathetic nervous stimulation. Glucagon secretion is *inhibited by* high levels of glucose, insulin, free fatty acids and the incretin hormone GLP-1 (Sharma et al. 2015).

Glucagon is used clinically as a deep subcutaneous or intramuscular injection to rapidly increase blood glucose levels in people with insulin-treated diabetes who are severely hypoglycemic and unable to take oral glucose-containing food or drink (Rowe et al. 2015), or in lower doses as part of their sick-day management plan (Chung and Haymond 2015), or in the acute management of people who have taken an overdose of insulin or insulin secretagogue oral hypoglycemic agents (White et al. 2014). Doctors, nurses, paramedics and lay community members with suitable training can administer glucagon, which is a lyophilized powder and requires suspension in liquid pre-injection. Research using glucagon in a 'bihormonal' insulin pump is underway (Bakhtiani et al. 2015; Shah et al. 2014), but hampered by the relatively poor stability of glucagon solutions. Intranasal glucagon is also likely to be available for clinical use soon (Pontiroli 2015).

Somatostatin

Somatostatin is a cyclic polypeptide secreted by the δ cells of the islets, and also by the hypothalamus, stomach and intestines. It has a circulating half-life of several minutes (Rai et al. 2015).

Somatostatin acts:

within the pancreas and the gut to

- ↓ Insulin secretion by the β-cells of the islets of Langerhans.
- ↓ Glucagon secretion by the α-cells of islets of Langerhans.
- ↓ Pancreatic exocrine secretion.
- ↓ Gastric emptying time and acid production.
- ↓ Splanchnic blood flow.
- ↓ Gastrin, CCK and other gut hormone levels; and

in the brain to

- ↓ GH release and
- ↓ Decrease release of other pituitary hormones, including thyroid-stimulating hormone (TSH) and prolactin.

Stimuli for the *release of somatostatin* tend to be the same as those for insulin and include glucose, arginine and gastrointestinal hormones (Arimura and Fishback 1981; Liu et al. 2010; Gahete et al. 2010).

Pancreatic Polypeptide

Pancreatic polypeptide (PP), a 36-amino acid peptide produced by both pancreatic gamma islet cells (also known as PP cells) and acinar cells, inhibits pancreatic secretion after a meal. Release of PP by a meal, primarily protein, occurs in a

biphasic manner, with an initial rapid release in response to vagal stimulation and a more prolonged rise in response to hormonal stimulation, predominantly CCK (Lonovics et al. 1981; Batterham et al. 2003).

Ghrelin

While mainly produced by cells in the stomach, and also by adipose tissue, this 28-amino acid peptide is also produced by the few ε cells in the islets of Langerhans. Ghrelin-producing cells are more abundant in the developing fetal pancreas than in the adult pancreas and likely play a role in pancreas development and β-cell apoptosis and survival. Ghrelin stimulates food intake (hence, it is sometimes referred to as 'the hunger hormone'), GH release, adipogenesis and glucose uptake, and inhibits lipolysis (Granata and Ghigo 2013). Ongoing research is testing ghrelin-derived fragments on human β-cell and pancreas islet survival and on insulin sensitivity and glucose control (Favaro et al. 2012; Poykko et al. 2003).

Incretins

Incretin hormones are a family of hormones, including GLP-1 and GIP, that are released from gut endocrine cells, predominantly in response to food and/or gut distension, which markedly influence islet insulin and glucagon secretion. As discussed above, incretins potentiate glucose-induced insulin secretion in a glucose-responsive manner, i.e., the greater the glucose load, the greater the incretin and hence insulin release. Incretins are thought to be responsible for 50–70 % of postprandial insulin secretion (Holst et al. 2009). While in the presence of elevated blood glucose, GLP-1 suppresses glucagon secretion, GIP most likely has a glucagonotrophic effect, thus differentiating itself in its actions from GLP-1 (Lund et al. 2014). Incretins also have other beneficial effects such as delaying gastric emptying, promoting satiety and weight loss and reduced risk of hypoglycemia (Holst et al. 2009).

Two types of incretin-based therapies are now used for glucose control in people with T2D and sometimes in T1D. There are synthetic GLP-1 agonists and inhibitors of the peptidase enzyme DPP-4, which rapidly break down GLP-1 in the circulation. GLP-1 has a short half-life of only 1–2 min in blood. Modified, more resistant to degradation, forms of GLP-1 agonists can be given by injection. The first such GLP-1 agonist (exenatide) is injected subcutaneously once or twice a day pre-meals, but longer-acting (weekly and monthly) forms are becoming available (Zhang et al. 2015). Major advantages in diabetes care are a low risk of hypoglycemia and weight loss, but nausea and vomiting are not infrequent side effects of this drug therapy. More well-tolerated orally active once daily DPP-4 inhibitors

('the gliptins,' e.g., sitagliptin) prolong the half-life of endogenous GLP-1 and are already often used in combination with other oral hypoglycemic agents (Sujishi et al. 2015; Furuhashi et al. 2015).

Hormones produced by the adrenal gland and by the pituitary gland have effects that counteract insulin's effects.

Catecholamines

Two catecholamines—adrenaline (also called epinephrine) and noradrenaline (or norepinephrine)—are secreted by the adrenal medulla. Noradrenaline is also produced in the central and peripheral nervous system. The catecholamines have a circulating half-life of several minutes and are water soluble, hence are excreted in urine (Guyton and Hall 1996; Greenstein and Wood 2011). Catecholamines are commonly called 'stress hormones,' as stressful physical or emotional situations stimulate their release, as does low blood glucose levels, particularly in healthy people.

Catecholamines cause peripheral vasoconstriction and increased heart rate, blood pressure and cardiac output, which form part of the body's 'fight-or-flight response' to acute stress. Catecholamines also have several actions which promote a rise in blood glucose levels, including:

- ↓ Insulin secretion by the β-cells of the islets of Langerhans.
- ↑ Glycogenolysis in liver and muscle.
- ↑ Lipolysis in adipose tissue (releasing fatty acids and glycerol into the circulation) (Tran et al. 1981).

Cortisol

Cortisol is another 'stress hormone' that counteracts insulin's blood glucose-lowering effects. This steroid hormone is synthesized and secreted by the adrenal cortex under the control of hormones from the brain's hypothalamus (corticotropin-releasing hormone, CRF) which then stimulates release of adreno-corticotrophic hormone (ACTH) from the anterior pituitary gland. Cortisol is secreted in a continuous manner with a diurnal pattern, peaking in the morning and being lowest between midnight and 4 a.m. Cortisol levels rise rapidly, within minutes of stress or hypoglycemia (Guyton and Hall 1996).

With regard to glucose control, cortisol causes:

(i) ↑ Protein breakdown and ↓ protein synthesis.
(ii) ↑ Gluconeogenesis in liver by:

  (a) Increasing relevant enzyme activities.
  (b) Increasing the hepatic response to glucagon and catecholamines.
  (c) Mobilizing substrate from muscle.

(iii) ↑ Glycogenolysis in liver.
(iv) ↑ Lipolysis in liver and adipose tissue.
(v) ↓ Insulin secretion.
(vi) ↑ Insulin resistance, decreasing glucose uptake from blood by muscle and adipose tissue (Dimitriadis et al. 1997).

Cortisol also has widespread other effects on bone, muscle, skin and mood, not discussed herein (Morelius et al. 2005).

