Insulins: An introduction

Created by South African experts, this unique interactive learning programme will help you to successfully initiate insulin therapy in your patients with diabetes and to confidently manage their continuing care.

What you will gain…

Participation in this fully accredited CPD programme gives you the opportunity to learn how:

- Appropriate selection of patients for insulin therapy can significantly improve prognosis;
- Insulin can be easily and safely initiated by understanding and applying some simple steps; and
- To select the right insulin for the right patient at the right time

How you will learn…

START offers you the opportunity to freely obtain CPD points

- **e-based learning** in five modules – each module earns 3 CPD points
- **Watch** accompanying advice and tips from South African experts
- **Download** practical materials supporting you and your patients when you initiate insulin

Expert panel

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Click here to watch the video

Module 2: Insulins: An introduction

Objectives of this module

- To provide clinical guidance on insulin choice in South Africa

The role of insulin in glucose homeostasis

Insulin is the pivotal endocrine peptide hormone that orchestrates an integrated response to food intake. It maintains glucose homeostasis by its direct effects on skeletal muscle, liver and adipocytes; these tissues play a distinct role in metabolic homeostasis through tissue-specific insulin signalling pathways (Figure 1).

When higher circulating insulin levels are necessary to achieve an integrated glucose-lowering effect, the individual is considered to be insulin resistant. Prediabetes, lipodystrophy, polycystic ovarian syndrome and non-alcoholic fatty liver disease are all characterised by increased fasting plasma insulin levels, and therefore insulin resistance. The increased production of insulin and consequent β-cell decompensation or loss is a major mechanism for the development of overt type 2 diabetes (T2DM).[1]

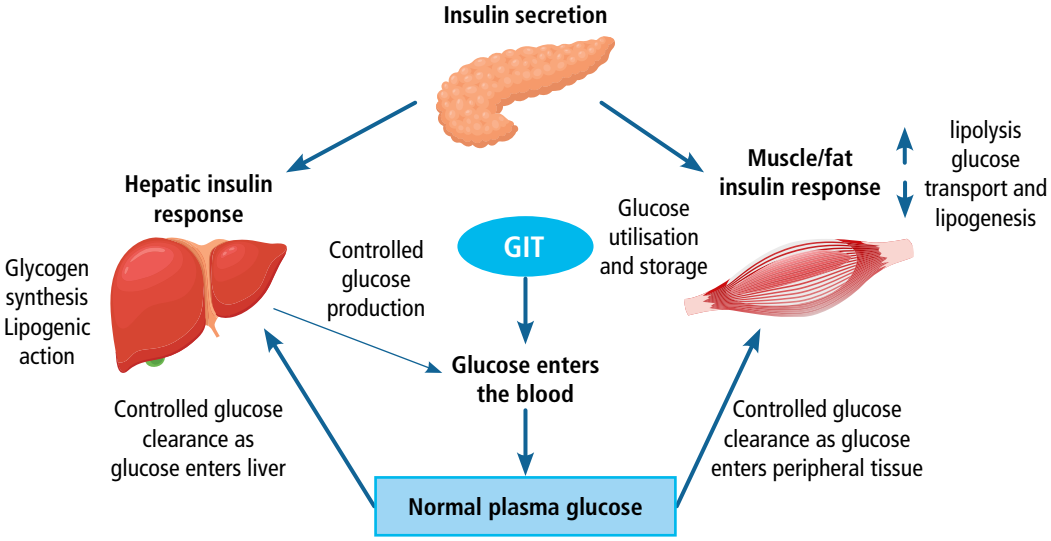


Figure 1. Normal regulation of plasma glucose

Type 1 diabetes (T1DM) on the other hand, is an autoimmune disease causing destruction of β-cells of the pancreas. This condition is characterised histologically by insulitis (inflammation of the Islet cells) and β-cell damage. The inflammatory damage to Islet cells is characterised by a decrease (or absence) of insulin-producing β-cells and infiltration of the tissues with T lymphocytes, B lymphocytes and macrophages.[2]

Other modules

Module 1
To explain when insulin use is appropriate and essential

Module 3
To support clinicians and build confidence in initiating insulin and intensifying therapy

