PRACTICAL GUIDE TO

INSULIN THERAPY IN TYPE 2 DIABETES MELLITUS

2ND EDITION (2024)

MEMS
Established 1981
Malaysian Endocrine & Metabolic Society

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Foreword

In Malaysia, the prevalence of known diabetes in the latest National Health and Morbidity Survey 2023 was 9.7% estimating 2.2 million adult Malaysians. This survey reported that 21.8% or one in five of those diagnosed with diabetes were treated with insulin therapy, approximating half a million adult Malaysians. It is expected that up to 99% of these individuals have Type 2 diabetes.

With longer disease duration of Type 2 diabetes, oral glucose lowering drugs given in combination frequently lose effectiveness, with an expectant need to initiate injectable therapy such as insulin which is a more accessible and affordable option compared to the newer non-insulin injectable therapies. The use of insulin therapy among patients with Type 2 diabetes within the Ministry of Health has continued to increase with the recognition of the need to attain and maintain good glycaemic control towards prevention of acute and long-term diabetes-related complications. Most recently there has been serious concerns about shortage of human insulin production and supply globally and locally. This highlights the need to ensure cost-effective use of insulin therapy in Malaysia.

Despite the high use of insulin therapy, many insulin-treated individuals with Type 2 diabetes are not able to achieve recommended treatment targets in terms of glycaemic control. There is a need for better understanding on the approach of prescribing insulin therapy for both primary and tertiary care settings in Malaysia. Therefore, this second edition of the Practical Guide to Insulin Therapy for Type 2 diabetes (2024) is crucial for us to have as a set of updated guidelines to standardize and strengthen insulin therapy practices among healthcare professionals.

I would like to congratulate all those involved who have worked tirelessly to develop this practical guide. The Malaysian Endocrine and Metabolism Society (MEMS) places high importance to this effort and prioritizes the commitment to educate Malaysian healthcare professionals in best current practices for diabetes management. MEMS has given full support from the beginning of the guide preparation and acknowledges the public and private partnerships involved in the development of this guide which I believe can strengthen the healthcare sectors especially in training and services.

I urge all of you to make full use of this second edition of the Practical Guide to Insulin Therapy in Type 2 Diabetes, towards improving patient outcomes and quality of diabetes care in Malaysia.

Dr Nurain Mohd Noor
President, Malaysian Endocrine and Metabolic Society (MEMS)

Preface

The therapeutic approach and pharmacotherapy options for glucose-lowering in patients with type 2 diabetes (T2DM) have continued to evolve in the past decade. The additional oral and injectable medications now available, with demonstrated evidence for long-term safety and benefits, have shifted the paradigm of treating T2DM. Treatment prescription strategies have gone beyond the conventional focus of glucose-lowering. Medication prescriptions also consider focusing on target organ protection and weight reduction, while minimising hypoglycaemia.

The newer glucose-lowering drugs (GLDs) have established cardiovascular (CV) and renal risk reductions that positively impact the risks of morbidity and mortality from diabetes-related complications. These GLDs are now prioritised and initiated early in accordance with the evidence-based recommendations from local and international T2DM treatment guidelines. Additionally, these medications have an insulin sparing effect and may potentially delay insulin initiation, reduce insulin dose requirement and enable simpler insulin regimen prescriptions requiring fewer injections. Ultimately, by fulfilling our patients' expectations, treatment acceptance and adherence can be improved. It could also potentially improve the cost-effectiveness of the overall management of T2DM.

It has been more than a decade since the introduction of the 2010 Practical Guide to Insulin Therapy for Type 2 Diabetes. The first edition guidelines recommended early initiation and intensification of insulin therapy to combat treatment inertia amongst physicians treating T2DM. Prior to implementing the guidance, prescription of insulin therapy among patients with T2DM in primary care clinics was relatively low. With better understanding of the applicability of insulin therapy in primary care, and the continuous training of prescribers, diabetes educators and patients, the practical step-by-step interventions recommended were well adopted and practised.

The successful implementation and wide uptake of the guidelines led to a significant increase in insulin prescription rates. Ten years after the launch of the guidelines, the 2020 National Diabetes Registry (NDR) reported that almost 1 in 3 individuals with diabetes was being insulin-treated. In tertiary care, several cross-sectional studies between 2003 and 2013 demonstrated an initial rise in insulin therapy rates, with almost 2 in 3 individuals with T2DM requiring insulin. However, with the newer pharmacotherapeutic options, insulin therapy rates among patients with T2DM in tertiary care plateaued. More recently, the use of insulin treatment has decreased.

Preface

Despite wider and earlier prescription of insulin therapy, and greater use of intensive multiple dose insulin regimens in those with T2DM, glycaemic control in the majority of insulin-treated patients have remained suboptimal. Non-adherence to multiple dose insulin regimens, over-insulinisation and lack of self-monitoring of blood glucose remain the apparent problems commonly encountered. These issues directly contribute to the failure to achieve and maintain optimal glycaemic control in insulin-treated patients with T2DM.

The second edition of the Practical Guide to Insulin Therapy for Type 2 Diabetes has been updated to address evolving insulin therapy strategies. The guidelines include newer insulin formulations, practical and simplified approaches to insulin intensification and the possible consideration for deintensification of insulin therapy in selected patients where indicated. We hope it will provide better awareness, knowledge and current best practices of insulin therapy.

This guidance is directed to all members of the diabetes care team which include doctors, nurses, dieticians and pharmacists, who manage patients with T2DM in primary and tertiary care. Improved insulin prescribing practices can lead to better patient outcomes, including reduced rates of hypoglycaemia, fewer glycaemic-related emergencies and hospitalisations, and potentially a decrease in chronic diabetes-related complications due to better long-term glycaemic control. We must commit to ensuring that insulin therapy for Malaysian patients with T2DM is safe, cost-effective, and preserves quality of life.