Growth Hormone

Growth hormone (GH), a 191-amino acid polypeptide hormone, is synthesized and secreted by cells in the anterior pituitary gland under the positive and negative control of growth hormone-releasing hormone (GHRH) and growth hormone inhibitory hormone (GHIH) or somatostatin.

GH release is stimulated by:

- Fasting,
- Hypoglycemia,
- Sleep (the GH rise during sleep is thought to contribute to the period of relative insulin resistance occurring at about 5 or 6 a.m. (the so-called dawn phenomenon), and
- Exercise.

GH release is suppressed by:

- Hyperglycemia and
- Glucocorticoids.

GH causes:

- ↑ Insulin resistance and ↑ glucose levels via ↑ gluconeogenesis and ↓ muscle glucose uptake.
- ↑ Lipolysis.
- ↑ Protein synthesis (Manson et al. 1988).

When present in excessive amounts, such as in acromegaly (due to a GH-producing pituitary tumor) or due to self-administration, as sometimes is used by bodybuilders or athletes, these actions can lead to glucose intolerance and diabetes mellitus. GH injections, including recombinant human GH in recent decades, are available for therapeutic use for some children with growth retardation, short stature, or for GH replacement therapy after pituitary tumor or for GH deficiency (Guyton and Hall 1996; Greenstein and Wood 2011).

Changes in these hormones in diabetes, in particular of those produced by the pancreatic islets, are discussed later in this chapter.

Types of Diabetes Mellitus

Tables 1.1 and 1.2 summarize and compare the major and some minor types of diabetes. The common types of diabetes are T1D, T2D and GDM. Diabetes, in particular T2D and GDM, can be asymptomatic. The classic symptoms are thirst, frequency of urination, including overnight (nocturia and sometimes bed-wetting) and, particularly in T1D, weight loss and hunger (in spite of increased food intake (Lebovitz and American Diabetes Association 2009). Due to low sensitivity and accuracy, fingerprick blood glucose meter readings should not be used to diagnose or exclude diabetes, but these devices are valuable aids for the home management of those diagnosed with diabetes, particularly if treated by exogenous insulin. In some countries, HbA1c levels, which reflect mean glucose levels over the preceding 2–3 months, are now approved for diagnostic purposes (Use of Glycated

Table 1.1 Types of diabetes mellitus

Type 2 diabetes
Type 1 diabetes
Latent autoimmune diabetes of adults (LADA)
Gestational diabetes mellitus (GDM)
Monogenic forms of diabetes (e.g., MODY)
Related to genetic syndromes (e.g., DIDMOAD)
Secondary to (acute or chronic) pancreatitis
Related to other endocrine disorders (e.g., acromegaly, Cushing's disease)
Drug-induced diabetes (e.g., corticosteroids, some antipsychotic drugs, HMG-CoA reductase inhibitors, some anti-HIV drugs)

Table 1.2 General characteristics of type 1 diabetes, type 2 diabetes and LADA

	Type 1 diabetes	LADA	Type 2 diabetes
Percentage of diabetes	5–15	1–2	85–90
Common age of onset	Youth, usually before 30 years	After 25–30 years	Usually middle age or older
Rapid clinical onset	+++	+/−	−
Family history of diabetes	Only in 10 %	+	+++
Personal or family history of autoimmune disease	++	++	−
Weight/BMI	Low, normal or increased	Normal or increased	Usually increased
C-peptide/insulin levels	Very low	Low	Normal or high
Autoantibodies	+++	++	−
Immediate need for exogenous insulin	+++	−	rarely
Acute complication risk	+++	+++	+++
Chronic complication risk	+++	+++	+++

Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus 2011), as well as for monitoring glucose control of those diagnosed with diabetes. However, some people may have diabetes based on fasting and postprandial blood glucose levels, or even on the 'gold' standard oral glucose tolerance test (oGTT), yet have a normal HbA1c level. Similarly, HbA1c levels may not accurately reflect blood glucose levels, such as due to renal failure, anemia or in hemoglobinopathies (National Glycohemoglobin Standardization Program 2013).

An excellent (online and free) resource related to the incidence and prevalence of diabetes globally is the International Diabetes Federation (IDF) atlas (International Diabetes Federation 2013).

Type 1 diabetes T1D usually accounts for 5–15 % of people with known diabetes and can occur at any age, but most commonly has its onset in childhood, presenting with days to several weeks of marked thirst, frequent urination and weight loss, and frequently with diabetic ketoacidosis (DKA) (a life-threatening state of marked hyperglycemia, ketosis, acidosis and dehydration) (Lebovitz and American Diabetes Association 2009). The incidence of T1D varies greatly between countries and ethnicities. The highest rates are in the Scandinavian countries, at approximately 35 new cases per 100,000 people per year; the lowest rates are in Asia. For example, in Japan and China the incidence is approximately 1 person per 100,000 per year. Australia, North America and Northern Europe incidence rates range between 8 and 17 new cases per 100,000 per year (International Diabetes Federation 2013).

T1D is usually due to the autoimmune destruction of the insulin-producing β-cells in the islets of Langerhans due to invasion of cytotoxic immune cells. Antibodies to islet proteins are usually present for years prior to clinical presentation. By the time a person presents clinically with T1D, it is estimated that they have lost about 50–60 % of their β-cell mass (Battaglia and Atkinson 2015). Sometimes soon after T1D diagnosis and after initiation of life-saving exogenous insulin injections (or delivery by an insulin pump), patients can experience what is commonly called a 'honeymoon' period (Lebovitz and American Diabetes Association 2009). The honeymoon period is a time in which people with recently diagnosed T1D can maintain normal or near-normal (non-diabetic) range blood glucose levels on low, and sometimes even no exogenous insulin therapy, for weeks to months, and sometimes more than a year. This relates to residual insulin production by surviving β-cells, which may improve in the presence of less hyperglycemia and elevated free fatty acid exposure ('glycotoxicity' and 'lipotoxicity') due to the exogenous insulin. In addition, the obvious symptoms of diabetes, leading to its diagnosis, may be precipitated by an intercurrent illness, which increases the body's stress hormones and insulin resistance. Once this temporary illness resolves, insulin requirements may be less. Sometimes people will attribute their T1D diagnosis to the related illness or injury, but it is almost certain that, had the temporary illness not occurred, they would still have been diagnosed with diabetes not long after. It is recommended that some exogenous insulin be continued during the honeymoon period as it helps preserve residual β-cell mass and also can lessen patient distress when insulin injections inevitably need to be restarted (if exogenous insulin was ceased during the honeymoon phase).

The autoimmune destruction of the insulin-producing islet cells begins years before and continues years after T1D diagnosis, particularly in the first two to three years after clinical presentation, often resulting in a need for a higher dose of injected insulin (Battaglia and Atkinson 2015). It is now recognized that some residual insulin production (reflected by circulating C-peptide levels) can remain, even in adults with over 50 years of T1D (Keenan et al. 2010). Residual endogenous insulin production has been associated with better clinical outcomes such as better glycemic control, including a lower risk of severe hypoglycemia and of vascular complications (The Diabetes Control and Complications Trial Research Group 1998). Postmortem examinations of the pancreata of people with T1D have also demonstrated the presence of some insulin within islets (Keenan et al. 2010). These findings support that the body can protect insulin-producing β-cells from destruction, such as by autoimmunity, glucotoxicity and lipotoxicity, and that β-cells may be able to regenerate. This naturally raises hope and potential for prevention of T1D. There are many national and international efforts, such as those led by Trialnet (https://www.diabetestrialnet.org/), directed at the early identification of people at high risk of T1D, usually based on family history, genetic and antibody profiles, and trials testing diets, supplements, vaccines and immune modulating therapies to retard or prevent T1D. As yet, none have proven clinically effective, but some major trials are still in progress, and some studies show promising changes in surrogate endpoints, such as antibody positivity. Ongoing research is merited, including the further development of the 'artificial pancreas,' an insulin pump linked with a glucose sensor, a controller and algorithm that is able to control a person's blood glucose usually better than by multiple daily insulin injection therapy (Battelino et al. 2015; Schmidt et al. 2015; Russell 2015).

