Diabetes in Hospital

A Practical Approach for Healthcare Professionals

Paula Holt

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For Ian, Matthew and Jonathan

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Preface

Today people are busier than ever but have more sedentary lifestyles. This, coupled with the increased abundance and availability of convenience foods, is contributing to rocketing levels of obesity. With this comes increasing numbers of people developing type 2 diabetes. As type 1 and type 2 diabetes transcend almost every system in the body, this will have a huge impact on health service delivery and will undoubtedly lead to more diabetes-related hospital admissions.

The aim of this book is to provide healthcare professionals with the knowledge and skills to be able to care effectively for these people during their time as a hospital in-patient. It considers the different types of specialist area a person with complications of diabetes may be admitted to, and goes on to discuss the care relevant to that person in that particular specialist setting.

The application of theory to practice is achieved through the use of different case studies to which an evidence-based, problem-solving approach is applied. The need for 'joined up', multidisciplinary working while considering fully the bio-psycho-social needs of the patient is emphasized.

The contents of the book are not 'profession specific' and readily relate to all members of the multidisciplinary team who are responsible for the care of the person with diabetes. It is aimed at providing help and guidance to those who do not have specialist knowledge of diabetes but believe their care of patients with diabetes could be improved. The advice and guidance offered is presented in a clear and logical way with evidence-based rationales so that the healthcare practitioner understands *why* they should be delivering the care in such a way.

While is it recognized that there will be an overlap of care in different care settings, the main complication for that specialism is dealt with in the appropriate chapter.

The first two chapters of the book provide the reader with the conceptual hooks that are required to understand the principles of diabetes, maintaining and achieving blood glucose control and the effective treatment of diabetes. From this,

subsequent chapters focus on caring for the person with diabetes in different hospital settings and specialisms. Within each chapter, different aspects of diabetes care and complications are highlighted. Thus, the reader is able to 'dip in and out' of the chapters relating to their specialism, but if the book is read as a whole a complete picture of diabetes care is provided.

Evidence-based rationales for care are provided, drawing upon key research findings, National Institute for Health and Clinical Excellence (NICE) guidelines and the diabetes National Service Framework (NSF). A practical and logical approach is adopted with key points highlighted in boxes throughout, and at the end of each chapter. Diagrams are used to help illustrate key points.

Paula Holt
August 2008

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Finally, my students at all academic levels, who bring to the classroom an array of experiences and clinical situations that have been drawn upon in writing this book.

Abbreviations

ABPI	Association of the British Pharmaceutical Industry
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ACTH	adrenocorticotrophic hormone
ARB	angiotensin II receptor blocker
ATP	adenosine triphosphate
BMI	body mass index
DAFNE	Dose Adjustment For Normal Eating
DCCT	Diabetes Control and Complications Trial
DESMOND	Diabetes Education and Self-management for Ongoing and Newly diagnosed
DPP	Diabetes Prevention Programme
DIGAMI	Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction
DKA	diabetic ketoacidosis
DPP-4	dipeptidyl peptidase-4
DSP	distal symmetrical sensory polyneuropathy
DVLA	Driver Vehicle Licensing Agency
FREMS	frequency-modulated electromagnetic neural stimulation
GAD	glutamate decarboxylase
GFR	glomerular filtration rate
GI	glycaemic index
GIK	glucose, insulin, potassium
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GP	general practitioner
3HB	3-beta-hydroxybyturate
HbA1c	haemoglobin A1c