Datuk Dr Zanariah Hussein
Chairperson,
Development Committee,
Practical Guide to Insulin Therapy for Type 2 Diabetes, 2nd edition

Objectives

The aim of the updated practical guide is to assist healthcare providers, particularly primary care physicians, to make key treatment decisions for initiating, optimising and intensifying insulin therapy and reducing the long-term morbidity risk among patients with type 2 diabetes mellitus (T2DM).

Clinical Questions

To achieve the objective of the practical guide, the updated content answers the following clinical questions relating to insulin therapy among patients with T2DM:

1. Why is insulin therapy needed?
2. How is insulin therapy initiated?
3. How are insulin doses optimised?
4. How are insulin regimens intensified?
5. How is insulin therapy deintensified?
6. How is glycaemia monitored?
7. What are the challenges and practical issues related to insulin therapy?

Target Population

The practical guide is applicable to adolescents and adults with T2DM.

Target Audience

The practical guide is meant for all healthcare providers involved in treating patients with T2DM. This includes all specialists, medical officers, family medicine specialists, primary care physicians, general practitioners, public health personnel, nurses, assistant medical officers, podiatrists, pharmacists, dieticians and diabetic nurse educators.

Disclosure

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Practical Guide Development Committee

Chairperson

Datuk Dr Zanariah Hussein	*Head, Endocrinology Unit, Endocrine Institute, Hospital Putrajaya*

Members

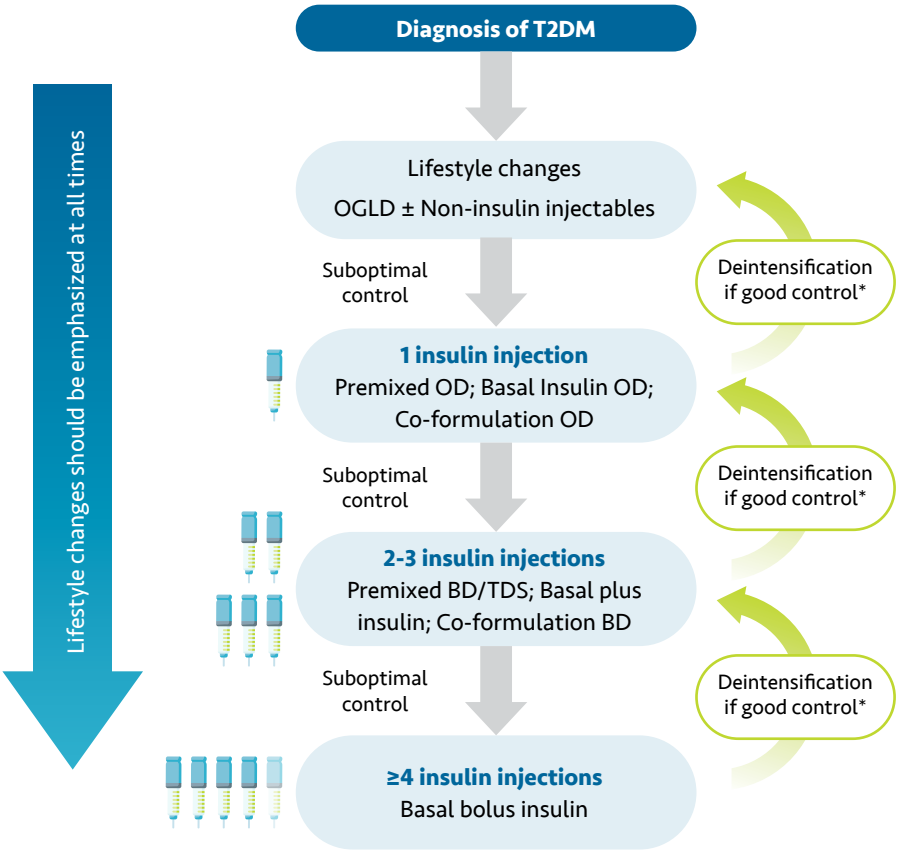
(In alphabetical order)

Dr Chan Pei Lin	*Endocrinologist, Hospital Umum Sarawak, Kuching, Sarawak*
Dr Chai Shu Teng	*Endocrinologist, Hospital Sultanah Aminah, Johor Bahru, Johor*
Dr Masliza Hanuni Mohd Ali	*Endocrinologist, Hospital Sultanah Nur Zahirah, Kuala Terengganu, Terengganu*
Dr Navin Kumar Loganadan	*Diabetes Clinical Pharmacist, Endocrine Institute, Hospital Putrajaya*
Dr Noor Rafhati Adyani Abdullah	*Endocrinologist, Hospital Sultanah Bahiyah, Alor Setar, Kedah*
Dr Teh Roseleen Nadia Binti Roslan	*Endocrinologist, Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan*
Dr Wong Hui Chin	*Endocrinologist, Hospital Tengku Ampuan Rahimah, Klang, Selangor*

External Reviewers

Dr Nurain Mohd Noor	*Head, Endocrinology Subspecialty Service, Ministry of Health Malaysia* *Endocrinologist, Hospital Putrajaya* *President, Malaysian Endocrine and Metabolism Society (MEMS)*
Puan Ezzatulakma binti Mohd Nadzri	*Diabetes Educator, Hospital Putrajaya*
Dr Foo Siew Hui	*Endocrinologist, Hospital Selayang*
Puan Lim Phei Ching	*Pharmacist, Hospital Pulau Pinang*
Dr Manohari a/p Balasingam	*Consultant Physician, Hospital Kajang*
Dr Noor Ashikin binti Ismail	*Physician, Hospital Putrajaya*
Dr Raja Nurazni binti Raja Azwan	*Endocrinologist, Hospital Putrajaya*
Dr Tong Chin Voon	*Endocrinologist, Hospital Putrajaya*
Dr Wong Ping Foo	*Family Medicine Specialist, Klinik Kesihatan Cheras Baru*

Overall Treatment Algorithm for T2DM Patients Requiring Insulin



*Consider deintensification if good glycaemic control, i.e., at individualised targets. BD, twice daily; OD, daily dose; OGLD, oral glucose lowering drugs; TDS, three-times daily.