While T1D is thought by most as being solely a disorder of the endocrine pancreas, there is also evidence of some subclinical exocrine gland dysfunction (Battaglia and Atkinson 2015; Atkinson 2005; Sun et al. 2015).

Latent Autoimmune Diabetes of Adulthood (LADA) A slower form of antibody-positive T1D is latent autoimmune diabetes of adulthood (LADA). LADA is usually diagnosed after the age of 25–40 years, but does not require exogenous insulin therapy for at least 6 months after diagnosis (Fourlanos et al. 2005). People with LADA usually require exogenous insulin within 5–12 years of diagnosis. It has been estimated that up to 10 % of people diagnosed with T2D have LADA.

Type 2 Diabetes The majority (85–90 %) of people with diabetes have T2D, which was previously regarded to be a condition of middle or older age onset, but now can occur earlier in life as obesity rates increase. Major risk factors for T2D include family history and ethnicity (e.g., Indigenous Australians, Indians, Inuits, Hispanics, Native American Indians, Maoris, Asians), as well as the modifiable risk factors of adiposity and physical inactivity (Lebovitz and American Diabetes Association 2009). With previously shorter life expectancies and less widespread screening for diabetes, lack of sharing of medical histories, previously higher 'cut-points' for diabetes diagnosis, and the possibility that T2D can be asymptomatic early in its natural history, many people are not be aware of their inherited risk for

T2D. Modulating factors such as age, weight, diet, smoking and physical activity will determine whether genetic risk becomes manifest as T2D, or its precursor of pre-diabetes (in which blood glucose levels are intermediate between normal and the elevated levels diagnostic of diabetes). Unfortunately, the modern lifestyle has increased obesity rates in youth, with 25 % of Australian children in 2011–2012 (Australian Health Survey: updated results 2011) and 4.9–8.5 % of children globally in 2010 (de Onis et al. 2010) being overweight or obese, and this has led to increased rates of pre-diabetes and T2D in youth, particularly those in high-risk ethnic (often insulin-resistant) groups. In countries with high rates of ethnic diversity, such as the USA, T2D now accounts for 18 % of diabetes in youth (Dabelea et al. 2014). As glucose tolerance declines with age, the proportion of people with T2D increases with age, with 14.8 and 14.2 % of adults over 65 and 75 years of age, respectively, having T2D, compared with 4.2 % of adults aged 45–54 years (Australian Health Survey: updated results 2011).

Gestational Diabetes The third most common form of diabetes is GDM which currently affects 5–8 % of pregnant women (Valente-Silva et al. 2015), including 4.6 % of pregnant women in Australia (Templeton MP-C 2008). The rates of gestational diabetes have increased several fold over recent decades related to increasing rates of obesity in women of child-bearing age, increased case ascertainment due to uptake of routine screening, and lower diagnostic cut-points (Nankervis et al. 2014). GDM commonly commences in the second or third trimester of pregnancy and usually resolves post-pregnancy, but it does signal that the mother is at increased risk of T2D (Di Cianni et al. 2003). Women with prior GDM have a 40 % risk of developing T2D at some stage later in life (Conrad Stöppler 2014). Such women should pay particular attention to maintaining a healthy diet, weight and exercise program and should be regularly screened for T2D. While not associated with the chronic vascular complications of diabetes, GDM, if untreated, is associated with increased risks to both mother and fetus/offspring, including increased rates of macrosomia (large babies) which increases rates of birth injury and need for caesarian section, pregnancy-induced (maternal) hypertension and pre-eclampsia, and in the child, increased risk of obesity, the metabolic syndrome, T2D and cardiovascular disease later in life.

The major features of these common types of diabetes are summarized and compared in Table 1.2. About 1–2 % of people with diabetes have a different form of diabetes than those described above, which are sometimes referred to as secondary forms of diabetes.

Secondary forms of diabetes have a different pathogenesis than that of T1D, LADA, T2D and GDM. Sometimes these secondary forms of diabetes can be reversed, such as if they are due to an underlying acquired illness or drug, and that illness resolves or the drug is removed. If not, the effects, such as those related to hyperglycemia, the long-term complications and the treatment and monitoring needed are similar to that of the more common T1D and T2D.

Secondary forms of diabetes include monogenic forms of diabetes, which may affect insulin secretion or insulin resistance, those associated with genetic

syndromes, acquired forms due to pancreatic damage, other endocrine diseases and drug-induced diabetes (Lebovitz and American Diabetes Association 2009) (Table 1.1).

Monogenic Diabetes Some forms of diabetes are monogenic in origin, unlike T2D, which is thought to be of polygenic origin. These forms are due to single-gene defects that are autosomal dominantly inherited. An excellent review article is that by Tallapragada et al. (Tallapragada et al. 2015). The first and more common types of monogenic diabetes (of the current eight known) to be identified as the causes of 'maturity-onset diabetes of the young' (MODY) are due to mutations in the glucokinase gene (MODY2) and in the hepatocyte nuclear factor 1α gene (MODY3). Another group of monogenic diabetes relate to the genetic defects in the potassium-ATP channel on the β-cell membrane. Single-gene defects can also induce diabetes by increasing insulin resistance. Examples include type A insulin resistance syndrome and lipoatrophic diabetes.

Diabetes may also be part of *other genetic syndromes*. Examples include 'DIDMOAD' or Wolfram syndrome, which includes diabetes insipidus, diabetes mellitus, optic atrophy and deafness. People with chromosomal disorders, such as Down's syndrome (Trisomy 21) and Turner's syndrome, are also at increased risk of diabetes (Lebovitz and American Diabetes Association 2009).

Acute and chronic forms of damage to the pancreas can lead to diabetes. Acute pancreatitis, such as due to excess alcohol, gall-stones, or severe hypertriglyceridemia, can induce sufficient β-cell loss so as to necessitate exogenous insulin therapy, which is often also associated with pancreatic exocrine deficiency requiring oral replacement of digestive enzymes with food in addition to micronutrient supplements (Fieker et al. 2011). Pancreatic cancer, trauma and the surgical removal of a major part of the pancreas can each lead to diabetes. Hemochromatosis can also damage the pancreas (and other organs such as the liver) due to iron overload. Fibrocalculous pancreatopathy, such as related to malnutrition and infection, is not a uncommon cause of diabetes in impoverished regions.

Other endocrine disorders can induce diabetes, usually related to an overproduction of hormones that act against insulin. Examples include Cushing's syndrome (corticosteroid excess), glucagonoma (glucagon excess), phaeochromocytoma (catecholamine excess), thyrotoxicosis (thyroid hormone overproduction) and very rarely somatostatinoma (somatostatin-producing tumor) (Lebovitz and American Diabetes Association 2009).