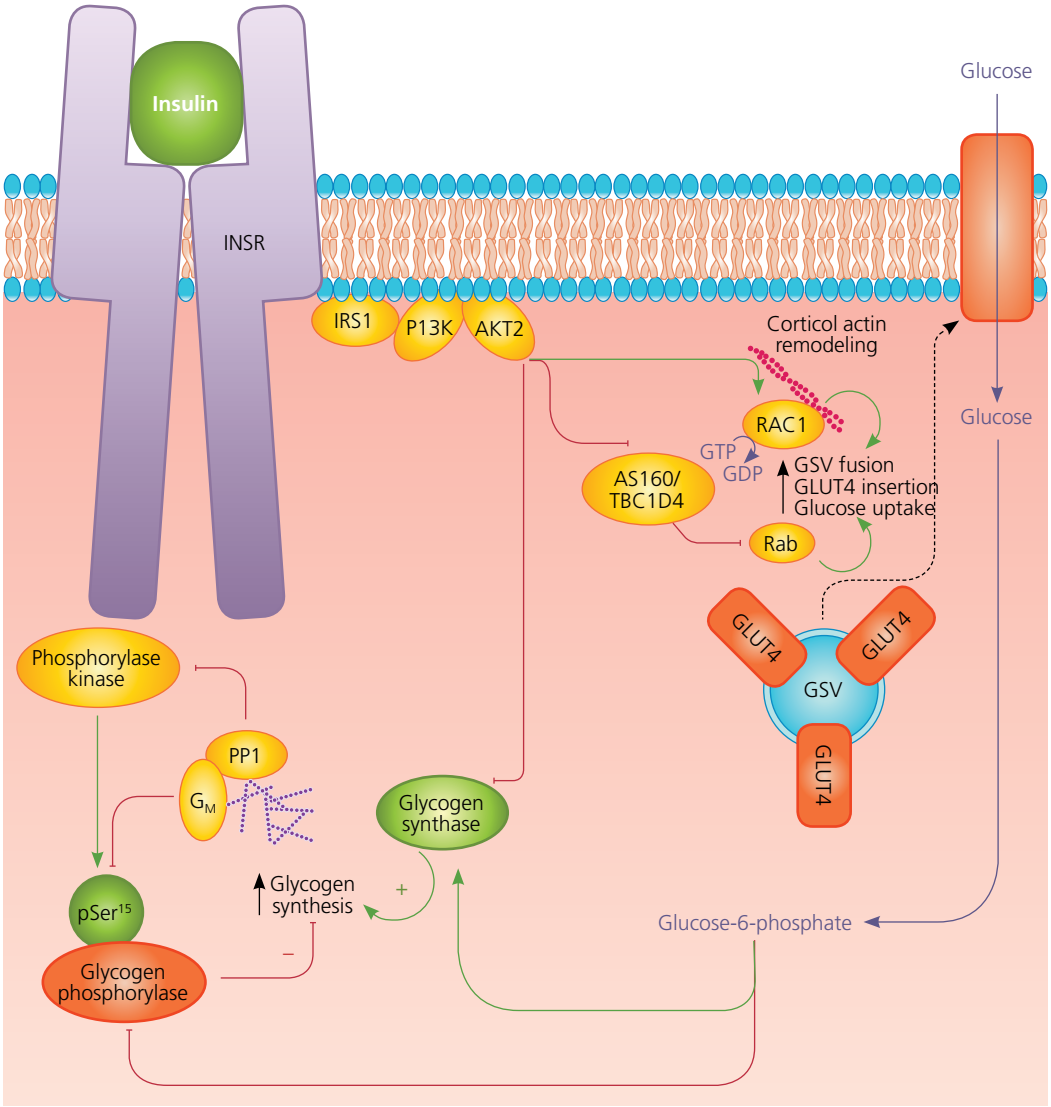
Module 4
To provide tools and guidance in the effective use of patient-centred insulin regimens

Module 5
To provide key clinical messages and tips from expert clinicians that are practical and easy to introduce in daily practice

The key cellular role of insulin in glucose metabolism

Insulin exerts all of its physiological effects by binding to the insulin receptor on the plasma membrane of target cells. The insulin receptor consists of α and β sub-units, occurring as A and B isoforms. The B isoform is much more specific and is the primary form expressed in the liver, muscle and white adipose tissue; currently, evidence indicates that one insulin molecule binds and activates one receptor.

Activation of the insulin receptor initiates downstream metabolic signalling (Figure 2),[1] including the glucose transporter-4 (GLUT-4)-containing storage vesicles (GSVs) which move to the surface of the plasma membrane, allowing glucose to be absorbed along a concentration gradient into the muscle cell. Simultaneously, glycogen synthesis and storage is initiated.