Note:

1. Metformin should be continued while on insulin therapy unless contraindicated or intolerant.
2. Sulphonylureas (SUs)/meglitinides should be discontinued once bolus insulin is used regularly with meals.
3. Insulin dose should be optimised prior to switching/intensifying regimens.
4. Steps to intensify/deintensify is as the algorithm above. However, multi-step changes (i.e. skipping step/s) may be considered on discretion.
5. Self-monitoring of blood glucose (SMBG) is required for all patients initiating insulin.

Section 1
Background

The most recent Malaysian National Health and Morbidity Survey (NHMS) in 2023 revealed that the prevalence of diabetes among adults 18 years old and above was 15.6%. Approximately 2 out of 5 cases were undiagnosed while the prevalence of known diabetes has steadily increased to 9.7%. It is estimated that more than 70% of adult Malaysians with known diabetes are treated in Ministry of Health primary care clinics.[1] Meanwhile, the 2022 National Diabetes Registry (NDR) report documented a total enrolment of 1.9 million patients with 800,000 active cases. Of the active cases enrolled in the NDR, 99.3% have type 2 diabetes mellitus (T2DM).[2]

Not surprisingly, with the rising prevalence of diabetes in Malaysia, there has been a rapid increase in insulin therapy over the past two decades. The 2006 3rd NHMS revealed a mere 7% insulin use among adults with known diabetes[3] while the National Medicines Use Survey (NMUS)[4] reported that insulin therapy contributed to only 8.2% of the overall glucose-lowering drugs (GLDs) utilisation in the same year. At that time, it reflected the low insulin utilisation rates compared to other countries. However, over a few short years, insulin therapy utilisation among individuals with T2DM in tertiary care had risen from 28% in 2003 to 50% in 2009.[5,6]

The first Practical Guide to Insulin Therapy in Type 2 Diabetes was developed in 2010 to address the low rates of insulin use in primary healthcare clinics and the high rates of poor glycaemic control. Its primary objective was to improve the understanding and practice of insulin therapy in primary care. Following its launch, healthcare professionals from primary and tertiary care were trained nationwide. A high level of implementation of the guidelines was achieved over the next few years, both in primary care and hospital-based diabetes clinics.

The rate of insulin use in primary care has been closely monitored every year and showed a steady incline from 11.7% in 2009 (NDR data) prior to introducing the insulin therapy guidelines to 28.8% in 2022 (NDR data) representing a 2.5-fold increase in the rates of insulin-treated individuals over 13 years. Similarly, the DiabCare Malaysia studies revealed that insulin therapy rates among individuals with T2DM in tertiary care had risen from 28% in 2003 to 50% in 2009[5,6] and up to 65.4% in 2013.[7] However, the recent availability and accessibility of newer GLDs in tertiary care have reduced the rates of insulin therapy. Findings from the Target T2D study of 2022 reported that insulin treatment was prescribed in 52.6% of a multicentre cohort attending diabetes clinics in 8 public hospitals in the Klang Valley.[8]

Early initiation of insulin therapy followed by treatment intensification and use of multiple dose insulin regimens, usually combined with oral GLDs (OGLDs) should expectantly enable better rates of glycaemic control in the majority of individuals with T2DM. However, the glycaemic control on insulin therapy is still suboptimal, with an average HbA1c of near 9% among those with T2DM on established insulin therapy.[9] In a prior study of people with T2DM treated in hospital-based diabetes clinics, the most frequently prescribed insulin regimen for T2DM was the premixed insulin regimen, followed by basal only and basal-prandial (bolus) insulin regimens.[7] Serial reports of the NMUS revealed a definite disproportionality with the utilisation of modern insulins or insulin analogues between the public and private healthcare sectors.[10]

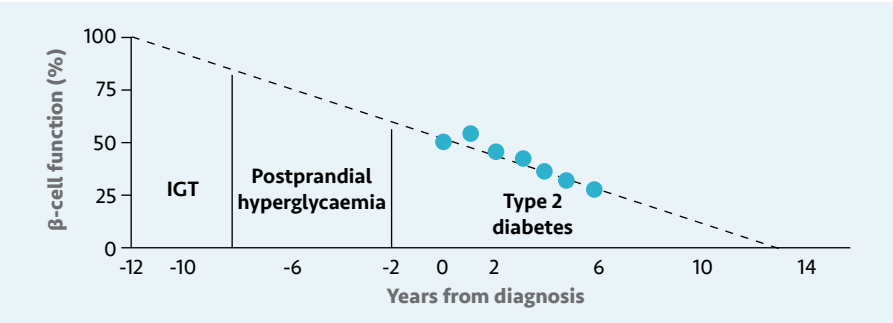
In the Hypoglycaemia Awareness Tool (HAT) study,[9] hypoglycaemia rates among insulin-treated individuals with T2DM in Malaysia were unexpectedly high, occurring in 1 in 3 (33%) individuals with a severe hypoglycaemia rate of 7%. Besides hypoglycaemia there are many other challenges in our current practice of insulin therapy for T2D that become barriers to achieving good glycaemic control. These include non-adherence, poor injection technique, inappropriate dosing, lack of blood glucose monitoring, lack of intensification of insulin regimens and inappropriate timing of injections.