HDL	high-density lipoprotein
HF	high-frequency external muscle stimulation
HH	hereditary haemochromatosis
HONK	hyperosmolar, non-ketotic acidosis
HT	hyperspectral technology
IDDM	insulin-dependent diabetes mellitus
IDF	International Diabetes Federation
IDL	intermediate-density lipoprotein
IL-6	interleukin-6
LADA	latent autoimmune diabetes in adults
LDL	low-density lipoprotein
LGV	larger goods vehicles
NHS	National Health Service
NIDDM	non-insulin-dependent diabetes mellitus
MI	myocardial infarction
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NEFAs	non-esterified fatty acids
NICE	National Institute for Health and Clinical Excellence
NODAT	new-onset diabetes following liver transplantation
NSF	National Service Framework
OGTT	oral glucose tolerance test
PCV	passenger-carrying vehicle
PP	pancreatic polypeptide
RAS	renin–angiotensin system
TENS	transcutaneous electrical nerve stimulation
TNFα	tumour necrosis factor α
TZDs	thiazolidinediones
UKPDS	United Kingdom Prospective Diabetes Study
VLDL	very-low-density lipoprotein
WHO	World Health Organization

1 Understanding diabetes

Aims of the chapter

This chapter will:

1. Outline the history of diabetes and insulin.
2. Identify the anatomy of the pancreas and the physiology of insulin secretion and action in a person who does not have diabetes.
3. Discuss the changes in the anatomy and physiology of insulin secretion that result in the development of both type 1 and type 2 diabetes.
4. Consider how diabetes is currently classified.
5. Discuss the aetiology and predisposing factors of type 1 and type 2 diabetes.

What is diabetes?

Diabetes mellitus is a metabolic disorder that has multiple causes and is characterized by the continued presence of fasting plasma glucose levels >7 mmol/l, with associated disturbances of carbohydrate, fat and protein metabolism. It results from: (1) defects in insulin secretion caused by autoimmune destruction of the pancreatic beta cells; (2) insulin action due to insulin resistance; or (3) both. Insulin resistance is where the action of insulin on its target cells, namely the liver, muscle and adipose tissue, is deficient due to abnormalities of carbohydrate, fat and protein metabolism.

Diabetes is a complicated, serious, potentially debilitating and life-threatening condition, which if left uncontrolled can lead to the progressive development of a series of complications. These include: retinopathy leading to blindness; nephropathy that may lead to renal failure; and/or neuropathy that may result in the person having an increased risk of developing foot ulcers, limb amputation, and

autonomic and sexual dysfunction. People with diabetes are also at an increased risk of developing cardiovascular disease, peripheral vascular disease and of having a cerebrovascular accident.

Diabetes currently affects 3.54% of the UK population and a known 2.2 million people in the UK have been diagnosed with the condition (Diabetes UK 2006a). However, due to the insidious nature of diabetes mellitus, Diabetes UK estimates that there are a further 750 000 to 1 million people in the UK who have diabetes, but have not yet been diagnosed. Current sedentary lifestyles and rising levels of obesity mean that the incidence of diabetes is escalating; consequently, increasing numbers of people with diabetes will be admitted to hospital with either a diabetes-related complication or their diabetes may impact on a different, non-related condition.

In order to deliver appropriate healthcare and management to the person with diabetes, it is important that the health practitioner and his or her team have an understanding of the anatomy, physiology and mechanics of diabetes and blood glucose management. The level of understanding presented in this chapter provides the groundwork upon which the remaining chapters are built.

History of diabetes and insulin

Diabetes has been recognized as a disease since ancient times – the word 'diabetes' coming from the Greek meaning 'to pass through'. It was first used by Aretaeus of Cappadocia in the 2nd century AD who described a serious condition involving the 'melting down of flesh and limbs into urine'. He went on to observe that 'life was short, unpleasant and painful, thirst unquenchable, drinking excessive and disproportionate to the large quantity of urine' (Williams and Pickup 2004). However, it was not until 1889 that diabetes began to gain significant interest from scientists and medical professionals when two German scientists, Oskar Minkowski (1858–1931) and Josef von Mering (1849–1908), discovered that when they removed the pancreas from a dog, it developed diabetes (Williams and Pickup 2004). They learnt from this that diabetes is related to a pancreatic disorder but unfortunately they did not follow up this finding.