Green circles and arrows represent activating events; red circles and arrows represent inhibitory events
GSK3: glycogen synthase kinase 3; PI3K: phosphoinositide-3-kinase; PP1: protein phosphatase 1

Figure 2. The insulin signalling cascade in skeletal muscle[1]
Insulin receptor (INSR) activation has two major metabolic functions in the skeletal myocyte: glucose uptake and glycogen storage. Insulin stimulation of glucose uptake occurs through translocation of GSVs to the plasma membrane. The resultant increase in intracellular glucose-6-phosphate production, together with a coordinated dephosphorylation of glycogen metabolic proteins, enables net glycogen synthesis.

Normal insulin secretion pattern

Normal insulin secretion patterns have been stylised, with the key features of a meal-stimulated peak that slowly decays over 2-3 hours and a sustained basal level that remains constant throughout the day (Figure 3).[3,4] The sustained basal level is due to insulin secreted from the pancreas in a pulsatile manner, as was shown in early studies of healthy fasting human subjects.[5]

Glucose is the most potent secretagogue for insulin secretion, as it induces robust release within a few minutes; this response is biphasic, with the first release occurring within a few minutes and the second phase beginning a few minutes later, increasing to a peak within 30-40 minutes.[6]

Sulphonylureas, thiazolidinediones and newer GLP-1 receptor agonists increase the amplitude of insulin release pulses but not the frequency, although the latter does increase the regularity of the insulin pulse.

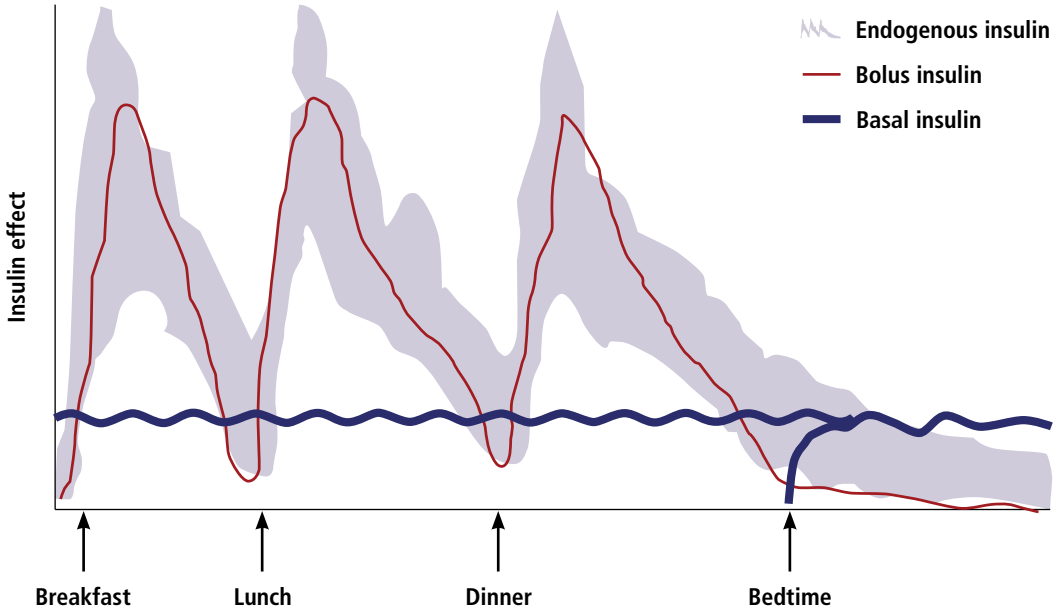
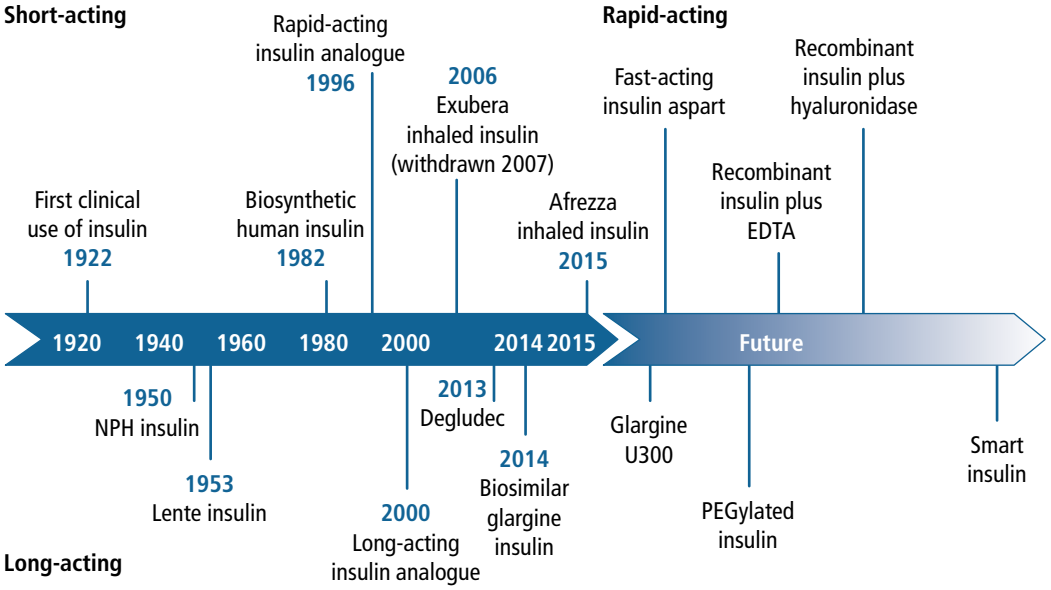