Section 2
Rationale for Insulin Therapy in T2DM

Insulin resistance and impaired insulin secretion are the two key factors for developing type 2 diabetes mellitus (T2DM).

- Both factors are already present at an early stage among those with prediabetes and worsen with time
- At diagnosis, as seen in the United Kingdom Prospective Diabetes Study (UKPDS), pancreatic beta-cell function was approximately 50% of normal, with a decline of approximately 5% per year[11]
- The estimated reduction in beta-cell function began 10-12 years before diagnosis of T2DM and approached <25% of normal function 6 years after diagnosis (Figure 2-1)

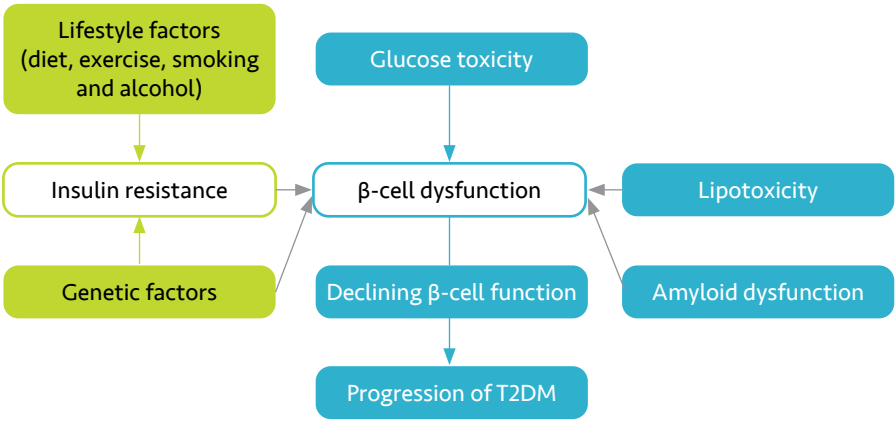
Figure 2-1 Progressive decline in beta-cell function in T2DM



IGT, impaired glucose tolerance.
Adapted from Holman et al. Diabetes Res Clin Pract 1998.[12]

- The causes of deterioration in beta-cell function are not completely understood, but prolonged exposure to saturated fatty acids (lipotoxicity) and high glucose (glucotoxicity) in genetically predisposed individuals have been proposed to contribute to beta-cell failure probably via mitochondrial dysfunction, endoplasmic reticulum stress and oxidative stress (Figure 2-2)
- The progressive decline in beta-cell function is characterised by worsening glycaemia, leading to gradual escalation of treatment options, starting from lifestyle modifications and oral glucose-lowering medications and often eventually resulting in the need for exogenous insulin therapy
- Timely initiation of insulin in individuals with T2DM has been associated with multiple benefits, such as decreasing the glucotoxic effects of hyperglycaemia, preserving beta-cell mass/function, improving insulin sensitivity and long-term protection from chronic complications[13,14]

Figure 2-2 Overview of factors influencing stages from insulin resistance to progression of T2DM



Insulin is widely accepted as the most effective treatment option available for lowering glucose levels, addressing acute and chronic elevations in blood glucose.

Insulin therapy has the following considerations:

- Is suitable at all stages of T2DM and for all ages
- Has a wide range of treatment options/regimens
- Has a well-documented safety profile and is generally well-tolerated
- Numerous randomised controlled trials (RCTs) and large observational studies have demonstrated that good glycaemic control can be achieved in patients with T2DM who are treated with insulin/insulin analogues and treatment algorithms
- Can be combined with other oral glucose-lowering drugs (OGLDS)
- Has demonstrated glycaemic control when combined with other injectable agents like glucagon-like peptide 1-receptor agonists (GLP1-RA)
- Glycaemic levels remain the main criteria for initiating insulin

The Malaysian Clinical Practice Guidelines (CPG) for the Management of T2DM (6th edition) recommends insulin therapy be considered in the following situations:

- When there is inadequate glycaemic control on optimal dose and number of OGLDs[15]
- As initial therapy in newly diagnosed T2DM,
  - → in the presence of symptomatic hyperglycaemia and evidence of ongoing catabolism[16]
  - → when the HbA1c is >10% or fasting plasma glucose (FPG) is >13.0 mmol/L[16]
  - → as part of an early insulinisation treatment regimen[17]

New insights into the pathogenesis of T2DM development have led to the discovery of new glucose-lowering drugs. The availability of these newer drugs provides an option to delay the initiation of insulin.

There is recent evidence to indicate that beta-cell dysfunction can be improved in certain individuals with T2DM. Restoration of beta-cell insulin production and release has been reported especially with significant weight loss from carbohydrate restriction, low-calorie diets, certain pharmacological treatments and bariatric surgery. In these circumstances, insulin-treated individuals with T2DM may be able to gradually reduce insulin requirement and deintensify insulin regimens. Certain individuals may even be able to discontinue prior insulin therapy.

Section 3
Barriers to Insulin Therapy

The International Diabetes Management Study (IDMPS) reported that despite the increasing use of insulin among people with type 2 diabetes mellitus (T2DM), and the number of available therapy options and drug delivery systems for insulin, there is no improvement in glycaemic control.[18]

There are various barriers to insulin therapy among patients and healthcare providers – barriers to insulin initiation, optimisation, intensification and persistence (Tables 3-1 and 3-2).