Diabetes may also be *drug induced*, which often resolves with drug cessation or the use of non-diabetogenic alternates if available. Commonly needed drugs that can induce (pre-diabetes and type 2) diabetes are the immunosuppressive, anti-inflammatory corticosteroids, such as used in organ transplant, connective tissue diseases (e.g., rheumatoid arthritis and temporal arteritis) and severe asthma exacerbations. Some antidepressant and antipsychotic drugs, as well as protease inhibitors for the treatment of HIV, have significant diabetogenic effects, while other very commonly used drugs such as thiazide diuretics and HMG-CoA reductase inhibitors have weak, but substantiated effects, on potentiating pre-diabetes or T2D (Lebovitz and American Diabetes Association 2009).

Diabetes Complications

All forms of diabetes, with the exception of GDM, increase the susceptibility of those affected, to the acute complications of diabetes and, if the diabetes duration is long enough, also to the chronic microvascular and macrovascular complications, discussed below and summarized in Tables 1.3 and 1.4.

Acute Glycemia-Related Complications of Diabetes

In people without diabetes, glucose levels are normally tightly regulated within a narrow range. People with diabetes, however, particularly those requiring exogenous insulin, are at increased risk of severe hypoglycemic and hyperglycemic crises, both of which can be life-threatening.

Table 1.3 Complications of diabetes

Acute complications
Dehydration and electrolyte imbalance
Hyperglycemia including diabetic ketoacidosis and hyperosmolar non-ketotic coma
Increased risk of sepsis
Poor wound healing
Mental health issues, e.g., anxiety, depression, diabetes distress
Pregnancy related
Increased risk of reduced fertility
Increased risk of miscarriage
Increased risk of pre-eclampsia
Increased risk of growth retardation or macrosomia
Increased risk of congenital malformations in offspring
Increased risk of diabetes and of cardiovascular disease in offspring
Chronic complications
Microvascular complications
Diabetic retinopathy
Diabetic nephropathy
Diabetic neuropathy—peripheral neuropathy
Macrovascular complications
Coronary artery disease (CAD)
Cerebrovascular disease
Peripheral vascular disease including foot ulcers and amputations
Cardiomyopathy (independent of hypertension and/or coronary artery disease)
Diabetes dementia

Table 1.4 Other health problems more common in diabetes

Cardiovascular disease
Hypertension
Congestive cardiac failure
Sudden death, most likely cardiac arrhythmia or CAD related
Transient ischemic attacks and cerebrovascular event
Peripheral vascular disease
Cardiomyopathy (due to hypertension, CAD and diabetes per se)
Eye
Glaucoma
Cataracts
Gastrointestinal tract
Nonalcoholic fatty liver disease (NAFLD)
Peptic ulcer disease
Cancer (except for decreased incidence of prostate cancer)
Increased risk infections including TB and fungal infections
Periodontal disease
Hearing loss (mild)—some debate

Hypoglycemia

Hypoglycemia is usually defined as a low blood glucose (<4.0 mmol/L). It usually causes symptoms and signs related to catecholamine release (e.g., anxiety, trembling, sweating and palpitations) and/or neuroglycopenia, i.e., related to lack of glucose to the brain (e.g., poor concentration, in-coordination, slurred speech, emotional outbursts, coma and seizures). The symptoms of sympathetic system activation usually occur, but not always, prior to life-threatening neuroglycopenic consequences of hypoglycemia, thus providing the person with diabetes early awareness a 'hypoglycemia warning system' (American Diabetes Association 2012, 2015; Cryer and American Diabetes Association 2013; Fox et al. 2009; Peters et al. 2013).

Mild to moderate hypoglycemia is defined as that which can be still self-managed by appropriate food or drink ingestion. Severe hypoglycemia is defined as that which causes marked impairment in consciousness, and even seizures, such that assistance by another person is essential for recovery, usually with administration of a glucagon injection or intravenous glucose.

Most people with T1D experience a mild hypoglycemic event on average once a week and a severe hypoglycemic event once per annum (American Diabetes Association 2012; Cryer and American Diabetes Association 2013).

Common precipitants of hypoglycemia are inappropriate (for subsequent carbohydrate intake and physical activity) insulin dosage, insulin administration issues, excess alcohol intake, recreational drug use, undiagnosed or uncontrolled

medical conditions such as food malabsorption (e.g., related to celiac disease) or adrenal insufficiency, which are more common in people with T1D (Lebovitz and American Diabetes Association 2009). Recurrent severe hypoglycemia can have adverse psychosocial and socioeconomic impacts (including accidents-, family-, schooling- or employment-related issues and loss of driving rights), as well as cause seizures, permanent brain damage/cognitive impairment and death. Also frequent or severe hypoglycemia can impair warning responses to hypoglycemia, called 'hypoglycemia unawareness' which increases the risk of recurrent severe hypoglycemia (Lebovitz and American Diabetes Association 2009; Hendrieckx et al. 2014). People who have experienced severe hypoglycemia often opt for less acceptable (high) blood glucose control to prevent recurrence, even though they know this will increase their own risk of long-term vascular and neurological complications.

About one in three or four people with T1D will experience reduced hypoglycemia awareness at some stage of their life. In many, but not all cases, hypoglycemia awareness can be improved by several weeks to months of avoidance of hypoglycemia. In many cases, recurrent severe hypoglycemia can be lessened by identification and treatment of the precipitating factors, frequent home blood glucose monitoring, adjustment of insulin type (to modern insulin analogues), change in insulin delivery dose or mode (e.g., insulin pump use, particularly linked with continuous glucose monitors which can suspend insulin delivery) and additional education regarding insulin dosage adjustment, nutrition and physical activity. For adults with T1D with particularly debilitating recurrent severe hypoglycemia, islet cell transplantation (discussed elsewhere in this book) is a treatment option that can be successful in eliminating hypoglycemia risk (O'Connell et al. 2013).

Hyperglycemia

Hyperglycemia in diabetes is usually due to a relative lack of insulin (and/or excess glucagon). In T1D, hyperglycemia can be associated with ketosis and a metabolic acidosis (DKA), which is a medical emergency, usually requiring IV insulin, fluids and electrolytes and treatment of the precipitating cause which can be an intercurrent illness. In people with T2D, there is usually enough insulin to prevent severe ketosis, but the resultant hyperglycemia due to a relative lack of insulin and/or hyperglucagonemia can still reach extreme levels. At its worst, there can be marked hyperglycemia (even up to 100 mmol/L, severe dehydration and metabolic disarray (hyperosmolar non-ketotic coma or hyperglycemic hyperosmolar syndrome) that is at least as serious and life-threatening as DKA (Lebovitz and American Diabetes Association 2009). Even with milder hyperglycemia, there is impaired immune function, resistance to sepsis and tissue healing and, if chronic, increased risk of vascular complications.