The next major milestone in the history of diabetes came in 1921 with the discovery of insulin at the University of Toronto, Canada. Collaborative work between the surgeon Frederick G. Banting (1881–1941), one of his students Charles H. Best (1892–1965), James B. Collip (1892–1965) a biochemist, and the physiologist J.J.R. Macleod (1876–1935) found that chilling the extracts of dog pancreas and then injecting them into a dog with diabetes caused a decline in the dog's blood glucose level (Williams and Pickup 2004). From this discovery, Collip went on to develop improved procedures for the extraction and purification of insulin from pancreas, and on 1 January 1922 the first person with diabetes was treated with insulin – a 14-year-old boy called Leonard Thompson.

Based on this discovery and the experiences of Leonard Thompson, the chemists Eli Lilly and Co. from the USA jumped on to the commercial bandwagon.

They worked out processes to refine insulin extraction and purification, resulting in insulin becoming commercially available in North America and Europe from 1923. This was to have a huge impact on the treatment of people with diabetes as, up until this time, if a person developed diabetes they died due to the lack of appropriate treatment. Fortunately though, the incidence of diabetes was quite low at this time, which helped to keep the death rate low.

The past 75 years has seen the development, redevelopment and marketing of different types of insulin, with varying peak onset and action times. The supply of insulin from cow and pig pancreas is declining, resulting in the advent of new genetically modified analogue insulins introduced into the market in 1983, again by Eli Lilly. These new-generation insulins such as Humalog® and more recently Novorapid® (Novo Nordisk Ltd) have been produced via scientific technology that enables human insulin to be commercially produced from the *Escherichia coli* bacteria using recombinant DNA or cloning (Wikipedia, 2007).

This brings us right up to date with the development of inhaled insulin (Exubera®), which was prescribed to patients who met National Institute for Health and Clinical Excellence guidelines on the use of inhaled insulin (NICE 2006). Unfortunately, Exhubera® has now been withdrawn from the market as it did not meet customer's needs or financial expectations. Patients who had been prescribed the inhaled insulin have been transferred on to a different insulin regimen, but it is hoped that as the technology has now been developed Exhubera® may return to the market in the future.

Anatomy and physiology in the absence of diabetes

As can be seen from the above history, the pancreas, a major organ in the body, has a significant role to play in the normal homeostasis of blood glucose control. The pancreas is a slender, tadpole-shaped organ, pale in colour, with an uneven, lumpy consistency that sits neatly within the 'J'-shaped loop of the duodenum, deep within the greater curvature of the stomach, within the abdominal cavity. The pancreas of an adult is approximately 20–25 cm long and weighs 80 g (Martini 2006).

The pancreas has both an exocrine and an endocrine function. The exocrine pancreas, representing approximately 99% of the total pancreatic mass, is made up of pancreatic acini, which are clusters of secretory gland cells attached to ducts. The role of the glands and the associated duct cells is to secrete pancreatic digestive enzymes that drain from the pancreas via the centrally located main pancreatic duct. These digestive enzymes are required to aid the process of food digestion and absorption in the small intestine. Any trauma or condition that impairs the secretion or drainage of pancreatic digestive enzymes will seriously impair the body's ability to digest food and absorb nutrients.

The exocrine function of the pancreas does not have significant importance in diabetes. It is only the endocrine function of the pancreas that healthcare professionals involved with people who have diabetes need to be conversant with.

The endocrine pancreas consists of small clusters of cells scattered among the exocrine cells, predominantly in the body and tail of the pancreas. These clusters of cells are known as pancreatic islets or the Islets of Langerhans, named after the German anatomist Paul Langerhans in 1869. There are approximately 1 million pancreatic islet cells in the adult pancreas and each islet contains in the region of 1000 endocrine cells (Rorsman 2005).