In developing countries, 1 in 7 insulin treated patient has poor persistence to insulin therapy. Poor persistence was associated with:[19]

- Age <40 years
- Recent diagnosis (<5 years)
- A low education level
- Non-possession of a blood glucose meter

While the main reasons for discontinuation of insulin were,[19]

- The treatment's impact on an individual's social life
- The cost of the insulin and glucose strips
- Fear of hypoglycaemia
- A lack of support and experience of dosing insulin

One of the most useful methods to overcome the patient's barrier to insulin initiation is for healthcare providers to have good communication skills and empathy, and provide a good demonstration of injection technique.[20]

- Overcoming patient-focussed barriers can assist the patient in their decision-making process to accept and adhere to insulin therapy
- As healthcare providers, it is important to identify the patient's barriers to insulin therapy and implement strategies to overcome or decrease them
- It requires sufficient time to empower and engage patients and can be effectively achieved using a team approach instead of relying on physicians to solely provide insulin education to patients[21]

Table 3-1 Patient barriers to insulin therapy and suggested solutions

Possible barriers	Suggested solutions and issues for patient discussion
Perceiving insulin initiation as a personal failure	• Start insulin discussions early, emphasising the pathophysiology of T2DM, i.e. about the disease progression that will eventually lead to needing insulin therapy • Ensure patients understand that insulin is not a punishment or an indication of failure • Explain that starting insulin at the right time will benefit their glycaemic control, and slow disease progression and its complications
Insulin causes complications and death	• Acknowledge the patient's fear • Sharing experiences from the clinician's point of view will be helpful • Provide information to counteract this belief. • Discuss and ensure the patient understands that insulin does not mean their health is deteriorating and it is an effective step to prevent the progression of T2DM and its complications
Insulin injections are painful	• Explain the benefits of using pen/injection devices • Demonstrate the insulin subcutaneous injection technique with a practice pen and highlight the injection sites • Let the patient try a test injection/placebo injection to experience the needle prick
Fear of hypoglycaemia	• Reassure the patient by sharing the strategies to prevent, recognise and manage hypoglycaemia to avoid severe hypoglycaemic episodes • Basal insulins have minimal risks
Perception that insulin regimes are inconvenient and impact social life; treatment restricts independence and concern about injecting in public areas	• Provide the patient information and discuss about insulin and the pen • Information to share and discuss should include: → Modern injection devices (insulin pens) are convenient, discreet and simple to use → Insulin can fit in with daily life → Selection of insulin types and regimens with maximum flexibility

Possible barriers	Suggested solutions and issues for patient discussion
Insulin is not effective	• Inform the patient that diabetes is an insulin-related problem, and the insulin used is very similar to that produced naturally • Offer a 3-month trial to get the patient used to the idea • Once patients try insulin they rarely want to change because it is successful
Fear of weight gain	• Inform that patient that lifestyle interventions with appropriate diet and exercise will continue to be important aspects • Refer the patient to a dietician to discuss strategies for preventing weight gain
Lack of confidence, finances, resources, and psychosocial support	• Refer the patient to diabetic care programs and a support group • Provide the patient access to a Diabetes Resource Centre or Diabetes Medication Therapy Adherence Clinic (DMTAC) that provides counselling and guidance from diabetes educators or pharmacists • Provide patient with guide tools on insulin therapy and diabetes self-care

*Resource relates to resource in diabetes care, e.g., knowledge, skills and guidance.

Table 3-2 Healthcare provider barriers to insulin therapy and suggested solutions[22,23]

Possible barriers	Suggested solutions
Lack of resources (drug costs, staff, skills) **Time constraints**	• Networking between diabetes educators, pharmacists and diabetes support groups
Lack of familiarity/ experience prescribing insulin **Concerns about efficacy**	• Continuous training and education via Continuous Medical Education events and workshops on new insulin therapy options and guidelines updates
Complex clinical tools/ algorithm	• Development and implementation of comprehensive algorithms for optimisation and intensification of insulin therapy
Concerns about adverse events (e.g., hypoglycaemia, weight gain, patient's quality of life)	• Arrange for timely patient follow-up to ensure patient adherence and identify and resolve potential difficulties and challenges
Concerns about the patient's ability for self-care and non-compliance to treatment **A lack of patient education tools**	• Providing comprehensive and effective patient education tools

Section 4
Insulin Types and Regimens

4.1 Insulin preparations

Insulin formulations have advanced from its beginnings of using animal sources (e.g., porcine and bovine sources) to human insulins engineered using DNA recombinant technology followed by insulin analogues that closely mimic human physiologic insulin.

More recently, biosimilar insulins have been introduced to the market. These are manufactured in living organisms such as yeast and bacteria, and have a close resemblance to their originator insulin.[24]

All these insulin formulations are available in Malaysia and are classified according to their pharmacokinetic properties (Table 4-1).

- **Bolus insulin** – administered pre-meal due to its short or rapid onset of action. It is used to control the post-meal glucose excursion and can be used with an insulin pump
- **Basal insulin** – administered once or twice daily due to its intermediate or long-acting profile. It covers the basal insulin requirements between meals and overnight secondary to endogenous hepatic glucose production
- **Premixed insulin** – biphasic insulin incorporating a combination of short or rapid-acting insulin with its intermediate-acting counterpart into a single formulation. It covers both post-prandial glucose excursions as well as basal insulin requirements simultaneously (Table 4-2)
- **Co-formulations** – a combination of two types of insulin or an insulin with a glucagon-like peptide-1 receptor analogue (GLP1-RA) such as:
  - → Insulin Degludec-Aspart (iDegAsp) – a combination of a rapid acting (insulin aspart) and an ultra-long-acting (insulin degludec) insulin in a single formulation, which can be injected once a day. It is given at the main meal(s) of the day and provides both bolus and basal insulin coverage
  - → Insulin glargine/lixisenatide – a combination of a long-acting insulin and a GLP1-RA in a single formulation. Insulin glargine provides the basal insulin while lixisenatide stimulates endogenous insulin secretion, and can be injected once a day by patients within an hour before their meal