The Vascular Complications of Diabetes

Microvascular Complications of Diabetes

The classically described microvascular complications include diabetic retinopathy, nephropathy and neuropathy. As a consequence of retinopathy, diabetes is a most common cause of vision loss in working-age adults (Facts About Diabetic Eye Disease 2015). Over 40 % of renal dialysis or transplant patients have renal failure due to diabetes (Collins et al. 2012). The various types of neuropathy cause various morbidities, but the most common would be peripheral neuropathy which contributes to diabetes being the most common cause for non-traumatic lower limb amputation. These major microvascular complications usually take at least 5 years to become manifest clinically, though subclinical damage can occur before this. Some people with T2D have diabetic microvascular complications at diagnosis, thought to be related to years of undiagnosed hyperglycemia. Not all people with diabetes will develop vascular complications, and in those (with T1D) who do not, their longevity is not substantially reduced (Mäkinen et al. 2008) relative to that of non-diabetic subjects. Most people with over 20 years of diabetes will have some evidence of diabetes complications, but in many it may not be at a degree to cause disability. For example, many will have 'background' diabetic retinopathy (King 2002) which does not threaten vision, but nonetheless needs regular review, including attention to risk factors (discussed below), so as to reduce the risk of progression to vision-threatening 'proliferative' disease. About a quarter of people with T1D who develop microalbuminuria will have spontaneous regression to normal levels of albumin excretion without loss of renal function. Good vascular risk factor control is thought to be of assistance in regression. It would seem prudent to assume so at this stage. As yet, it is unclear if these people who develop early microvascular damage and regress are at an increased risk of recurrence and progression of microvascular complications later on. If detected early, tight glucose, blood pressure, lipid and weight control, non-smoking, and the use of angiotensin-converting enzyme (ACE) inhibitor drugs (even if 'normotensive'), microvascular complications can be reversed or their progression slowed (Fowler and Vasudevan 2010). The onset of T2D in youth has recently been shown to be associated with high rates of early and severe vascular complications. Compared to people with T1D of similar diabetes duration, early onset T2D also has higher age-adjusted mortality rates (Craig et al. 2009; Wong et al. 2008a, b).

In general, if a person with diabetes develops one microvascular complication, they are at a higher risk of developing the other microvascular complications, as well as accelerated atherosclerosis and the related macrovascular complications (Rhee and Kim 2015; Bowling et al. 2015). We shall now briefly describe the major microvascular complications.

Diabetic Retinopathy

Diabetic retinopathy is typically divided into background diabetic retinopathy (which can be further subdivided into mild, moderate and severe background retinopathy) and proliferative retinopathy. There is no doubt that a preclinical stage, prior to the appearance of the first microaneurysms or hemorrhages, also exists. Figure 1.7 shows an image of a normal retina and of the various clinical stages of diabetic retinopathy. Nonproliferative retinopathy includes microaneurysms, soft exudates (retinal infarcts) and hard exudates (lipid deposits). The advanced-stage, proliferative retinopathy involves new fragile blood formation. These vessels are prone to leaking, which can cause sudden severe vision loss. Retinal hemorrhages can also induce fibrous tissue formation which can contract and cause retinal detachment.

Diabetic retinopathy is also associated with dysfunction and damage of the neural retina. The relative time course of the retinal neural and vascular damage is debated.

Diabetic Nephropathy

There are two aspects of renal function that can become abnormal in diabetes, and either one or both aspects can be abnormal. One aspect is the leakage of albumin (and other proteins) into the urine, and the other is failure of the filtration process. In periods of poor glucose control, particularly at T1D diagnosis, the glomerular filtration rate (GFR) is above normal (termed hyperfiltration). With progressive renal impairment, the GFR returns to within 'the normal range' and then declines toward, and may reach the level of needing renal replacement therapy of dialysis (often initially by peritoneal dialysis, then by hemodialysis) or by kidney transplant. Chronic kidney disease (CKD) is usually divided into five stages shown in Table 1.5. Normal renal function can be described as stage 0.

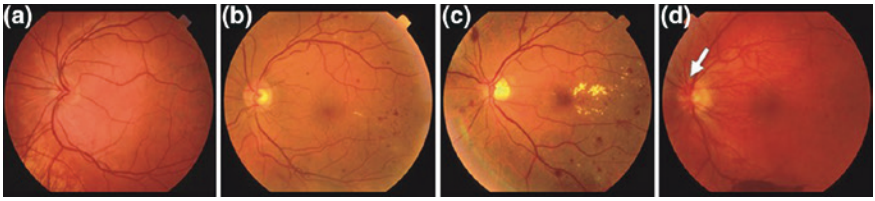

Fig. 1.7 Normal retina and stages of diabetic retinopathy. Fundus photographs showing the clinical stages of diabetic retinopathy: **a** a normal retina; **b** mild nonproliferative diabetic retinopathy, with hemorrhages, microaneurysms and hard exudates; **c** nonproliferative retinopathy; **d** proliferative diabetic retinopathy, with the optic disk (*white arrow*) and pre-retinal hemorrhage in the inferior retina. Taken from our publication—Farr et al. (2015). Licensed under CC BY 4.0 via http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4649912/figure/f3/

Table 1.5 Stages of chronic renal disease

Stage	eGFR (mL/min/1.73 m^2)	Description (renal structure and function)	Predominant AER status
0	≥90	No damage/normal kidney function	
1	≥90	Kidney damage with normal/high GFR	Micro
2	60–89	Kidney damage with mild reduction in GFR	Micro
3	30–59	Kidney damage with moderate reduction in GFR	Macro
4	15–29	Kidney damage with severe reduction in GFR	Macro
5	<15	Kidney failure	

AER albumin excretion rate, *eGFR* estimated glomerular filtration rate

In persons with diabetes, *Stage 1* CKD, which is asymptomatic, is characterized by renal hypertrophy, hyperfiltration, normal serum creatinine levels, and often by increased urinary albumin loss, using in the microalbuminuric range. This albuminuria is usually worsened during and shortly after physical exercise or by poor glycemic control. Blood pressure is usually normal. This stage may regress spontaneously or by risk factor reduction and ACE inhibitor treatment.

Stage 2 CKD, also called incipient diabetic nephropathy, is also silent and characterized by normal GFR and abnormal renal morphology (though biopsies are not often performed unless there are atypical features, such as hematuria). Albuminuria is likely to be more permanent in stage 2 CKD, but will still be in the microalbuminuric range.

Stage 3 CKD is the initial stage of overt diabetic nephropathy. Its main manifestations are albuminuria (15–300 μg/min) and an early increase in serum creatinine (and fall in GFR). A slow, gradual increase over years in the amount of albuminuria is usual, and blood pressure usually also rises.

Stage 4 CKD, established overt diabetic nephropathy, is defined as persistent proteinuria (>0.5 g/24 h) and a fall in the eGFR to <60 mL/min/1.73 m^2, which is usually associated with hypertension. In the absence of antihypertensive agents (usually starting with an ACE inhibitor), GFR declines at a mean rate of about 1 mL/min/month. Long-term antihypertensive treatment reduces the rate of fall by about 60 %, substantially delaying renal failure.

Stage 5 CKD is end-stage renal failure, characterized by rising serum creatinine levels and an eGFR falling below 15 mL/min/1.73 m^2. Renal replacement therapy (dialysis or transplantation) is usually required (Lebovitz and American Diabetes Association 2009).

For people with T1D and end-stage renal failure, combined kidney–pancreas transplantation is an option when cadaver donors are available, resulting in improved survival (Kaku et al. 2015; Lindahl et al. 2014a, b; Light and Tucker 2013). The pancreas transplant is usually, but not always, performed at the same time as the renal transplant.

Diabetic Neuropathy

Neuropathy in diabetes is thought to have both a vascular and metabolic etiology. Several types of neuropathy may occur: peripheral neuropathy, autonomic neuropathy, 'plexopathy' or mononeuritis multiplex. Diabetes is also thought to be associated with a 'diabetes dementia' (Hatanaka et al. 2015; Shiue 2015).