Figure 3. Idealised pattern of insulin secretion for a healthy individual who has consumed three standard meals[3,4]

Classification of insulin

Insulins can be categorised according to their duration of action and, in the case of analogues, their similarity with human insulin. Today's human insulins are synthesised using recombinant DNA technology, to have the identical amino acid sequence and physico-chemical properties of the native human insulin. Analogue insulins are not naturally occurring but are manipulations of the insulin molecule, aimed at providing specific characteristics such as rapid or prolonged action.

The timeline of the development of insulin starts in 1922 with the first clinical use of insulin and, in subsequent decades since 1982, new biosynthetic human insulins were developed (Figure 4)[7] to provide different pharmacokinetic properties.



NPH: neutral protamine Hagedorn; PEG: polyethylene glycol; EDTA: edetic acid

Figure 4. Timeline for the development of short-acting, long-acting, and future rapid-acting analogues of insulin[7]

Time action profiles of individual insulins

The most useful classification is based on the time action of the individual insulin. Within this time action profile, the clinician and individual patient additionally face a choice of opting for either a human insulin or an analogue version. Table 1 provides a time action-based index of these insulins, with the analogue option banded in light blue.

Extensive clinical trials of these registered insulin therapies have been conducted globally, and specific South African trials have been conducted for clinical purposes to address aspects of our particular diverse populations and circumstances. (A selection of these studies are provided at the end of this module for interested clinicians.)

Table 1. Time action profiles of insulin[7]

Type	Onset	Peak	Duration
Short-acting regular human insulins	30-60 minutes	2-3 hours	Up to 7-8 hours
Rapid-acting analogue insulin			
Aspart	12-18 minutes	30-90 minutes	3-5 hours
Glulisine	12-30 minutes	30-90 minutes	3-5 hours
Lispro	15-30 minutes	30-90 minutes	3-5 hours
Intermediate-acting (basal) human insulins			
NPH – neutral protamine Hagedorn	120-240 minutes	4-10 hours	10-18 hours*
Lente	90 minutes	4-8 hours	22-24 hours*

Long-acting (basal) analogue insulins Glargine U100 Glargine U300	 120-240 minutes 120-240 minutes	 No peak No peak	 Up to 24 hours* Up to 36 hours*
Pre-mixed human (biphasic) insulins 30% regular + 70% NPH	30-60 minutes	Dual peak 2-4 hours	10-16 hours
Pre-mixed analogue insulins Rapid-acting plus basal Biphasic aspart Biphasic lispro Rapid-acting plus ultra-long-acting basal Pre-mixed aspart/ degludec	 5-15 minutes 5-15 minutes	 Dual peak Dual peak	 10-16 hours >24 hours
*The duration of action of intermediate- and long-acting insulins is dose dependent			

Novel developments that improve the patient experience and acceptability of insulin therapy

When considering which insulin and its associated device is most appropriate for the individual patient, it is useful to also look at what the research on patient-reported outcomes and opinions can teach us.