Table 4-1 Insulin preparations available in Malaysia

Insulin type	Conventional	Analogue Brand (Generic)
Bolus	Short-acting regular human insulin • Actrapid® • Insugen R®*	Rapid-acting • NovoRapid® (insulin aspart) • Humalog® (insulin lispro) • Apidra® (insulin glulisine) Faster rapid acting insulin • FiAsp® (insulin aspart)
Basal	Intermediate-acting or NPH insulin • Insulatard® • Insugen N®*	Long-acting insulin • Lantus®/Lantus® SoloStar® (U-100 insulin glargine) • Basalog One®* (rDNA insulin glargine) • Toujeo® SoloStar® (U-300 insulin glargine) • Levemir® (insulin detemir) Ultra-long-acting insulin • Tresiba® (insulin degludec)
Premixed	Combination of short & intermediate-acting insulin: 30% regular insulin + 70% NPH • Mixtard® 30 • Insugen® 30/70*	Combination of rapid-acting analogue & protaminated insulin • NovoMix® 30 (30% aspart + 70% aspart protamine) • Humalog® Mix25™ (25% insulin lispro + 75% insulin lispro protamine) • Humalog® Mix50™* (50% insulin lispro + 50% insulin lispro protamine)
Co-formulation		Combination of rapid-acting & long-acting insulin • Ryzodeg® (30% insulin aspart + 70% insulin degludec; iDegAsp) Combination of a long-acting insulin and a GLP1-RA • Soliqua™ (insulin glargine + lixisenatide)

*Biosimilar insulin.
GLP1-RA, glucagon-like peptide 1 receptor agonist; NPH, neutral protaminated Hagedorn; rDNA, recombinant DNA.

Table 4-2 Pharmacokinetic profiles of various types of insulin[25,26]

Brand (generic) name	Onset	Peak (H)	Duration (H)	Timing of insulin
Short-acting, regular				
• Actrapid®**	30 min	1.5-3.5	8	30 min before meals
• Insugen R®**	30 min	2-4	6-8	
Rapid-acting analogue				
• NovoRapid® (insulin aspart)**	10-20 min	1-3	3-5	5 -15 min before or immediately after meals
• Humalog® (insulin lispro)**	0-15 min	1	3.5-4.5	
• Apidra® (insulin glulisine)**	5-15 min	1-2	3-5	
Faster rapid-acting				
• FiAsp® (insulin aspart)	5 min	0.5	3-4	At the start of the meal or within 20 min of meal
Intermediate-acting, NPH				
• Insulatard®**	1.5 H	4-12	18-23	Pre-breakfast / Pre-bed
• Insugen N®**	1 H	4-10	16-18	
Long-acting analogue				
• Lantus®/Lantus® SoloStar® (U-100 insulin glargine)**	2-4 H	Peakless for all	20-24	Same time every day at any time of the day
• Basalog One® (rDNA insulin glargine)**	2-4 H		30	
• Toujeo® SoloStar™ (U-300 insulin glargine)**	1 H		17-23	
• Levemir® (insulin detemir)**	1-2 H		16-24	
Ultra-long-acting analogue				
• Tresiba® (insulin degludec)	30-90 min	Peakless	42	Same time every day at any time of the day
Premixed human (30% regular insulin+70% NPH)				
• Mixtard® 30**	30 min	Dual	18-23	30 min before meals
• Humulin® 30/70* *	30 min	Dual	16-18	

Brand (generic) name	Onset	Peak (H)	Duration (H)	Timing of insulin
Premixed analogue				
• NovoMix® 30 (30% aspart + 70% aspart protamine)**	10-20 min	Dual	18-23	5-15 min before meals
• Humalog® Mix25™ (25% insulin lispro + 75% insulin lispro protamine)**	0-15 min	Dual	16-18	
• Humalog® Mix50™* (50% insulin lispro + 50% insulin lispro protamine)**	0-15 min	Dual	16-18	
Co-formulation				
• Ryzodeg® (30% insulin aspart + 70% insulin degludec; iDegAsp)**	9-14 min	0.5-1.5	>24	5-15 min before the main meal/s
• Soliqua™ (insulin glargine + lixisenatide)	2 H	3.5	20-24	Within 1 H before meal

**Available in the Ministry of Health setting.
H, hours; min, minutes; NPH, neutral protaminated Hagedorn; rDNA, recombinant DNA.

Note:
- The time course of action of any insulin may vary depending on the individual or at different times or injection sites in the same individual
- Due to such variations, the time periods described above should only be used as general guidelines
- Although short- and intermediate-acting insulins can be self-mixed as an alternative to the human premixed insulin, this is not encouraged due to the significant reduction in the reproducibility of insulin action

4.2 Comparison of conventional insulin and insulin analogues

Insulin analogues are derived from human insulin in which the amino acid sequence is intentionally altered to produce an improved pharmacokinetic profile mimicking physiological insulin secretion.

- **Bolus analogue** mimics the first phase of insulin secretion in response to a meal
- **Basal analogue** mimics the physiological basal insulin secretion in between meals and overnight
- **Premixed analogue** consists of both rapid- and intermediate-acting insulin analogues and were developed to closely mimic physiological endogenous insulin secretion. Premixed analogues meet the needs of patients who require basal and bolus insulin, but wish to limit the number of daily injections

The differences between bolus, basal and premixed analogues, and human insulin are summarised in Table 4.3.