T1D and T2D are common causes of *peripheral neuropathy*, which usually leads to sensory loss affecting the feet and hands in a 'glove and stocking' distribution, which may progress proximally. The major loss is usually sensory, but motor loss and muscle wasting can also occur.

Diabetes may also affect the *autonomic nervous system*, which can cause postural hypotension, abnormal cardiac reflexes, no pain (silent) or atypical pain during myocardial ischemia, erectile dysfunction, delayed gastric emptying, alternating diarrhea (particularly nocturnal) and constipation, incomplete bladder emptying and abnormal sweating (such as in response to eating) (Vinik et al. 2003).

An uncommon and painful cause of (often sudden onset unilateral) quadriceps, hip and buttock muscle wasting and weakness is a neuropathy affecting the lumbosacral plexus. This condition is also known as diabetic amyotrophy, proximal diabetic neuropathy, diabetic lumbosacral plexopathy or diabetic polyradiculopathy (Lebovitz and American Diabetes Association 2009).

Macrovascular Disease in Diabetes

In general, relative to their non-diabetic peers, people with diabetes are at a two- to four-fold increased risk of coronary artery disease, cerebrovascular disease and peripheral vascular disease. With regard to lower limb amputations, diabetes is associated with a 15-fold greater risk than non-diabetic subjects (Markakis et al. 2016; Wu et al. 2007; Young et al. 2003).

Accelerated Atherosclerosis

In diabetes, atherosclerosis is accelerated relative to that of similar aged non-diabetic subjects. While there are many similarities in the pathology of atheroma in diabetic and non-diabetic subjects, diabetes atheroma usually occurs prematurely with a greater plaque burden extending more distally. The plaques tend to be more lipid rich with a greater degree of inflammation and calcification and are therefore inherently more unstable in people with diabetes. Arterial collateral formation and wound healing are also more often impaired in diabetes subjects, and due to the more severe and distal disease, revascularization interventions are less often feasible for advanced vascular disease (Markakis et al. 2016). For these same reasons, clinical outcomes of cardiovascular disease events (e.g., myocardial infarction) are often worse with greater mortality in people with diabetes (Lima et al. 2013).

Peripheral Vascular Disease

Lower limb amputation in a person with diabetes is most often due to a combination of macrovascular, microvascular damage, neuropathy, tissue infection and impaired wound healing (Markakis et al. 2016). Macrovascular disease usually leads to a major above or below knee amputation, while microvascular disease usually leads to a non-healing foot ulcer and/or amputation of a toe or forefoot.

Cardiomyopathy

The incidence of congestive cardiac failure is also increased several fold in people with compared to without diabetes and has a poorer prognosis. While coronary artery disease, small arterial vessel disease (sometimes called syndrome little x), hypertension and renal failure, which are common in diabetes, can cause a cardiomyopathy, it is now accepted that diabetes per se can cause a metabolic cardiomyopathy (Felicio et al. 2015; Liu et al. 2014; Letonja and Petrovic 2014). This problem is thought to be more common in women with diabetes and to involve a hormonal basis.

The Pathology of Diabetes Vascular Damage

Endothelial dysfunction in both large and small blood vessels is a feature of diabetic vascular damage (Jenkins et al. 2004a). The vascular endothelium is more than an inert lining of blood vessels. As summarized in Table 1.6, the endothelium has a barrier function, modulates vascular tone and blood pressure, plays roles in inflammation, thrombosis and fibrinolysis, lipoprotein metabolism and angiogenesis.

Table 1.6 Endothelial dysfunction

Endothelial function	Feature in diabetes
Structural	Thick basement membranes
Barrier	↑ Permeability
Cell growth/angiogenesis (VEGF)	Cell proliferation/death/angiogenesis
Modulate thrombosis/fibrinolysis, platelets	↑ Thrombosis, ↓ tpa, ↑ PAI-1, platelet activation
Influences inflammation	↑ CAMs/monocyte adhesion
Modulate vascular tone (ET-1, NO, ACE)	Altered blood flow/↑ BP and capillary pressure
Lipid metabolism (LPL)	Dyslipidemia

ACE angiotensin-converting enzyme, *BP* blood pressure, *CAMs* cell adhesion molecules, *ET-1* endothelin 1, *LPL* lipoprotein lipase, *NO* nitric oxide, *PAI-1* platelet activator inhibitor 1, *tpa* tissue plasminogen activator, *VEGF* vascular endothelial growth factor

Common Mediators

Hyperglycemia together with disordered lipid and protein metabolism contributes to atherogenesis. Hyperglycemia results in a cascade of both intracellular and extracellular perturbations, including quantitative and qualitative changes in lipoproteins, increased inflammation and oxidative stress, including the formation of a family of compounds called advanced glycation end-products (AGEs) (Fig. 1.8) (Jenkins et al. 2004a).

Michael Brownlee has suggested a common intracellular pathway within endothelial cells that links hyperglycemia and vascular complications via induction of increased mitochondrial oxidative stress which then activates the polyol, hexosamine, protein kinase C and methylglyoxal/AGEs pathways. His excellent article and related American Diabetes Association Banting Best lecture are well worth reading/viewing (Atkinson 2005). This 'unifying hypothesis' explains why inhibition of single pathways, such as the PKC pathway (Deissler and Lang 2016; Tuttle et al. 2015) or AGE formation (Brownlee 2001, 2005) only partially reduces vascular complications, as glucose still activates the other pathways. Inhibition of common proximal modulators (such as improving glucose levels) and/or of common distal mediators, such as increased mitochondrial oxidative stress, as proposed and tested by Brownlee, is required. The Diabetes Control and Complications Trial (DCCT) (an intervention study) and its longitudinal observational follow-up study

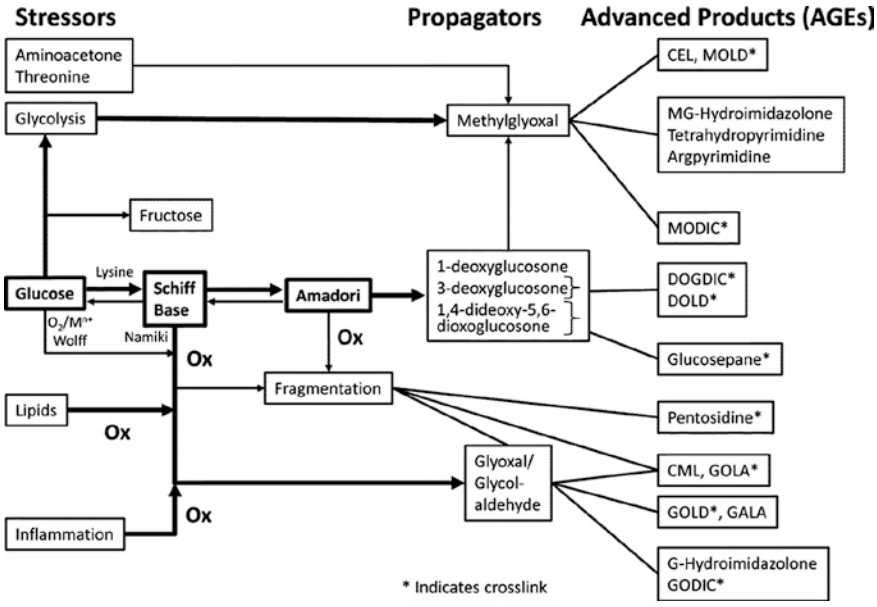

Fig. 1.8 Pathways of AGEs formation. Reproduced with permission, from Monnier and Wu (2003)

Epidemiology of Diabetes Interventions and Complications (EDIC) demonstrate efficacy of improved glucose control in reducing vascular complications in people with T1D (The Diabetes Control and Complications Trial Research Group 1998; White et al. 2008). The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated similar benefit in people with T2D (Holman et al. 2008a, b).