Patient satisfaction ratings are higher with insulin pens than with vial and syringe.[8] Of 43 studies published in a 25-year period, only two studies reported better satisfaction with vial and syringes, but this was in the early stages of the development of pen technology. Advantages of pens include better dosing accuracy, easy dosing and administration, convenience, flexibility, discreetness of injection and lessening of injection pain.

Innovation over time has led to pen needles becoming thinner and shorter. The amount of injection force required to initiate the injection has also been reduced. Additional features of newer pens, such as large visual dosage displays and a memory feature, help patients to administer the correct dose to achieve glycaemic control. Potential disadvantages of the insulin pens include the need for two injections if large amounts of insulin are required and in cases where patients require very small dose increments (<lu).

While cost and co-payment issues abound, patients should be encouraged to access an easier administration route that builds confident and regular use of prescribed insulin (Table 2). Other delivery systems, such as insulin pumps with/without sensors, are also useful for individual patients (Table 3).

Table 2. Insulin preparations available in South Africa

Insulin type	Active ingredient	Dosage form	
Short-/rapid-acting insulins			
Short-acting human insulins	Regular human insulin (rDNA)	3x5ml cartridge	3x5ml pen
Rapid-acting analogue insulins	Insulin lispro Insulin aspart Insulin glulisine	3x5ml cartridge 3x5ml cartridge 3x5ml cartridge	3x5ml pen 3x5ml pen 3x5ml pen
Basal insulins			
Intermediate-acting human insulins	Lente human insulin Isophane human insulins	3x5ml cartridge 3x5ml cartridge	3x5ml pen 3x5ml pen
Basal analogue insulins	Insulin glargine U100 Insulin glargine U300 Insulin detemir	3x5ml cartridge INJ 3x5ml cartridge 3x5ml cartridge	3x5ml pen 3x5ml pen 3x5ml pen
Pre-mixed insulins			
Pre-mixed human insulins	Biosynthetic human insulin: 30% regular insulin + 70% isophane insulin	3x5ml cartridge	3x5ml pen
Pre-mixed analogue insulins **Combination**	Insulin lispro + insulin Lispro protamine Biphasic insulin aspart + NPH (30/70) Insulin degludec + aspart	3x5ml cartridge 3x5ml cartridge 3x5ml cartridge 3x5ml cartridge	3x5ml pen 3x5ml pen 3x5ml pen 3x5ml pen

Source: South African Medicine Registry (with prices) https://mpr.code4sa.org/

Table 3. Routes of exogenous insulin delivery

Subcutaneous	Vial and syringes Pen delivery Disposable pen
IVI	Continuous infusion/hourly injections (hospital)
CSII	Continuous subcutaneous insulin infusion
Sensor-augmented pump therapy (SAP)	In development: closed loop insulin pump systems/artificial pancreas
IMI	Transient e.g. diabetic ketoacidosis (DKA) *en route* to hospital (10u)

Which South African clinical trials are readily available to the interested clinician?

Randomised clinical trials and product dossiers support the registration of insulin offerings in South Africa. Less accessible to clinicians in general practice are relevant trials done in South Africa dealing with our diverse populations and their health challenges. We have selected some recent trials and provide links to their abstracts and, where possible, the full text of the article.

- Self-monitoring of blood glucose measurements and glycaemic control in a managed care paediatric type 1 diabetes practice.
- The success of various management techniques used in South African children with type 1 diabetes mellitus.
- Effects of exogenous human insulin dose adjustment on body mass index in adult patients with type 1 diabetes mellitus at Kalafong Hospital, Pretoria, South Africa, 2009 - 2014.
- Original paper: Efficacy and safety analysis of insulin degludec/insulin aspart compared with biphasic insulin aspart 30: A phase 3, multicentre, international, open-label, randomised, treat-to-target trial in patients with type 2 diabetes fasting during Ramadan.
- Durability of insulin degludec plus liraglutide versus insulin glargine U100 as initial injectable therapy in type 2 diabetes (DUAL VIII): a multicentre, open-label, phase 3b, randomised controlled trial.
- The Biosulin equivalence in standard therapy (BEST) study – a multicentre, open-label, non-randomised, interventional, observational study in subjects using Biosulin 30/70 for the treatment of insulin-dependent type 1 and type 2 diabetes mellitus
- Similar glucose control with basal-bolus regimen of insulin detemir plus insulin aspart and thrice-daily biphasic insulin aspart 30 in insulin-naive patients with type 2 diabetes: Results of a 50-week randomized clinical trial of stepwise insulin intensification.

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Click on reference to access the scientific article

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