Table 4-3 Comparisons of conventional and analogue insulin[27-29]

Characteristics	Conventional	Analogue
Bolus Insulin		
Onset	Delayed	Immediate
Administration	30 min before meals	With meals
Post-prandial glycaemic control	+	++
Inter-meal hypoglycaemia	++	+
Inter-meal hyperglycaemia	+	++
Dosing flexibility	+	++
Pharmacokinetics	Less physiological	More physiological
Cost	Lower	Higher
Basal Insulin		
Duration	< 24 H	~24 H
Peak	Pronounced	Absent/minimal
Nocturnal hypoglycaemia	++	+
Absorption	Variable	Reproducible
Weight gain	++	+/- (insulin detemir)
Pharmacokinetics	Less physiological	More physiological
Cost	Lower	Higher
Premixed Insulin		
Administration	30 min before meals	With meals
Post-prandial glycaemic control	+	++
Inter-meal hypoglycaemia	++	+
Dosing flexibility	+	++
Dosing interval	Once or twice daily	Once to thrice daily
Pharmacokinetics	Less physiological	More physiological
Cost	Lower	Higher

H, hour; min, minutes.

The different types of insulin analogue therapy may be considered for certain situations.

Rapid-acting analogues

- Patients with delayed inter-meal hypoglycaemia prohibiting achievement of post-prandial glycaemic targets when treated with regular short-acting insulin
- Patients with lifestyle restrictions, e.g., a job schedule that might not allow the patient to eat immediately after an insulin injection
- Patients who have variable carbohydrate intake

Long-acting analogue

- Patients with nocturnal hypoglycaemia on intermediate-acting insulin (NPH) prohibiting achievement of target fasting plasma glucose (FPG)
- Patients with inadequate basal insulin coverage with a once-daily intermediate-acting insulin (NPH) who are unwilling to use NPH twice daily

Co-formulation

- Patients with difficulty adhering to multiple daily injections are suitable for the once daily iDegAsp
- iDegAsp can be used for patients with nocturnal hypoglycaemia as the risk of hypoglycaemia is significantly lower
- Insulin glargine/lixisenatide is suitable for patients with obesity and overweight who require basal insulin and when weight loss is intended

4.3 Insulin regimens

An ideal insulin regimen should mimic the physiological insulin response to meals and endogenous hepatic glucose production. The various types of insulin regimens are classified in Table 4.4.

The choice of insulin regimen should be individualised based on the patient's glycaemic profile, dietary pattern, personal lifestyle and desired flexibility.

Table 4-4 Insulin regimens and frequency of injections per day

No. of injections per day	Insulin regimen	Type of insulin and timing
1	**Basal**	Intermediate-acting (NPH) insulin: Pre-bed
	Basal	Long-acting or ultra-long-acting analogue: Once daily
	Premixed OD	Premixed/premixed analogue: Pre-dinner
	Co-formulation	iDegAsp: Once daily at the main meal Insulin glargine/lixisenatide: Once daily within 1 hour before meal
2	**Basal**	Intermediate acting (NPH): Pre-breakfast and pre-dinner
	Premixed BD	Premixed insulin: Pre-breakfast and pre-dinner
	Basal-plus (1)	Basal insulin: Pre-bed + 1 Bolus insulin
	Co-formulation	iDegAsp: Twice daily at two main meals
	Co-formulation plus (1)	iDegAsp: Once daily at the main meal Bolus insulin: 1 at the other meal Insulin glargine/lixisenatide: Once daily within 1 hour before meal Bolus insulin: 1 at the other meal

No. of injections per day	Insulin regimen	Type of insulin and timing
3	**Basal - plus (2)**	Basal insulin: Once daily Bolus insulin: Twice daily
	Bolus	Bolus insulin: 1 pre-breakfast + 1 pre-lunch + 1 pre-dinner
	Premixed TDS	Premixed analogue: 1 pre-breakfast + 1 pre-lunch + 1 pre-dinner
	Premixed - plus	Premixed insulin: 1 pre-breakfast + 1 pre-dinner Bolus insulin: 1 pre-lunch *OR* Premixed insulin:1 pre-dinner Bolus insulin: 1 pre-breakfast + 1 pre-lunch
	Co-formulation plus (2)	iDegAsp: Once daily at the main meal Bolus insulin: At two other meals Insulin glargine/lixisenatide: Once daily within 1 hour before meal Bolus insulin: At two other meals
4	**Basal – bolus**	Basal insulin: Once daily Bolus insulin: 1 pre-breakfast + 1 pre-lunch + 1 pre-dinner
5*	**Basal - bolus**	Intermediate acting (NPH) insulin: 1 pre-breakfast + 1 pre-dinner Bolus insulin: 1 pre-breakfast + 1 pre-lunch + 1 pre-dinner

*Only for selected cases.
BD, twice daily; iDegAsp, insulin deglutide aspart; NPH, neutral protaminated Hagedorn; OD, once daily; TDS, three times daily.

Apart from insulin pump therapy, basal bolus therapy using long-acting basal and rapid-acting analogue combinations offer the regimen that most closely mimics the endogenous insulin action at the expense of increased number of injections.