Risk Factors for the Vascular Complications of Diabetes

Beta-Cell dysfunction and the resultant hyperglycemia and glycemic variability bring about and/or are compounded by multiple risk factors that can promote vascular damage. The risk factors, which are often inter-related, are usually divided into traditional and novel risk factors, as summarized in Table 1.7 (Jenkins et al. 2015). Risk factors may be further subdivided into those that are unmodifiable and modifiable.

Table 1.7 Risk factors for the chronic complications of diabetes

Traditional risk factors
Age (including age of onset)
Diabetes duration
Glycemic control
–hyperglycemia
–glycemic variability
–frequent hypoglycemia
Obesity
Increased waist circumference
Smoking
Hypertension
Dyslipidemia
High triglycerides
High LDL cholesterol
Low HDL cholesterol
Family history
Novel risk factors
Qualitative and quantitative changes in lipoproteins
E.g., lipoprotein glycation and/or oxidation
Inflammation
Oxidative distress
Advanced glycation end-product (AGE) formation
Insulin resistance
Angiogenesis-related growth factor disturbances
Genetics
Epigenetics
Changes in telomeres/telomerase-modifying enzymes
Histone modification
Unfavorable microRNA profiles

Traditional risk factors which are unmodifiable include age of diagnosis, which can be delayed for T2D, but not as yet for T1D, longer diabetes duration, gender, and an adverse family history. With regard to gender, both men and women are at high risk of macrovascular disease. Men tend to be at higher risk of microvascular complications, though the subgroup of females with prepubertal onset of T1D tend to have a higher risk than their male counterparts. The reasons for this are not fully elucidated. With regard to family history, the risk of diabetes complications is higher in subjects with other family members with diabetes complications, or in T1D patients with hypertension or T2D in their non-diabetic family members.

Modifiable traditional risk factors, which are also influenced by genetic and environmental factors, include hypertension, dyslipidemia and obesity. Obesity, in particular central obesity or an increased waist circumference, may compound hypertension, dyslipidemia and insulin resistance, but is also thought to act independently (The Diabetes Control and Complications Trial Research Group 1998; White et al. 2008). This may be via increased levels of inflammation and also by increased insulin resistance.

Most studies relate to factors associated with diabetes complications, but importantly there are several studies evaluating people with T1D who do not develop clinically significant complications.

Factors associated with a very favorable outcome of T1D, as reflected by living 50 or more years with it, but with no or only early vascular damage, include a normal weight, non-smoking status, a favorable lipid profile characterized by a high HDL cholesterol level, and a family history of parental longevity. There is marked concordance in the characteristics of these 50 or more year survivors with T1D who comprise the British 'Golden Years' Cohort and the Joslin Medalist's (Bain et al. 2003). Studies of the genetics and epigenetics of such patients are underway. Such knowledge may provide insight into treatments that can reduce the devastating complications of diabetes, while the 'cure' for diabetes is awaited.

Novel Risk Factors. Hyperglycemia in addition to increasing inflammation, oxidative stress and AGE formation can cause non-enzymatic glycation of many short-lived proteins (such as lipoproteins) and long-lived proteins (such as basement membranes and skin collagen). We have previously reviewed the adverse effects of hyperglycemia-induced modifications of lipoproteins (Jenkins et al. 2004b), which include adverse effects on arterial, retinal and renal cell survival and function.

Other novel risk factors include genetic factors, which require very large studies to explore, and more recently, epigenetic factors. As yet, no genetic or epigenetic markers are used in clinical practice. There are many excellent review articles.

Insulin resistance, while commonly associated with T2D, is also a feature of non-diabetic subjects (Festa et al. 2004) and people with T1D (Greenbaum 2002). Insulin resistance has been associated with increased risk of cardiovascular disease in non-diabetic subjects and of vascular complications in people with T1D (Bjornstad et al. 2015). As discussed later in this chapter, insulin-sensitizing drugs are often used in pre-diabetes (type 2), T2D and GDM, and sometimes in T1D.

Metabolic Memory for Glucose Control

The impacts of hyperglycemia and hypoglycemia on higher cerebral function and mood are evident immediately, but the effects on the vasculature are not evident for years. Importantly, the level of glycemic control in one decade can influence vascular complications a decade or even more later, irrespective of the level of control in the second decade. This phenomenon, called 'metabolic memory' or the 'legacy effect' (which are comparable terms), was initially coined in relationship to T1D studies in the DCCT/EDIC cohort (White et al. 2008) and in the 10-year follow-up of the UKPDS, respectively (Holman et al. 2008a).

Susceptible tissues for metabolic memory include retina, kidneys, nerves and arteries. A non-glucose-related example of a legacy effect is the persistence of a smoking-related increase in heart disease and cancer risk that persists for years after smoking cessation. A legacy effect for lipid and blood pressure control for the vasculature has also been demonstrated, but predominantly in non-diabetic subjects (O'Neal and Jenkins 2009). As yet, there are no specific lipid-related studies in diabetes for which the legacy effect has been evaluated, and given the major benefit of lipid-lowering drugs in diabetes, it will now be difficult to conduct such a study prospectively.

The timeframe of metabolic memory in T1D is best evidenced by the DCCT/EDIC study, in which ≈5.9 years of intensive versus conventional diabetes management (HbA1c 9 vs. 7 %) lowered vascular complication rates for at least 8–12 years (Aiello et al. 2015). The T2D UKPDS data demonstrate a similar legacy effect of glycemia that lasts for 10 years after having a HbA1c ≈ 7.0 % for 10 years (Manley 2003). Due to the low number of long-term glycemic control intervention studies with adequate follow-up, it is not yet clear if there is a threshold level for metabolic memory and how long the effect is maintained for a given time at each HbA1c level across the full HbA1c spectrum.

Potential mediators of glucose metabolic memory are epigenetic changes, which are acquired changes in DNA function without changes in DNA sequence (Okabe et al. 2012; Thomas 2014; Keating and El-Osta 2015; Mathiyalagan et al. 2015). Epigenetic changes include DNA and histone methylation, histone acetylation and telomere shortening. Glucose- and AGE-induced modifications of long-lived tissues such as vascular basement membranes may also mediate metabolic memory and also be a therapeutic target (Jenkins et al. 2004a). Some currently used drugs, such as ACE inhibitors, 'statins' and metformin also have anti-AGE and DNA-protective effects, as well as their primary actions related to blood pressure, lipid and glucose lowering, respectively. Novel drugs such as histone deacetylase inhibitors, which reduce epigenetic damage, are currently in human cancer clinical trials and protect against diabetic nephropathy in an animal model (West and Johnstone 2014).

Diabetes Treatments

Current research strategies for both T1D, T2D and GDM also include approaches related to diabetes prediction, diabetes prevention, diabetes control (using a range of drugs and insulin delivery devices), and the ultimate, but currently elusive, cure. Other chapters in this book, by experts in their area, include potential preventative strategies for islet damage that leads to T1D, to pancreas or islet cell transplantation (which are clinically available in some affluent countries for a very small proportion of people with T1D), to islet β-cell replacement with stem cell therapy.