Knowing that there are very few, if any, Islets of Langerhans in the head and neck areas of the pancreas is important, particularly if a person develops carcinoma of the head of pancreas, a tumour of the bile duct, or has acute or chronic pancreatitis. Each of these conditions may result in the person undergoing a pancreaticoduodenectomy, also known as the Whipple procedure, in which the head of the pancreas is removed. As the body and tail of the pancreas will be left, along with the alpha and beta cells, the person should not develop diabetes as a result of the surgical procedure.

Within each Islet of Langerhans there are four main types of cells, each associated with secretion of a different peptide hormone:

- Alpha (α) cells – make up approximately 20% of all cells in each Islet of Langerhans. They are predominantly situated around the periphery of the islet and secrete glucagon.
- Beta (β) cells – are the majority of the cells found in each Islet of Langerhans, accounting for 75% of the islet cells. Their function is to produce insulin.
- Delta (δ) cells – are the majority of the remaining cells in each Islet of Langerhans. These cells secrete somatostatin, which is a growth-hormone-inhibiting hormone, the effect of which is to suppress the release of glucagon and insulin and slow the rate at which food is absorbed.
- F cells – also known as PP cells as they produce the hormone pancreatic polypeptide (PP). There are very few F cells scattered throughout each Islet of Langerhans and the pancreatic polypeptide that they secrete inhibits contractions of the gallbladder and also regulates the production of some pancreatic enzymes (Martini 2006).

As the hormones insulin and glucagon are predominantly responsible for the homeostatic regulation of blood glucose levels, these will be considered in greater depth.

Insulin

Insulin is a polypeptide hormone that has a key role in the instigation of food metabolism. It is synthesized and stored in the beta cells and is released in response to the blood glucose level rising above the normal range of 4–7 mmol/l. In a healthy, normal-weight person, the average daily secretion of insulin is equivalent to 30–40 units. This is secreted via a pulsing action of the pancreas activated 300–400 times per day. It is this pulsing action, in which small amounts of insulin can be secreted frequently throughout the day and night, that makes it

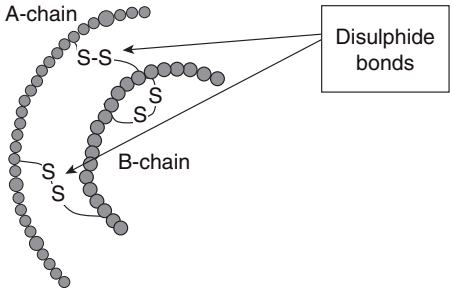

Figure 1.1 Structure of insulin.

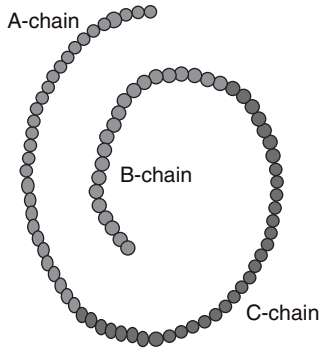

Figure 1.2 Structure of pro-insulin.

very difficult for scientists and researchers to be able to mimic the action of the pancreas accurately when giving synthetic, subcutaneous insulin. Even insulin delivered by a specially designed insulin pump, which is able to deliver insulin much more frequently than a person having insulin injections, still does not come close to the natural action of the pancreas.

Insulin consists of two polypeptide chains – an A chain of 21 residues and a B chain of 30 residues, which are joined together by two disulphide bonds (Figure 1.1).

The formation of insulin is controlled by a gene on the short arm of chromosome 11 and insulin production begins in the rough endoplasmic reticulum of the beta cells. This results in the production of pre-proinsulin, which is a precursor molecule to insulin. Pre-proinsulin is a single, long polypeptide chain containing the A chain, B chain and an additional C chain. As the development of insulin progresses, pre-proinsulin passes from the rough endoplasmic reticulum to the Golgi apparatus, still in the beta cell. During this phase it loses a chain of 24 amino acids from the end of the long chain and pro-insulin is formed (Figure 1.2). Pro-insulin has the disulphide bonds of insulin but has only one single chain of

81–86 amino acids, depending on the species, as opposed to the two separate chains of insulin (Brook and Marshall 2001). At this stage of synthesis, pro-insulin has very minimal insulin-like activity.