Other drugs related to blood pressure, lipid control and novel modalities to retard or treat the vascular complications of diabetes, such as anti-VEGF agents for diabetic retinopathy and dialysis for renal failure, are also relevant to the care of many people with diabetes, but of relevance to the book topic, in this section we focus on glucose control agents.

Most existent treatments for glucose control in diabetes have mechanisms of action that are linked to pancreatic islet hormones, as described earlier in this chapter. Drug classes for glucose control are summarized in Table 1.8 and reviewed in more detail in other excellent books such as by the American Diabetes Association (Lebovitz and American Diabetes Association 2009).

Broadly, the drugs for glycemic control are mostly glucose lowering for daily use, but drugs to elevate glucose are used on an occasional basis for the treatment of hypoglycemia. There is an increasing number of insulin formulations available for T1D or for insulin-requiring GDM or T2D. On average, within 10 years of T2D diagnosis, many people will need exogenous insulin due to β-cell failure. Insulin delivery devices, also an active area of research, include syringes, disposable and reusable syringes, as well as external and implantable insulin pumps, including the 'artificial pancreas,' also known as a closed loop insulin pump. Ongoing research aims to improve exogenous insulin therapy, with approaches including faster onset of action, longer duration and 'smart insulins' that have responsiveness to glucose levels (so as to reduce the risk of hypoglycemia). Insulin secretagogues are usually used mainly in T2D, with the exception of non-sulfonylurea drugs, which are also approved for T1D use (always in conjunction) with insulin.

Insulin sensitizers, incretin-based therapies, glycosuria-inducing drugs and drugs used to delay dietary carbohydrate absorption are mainly used for T2D, but some have shown benefit in people with T1D, as an adjunct to insulin therapy. This is an active area of clinical research. Combination therapies of oral agents or of injectable and oral agents, always including insulin, are commonly needed for individuals with T1D. Many diabetes associations recommend treatment algorithms for T2D (Gunton et al. 2014), when lifestyle measures alone are inadequate to achieve optimal glucose control.

Glucagon, which can only be delivered by injection, is usually used to treat severe hypoglycemia by trained carers or healthcare staff to raise blood glucose levels. Insulin pump-related research is exploring glucagon administration, but

Table 1.8 Glucose control drugs used in diabetes

Drug class	Type 1 diabetes	Type 2 diabetes	Gestational diabetes
Glucose lowering			
Insulin[a]			
Rapid-acting	X	X	X
Short-acting	X	X	X
Intermediate-acting	X	X	X
Long-acting	X	X	X
Pre-mixed (short and intermediate)	X	X	X
Insulin secretagogues			
Sulfonylureas		X	
Non-sulfonylurea related			
Meglitinides (e.g., repaglinide)		X	
Insulin sensitizers			
Metformin	–[b]	X	X
Thiazolidinediones	–[b]	X	
Incretin-based therapies			
GLP-1 agonists[a]	–[b]	X	
DPP-IV inhibitors	–[b]	X	
Amylin related[a]	X	X	
Glycosuria-inducing drugs			
SGLT2 inhibitors	–[b]	X	
Agents to delay complex carbohydrate absorption			
α-Glucosidase inhibitors	–[b]	X	X
Hypoglycemia treatment			
Glucagon injection[a]	X	X	X
Glucose tablets or gels	X	X	X
IV glucose	X	X	X

[a]Injectable drug
[b]Emerging or off-label use

is hampered by poor glucagon stability, currently necessitating a fresh glucagon solution daily. Other treatments for hypoglycemia, apart from food, include oral glucose tablets or gels or intravenous glucose fluids. Much important drug-related research continues alongside endeavors to protect, regenerate and replace the hormones produced by the pancreatic islets.

Glucose Monitoring

To guide the type and amount of glycemic control therapies used by the person with diabetes, doctors commonly measure the HbA1c level in blood. The HbA1c is a measure of the amount of non-enzymatic glycation of hemoglobin, and this

reflects mean blood glucose control over the previous 2–3 months. People with insulin-treated diabetes usually test their own blood glucose levels regularly (often four times a day or more if they have T1D). Special portable blood glucose testing meters and strips have been available for this over the past four decades. The glucose meters are becomingly increasingly smaller, more accurate and with added features such as memory, glucose profile recognition and the capacity (with healthcare professional setup) to calculate optimal insulin doses for the individual person according to their glucose level at that time and what they are about to eat (i.e., 'smart meters').

Home urine glucose monitoring, used clinically since the early 1900s, is now infrequently used. Some patients with diabetes, usually with T1D, have access to continuous glucose monitoring (CGM); however, the cost is prohibitive to most patients for regular use. In some countries, the government or health insurers will cover CGM. CGM requires a disposable glucose sensor (each lasts 5–7 days) to be placed into the subcutaneous fat for quantification of interstitial fluid glucose levels every few minutes using enzymatic glucose oxidase chemistry, as for blood glucose testing (Davis et al. 2015; DeSalvo and Buckingham 2013). If linked with a compatible insulin pump, a CGM can trigger the pump to suspend insulin delivery in the setting of a low or predicted low glucose level and to restart insulin delivery when the glucose level has risen to a safe level or the user restarts insulin delivery. Earlier versions, still available, can suspend insulin delivery at a low glucose level for up to 2 h (Choudhary et al. 2015; Prazny 2015; Tauschmann and Hovorka 2014; Agrawal et al. 2011; Pickup 2011). The use of CGM communicating with pumps and using the 'low glucose suspend' option can significantly improve glucose control, quality of life and reduce risk of severe hypoglycemia (Buckingham et al. 2015; Thabit et al. 2015). Excellent progress is being made with successful clinical trials in the home use of the 'closed loop' system, particularly for nocturnal use. This system includes CGM and an insulin pump with inbuilt control algorithm software for insulin adjustment according to interstitial fluid glucose levels (Tauschmann et al. 2015). All-day closed loop systems with insulin or with insulin and glucagon (van Bon et al. 2014) are also progressing well in clinical trials, so it is expected that fully closed loop insulin pumps (i.e., 'artificial' or 'bionic' pancreases) will be available for clinical use in our lifetime (Battelino et al. 2015; Russell 2015; Malchesky 2015).

Conclusion

Diabetes was known to physicians from about 2500 BC, and the term 'diabetes' was first used by the Greeks about 250 BC, yet it is only since 1922 when Banting, Best, McLeod, Collip and their colleagues first injected insulin into humans that long-term survival for people with T1D has greatly improved, and the lives of those with insulin-requiring T2D or with GDM has improved. In the last few decades, we are still discovering hormones produced by the pancreatic

islets. Pleasingly, we also have learnt how to mass-produce and safely use drugs that replace or replicate the actions of the pancreatic islets, improve peripheral insulin sensitivity or modulate gut or renal tract glucose handling to improve glucose control. We have also learnt lifestyle and medical and surgical means to reduce the risk of the many potential acute and chronic complications of diabetes. Whole pancreas or pancreatic islet transplantation is also clinically available to some people with T1D, and this is also an exciting area of ongoing research. While much has been learnt about pancreatic islets and the effects and interactions of the body's various glucose control hormones and mechanisms, much remains to be learnt and translated into clinical practice for even better outcomes for those with or at risk of diabetes.

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