The C chain, also known as C-peptide, is referred to as a connecting chain as it connects the A and B chain of insulin together. C-peptide has no known biological activity but is secreted into the blood stream in equal quantities to insulin (Kettyle and Arky 1998). Occasionally, in diagnosing diabetes, the levels of C-peptide in a person's blood stream will be measured to give an indication of how much insulin, if any, the person is producing.

Within the Golgi apparatus of the beta cell, pro-insulin is converted into 'active' insulin by the cleavage of the C-peptide. When blood glucose levels begin to rise, this stimulates the need for insulin to be released and causes the A and B chains and the free floating C chain to fuse with the surface membrane of the beta cells and eventually for insulin to be released into the blood stream. The effect of this is to lower the rising blood glucose levels. Insulin can be stored in the beta cells for several days prior to its release into the blood stream. It is released into the portal vein, resulting in the liver being the first organ to be exposed to, and react to, the newly released insulin (Rorsman 2005).

Triggers for insulin secretion

As mentioned above, insulin secretion is triggered by a rising blood glucose level, which is detected in the beta cells. Conversely, insulin secretion is suppressed by falling or low blood glucose levels. The beta cells have the ability not only to detect rising or falling blood glucose levels but also to determine the rate of change in the blood glucose concentration. The beta cells are able to respond to these changes by releasing insulin at a continuous, low rate of approximately 1–2 units per hour. This is called the 'basal rate' or late-phase insulin release. Yet the beta cells are also able to secrete insulin at much higher levels for a short period of time in response to a rapidly rising blood glucose level which happens, for example, just after the person has eaten. This is known as a 'bolus' or early-phase insulin release and will have implications when insulin treatments are discussed in Chapter 2.

There are three main situations in which insulin release will be triggered:

- An increase in blood glucose concentrations.
- An increase in amino acid concentrations.
- Increased parasympathetic input.

1. Increase in blood glucose concentrations

When both simple and complex carbohydrate foods such as pasta, potatoes, bread, cakes, sweets, etc. are eaten, the sugar from these foods gets absorbed from the stomach and small intestine into the blood stream, causing a rise in blood glucose concentrations.

2. Increase in amino acid concentrations

Amino acids are fundamental constituents of protein and can be found in the protein in our diet, as well as being synthesized by the body. Between meals or during a fast, amino acids are released from muscle cells into the blood stream. When they reach the liver, in response to a falling blood glucose level, the liver converts the amino acids into glucose via a process called gluconeogenesis. This 'new' glucose is then transported into the blood stream and blood glucose levels rise. At the same time the glucose that has been stored in the liver in the form of glycogen is broken down by a process known as glycogenolysis, meaning the breakdown of glycogen, and again released into the blood stream. These processes are part of the body's compensatory mechanism to ensure that the vital organs such as kidneys and brain, which do not have insulin receptors, obtain their continuous required levels of glucose.

3. Increased parasympathetic output

As part of the 'fight or flight' sympathetic mechanism, which is triggered when faced with a dangerous, difficult or frightening situation, the body will make and release glucose to provide the person with the extra energy that may be required to escape the situation. This results in blood glucose levels becoming raised. Once the fight or flight situation has abated, the parasympathetic nervous system triggers the release of insulin to reduce the elevated blood glucose levels back to within normal limits.

Effects of insulin on target cells

The mechanisms by which insulin reduces blood glucose levels are now considered. The main aim of this process is to remove the circulating glucose from the blood steam either by utilizing it for energy and growth, absorbing and storing it elsewhere in the form of glycogen, or converting it into triglycerides. This is achieved via a number of different mechanisms (Figure 1.3).

Insulin degradation

Once secreted, insulin is rapidly degraded and removed from the circulation by the liver and kidneys. This is done by breaking down the disulphide bonds that connect the A and B chain together. This occurs quite rapidly after secretion, giving insulin an active biological half-life of only 6–10 minutes. It is expected that all insulin produced will be broken down within 12–20 minutes of it being secreted, which highlights the need for the pancreas to produce insulin on average 300–400 times per day. This biologically short life of insulin helps to ensure that the ever-fluctuating blood glucose levels are kept within the normal range of 4–7 mmol/l and the person does not experience frequent hypoglycaemic episodes.

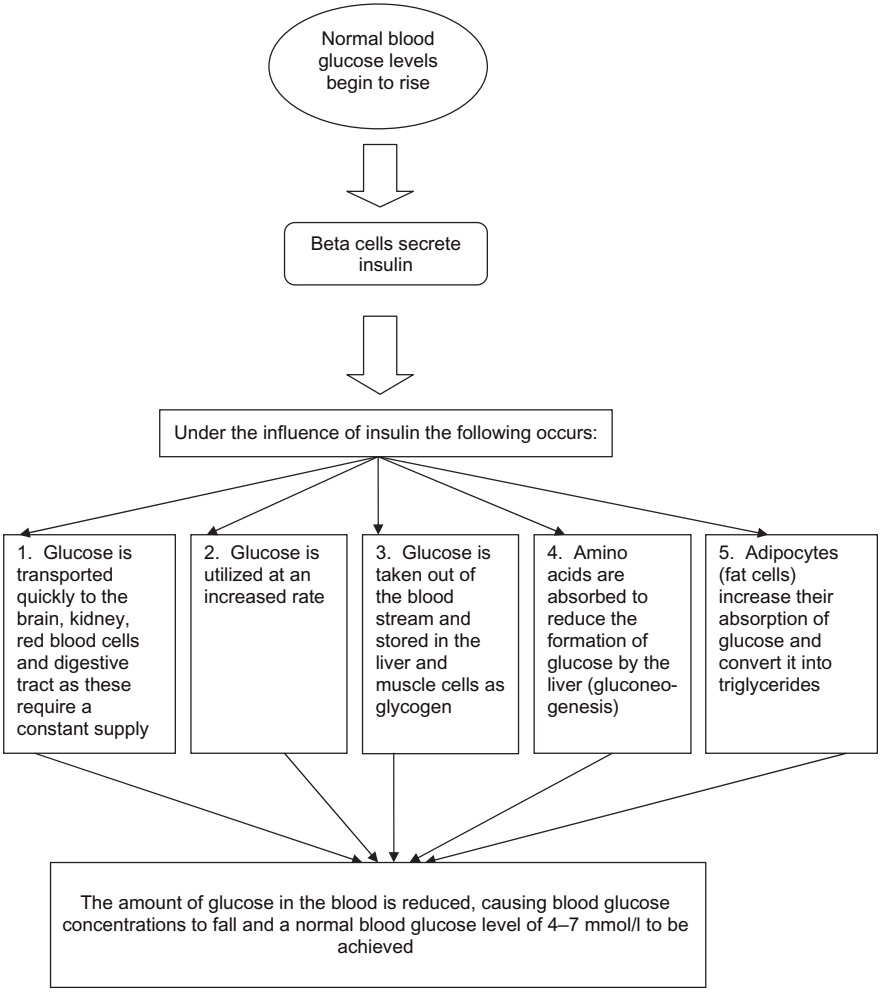

Figure 1.3 Action of insulin on target cells.

Glucagon

Glucagon, which is secreted by the alpha cells in the Islets of Langerhans, has an equal part to play with insulin in the regulation of blood glucose levels. While the action of insulin causes blood glucose levels to fall, glucagon has the opposite effect and causes them to rise. Similarly, the release of glucagon is stimulated by falling blood glucose levels and suppressed by the release of insulin, which is secreted when blood glucose levels rise.

When blood glucose levels start to fall, the sequence of events shown in Figure 1.3 is reversed. The body mobilizes its stores of glycogen that have been laid down