Section 5
Insulin Initiation and Optimisation

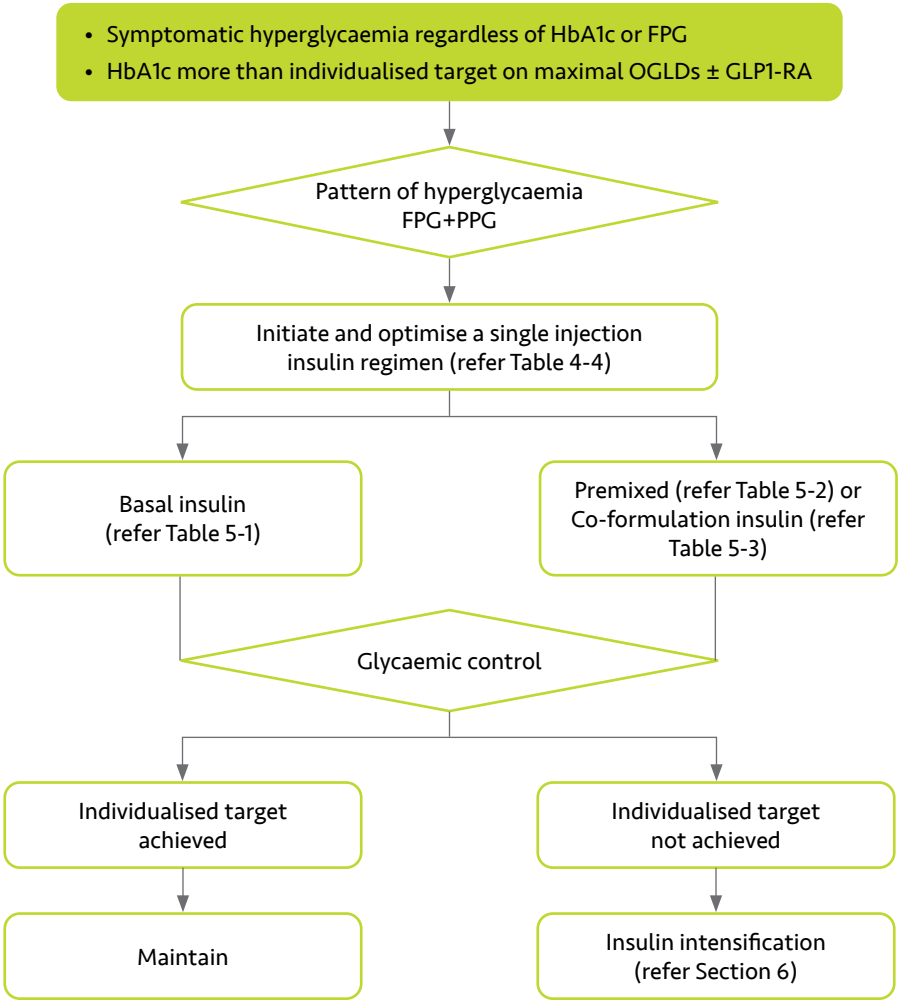
The choice of the insulin regimen should be individualised, based on the patient's glycaemic profile, dietary pattern and lifestyle.

Implementing a successful insulin therapy requires a 3-stage process:

- **Initiation** – starting insulin requires the selection of an appropriate insulin regimen, insulin type and starting dose, and can be done safely in the outpatient setting
- **Optimisation** – dose titration/adjustment requires a gradual, safe and prompt titration of insulin dose according to the patient's self-monitoring of blood glucose (SMBG)
  - → The dose adjustment should aim towards an optimal dose to ensure the maximum benefit from the prescribed insulin treatment
  - → Optimisation should be an interactive process between the healthcare provider and the patient, and should be done within the first few months of starting insulin
  - → This can be done at a diabetic resource centre either in-person or virtually
- **Intensification** – modification of an insulin regimen to achieve better glycaemic control requires switching to more intensive regimens

See Figure 5-1, algorithm for initiating and optimising insulin, and Section 6 for intensification of insulin.

Figure 5-1 Initiation and optimisation of insulin therapy



Algorithm for initiating and optimising insulin with a single injection insulin regimen (basal, premixed or co-formulation insulins) in insulin-naïve patients with T2DM. If glycaemia control on maximal OGLDS ± GLP1-RA and optimised single injection insulin does not achieve individualised target, insulin will need to be intensified (see Section 6). Details of initiating and optimising the single injection insulin regimen is detailed in the relevant tables. FPG, fasting plasma glucose; GLP1-RA, glucagon-like peptide 1 receptor agonist; OGLDS, oral glucose-lowering drugs; PPG, prandial plasma glucose.
Adapted from the Management of T2DM CPG, 6th edition, 2020.[30]

5.1 Basal insulin initiation and optimisation

Basal insulin is the most convenient initial insulin to be added into the type 2 diabetes mellitus (T2DM) treatment regimen. (Table 5.1)

- Basal insulin can be **initiated** at pre-bed using an intermediate- or long-acting insulin at 10 units (U)/day or based on body weight at 0.1-0.2 U/kg/day
- For patients with a risk of hypoglycaemia, such as the elderly, patients who are lean or those with milder (lower) fasting hyperglycaemia, a lower starting dose should be considered
- Basal insulin **optimisation** can be done by titrating the insulin dose based on the pre-breakfast plasma glucose readings (Table 5.2)
- Dose adjustments should be done after 3-7 days of initiating the last dose, with at least 3 consecutive readings, to achieve the individualised target fasting plasma glucose (FPG) without hypoglycaemia

Table 5-1 Initiating and optimising basal insulin[16,22]

Treatment	Insulin dose	
Initiation	• **10 U** or **0.1-0.2 U/kg** at bedtime of a NPH or at any time of the day for a basal insulin analogue	
Monitoring & targets	• Monitor pre-breakfast plasma glucose • Target pre-breakfast plasma glucose is at 4.4-7.0 mmol/L in most patients, based on individual patient's profile (Table 5.2)	
Optimisation	• Adjust insulin doses every 3-7 days after 3 consecutive plasma glucose readings • Example for target plasma glucose range 4.4-7.0 mmol/L:	
	• **<4.4 mmol/L** (>1 of 3 readings) • **4.4-7.0 mmol/L** (all 3 readings) • **>7.0 mmol/L** (>1 of 3 readings and no hypoglycaemic episodes)	• Reduce the dose by 2 U or 10-20% • Maintain current dose • Increase the dose by 2 U or 10-20%
Optimal dose	• Lean patients • Most patients • Obese patients	• 0.2-0.3 U/kg • 0.4-0.5 U/kg • Up to 0.7 U/kg
Caution	• Watch for nocturnal hypoglycaemia • If hypoglycaemia is the limiting factor to achieve optimum dose, conventional intermediate-acting insulin (NPH) may be switched to basal insulin analogue • If glycaemic target is not achieved after optimisation of NPH dose, consider converting to twice daily NPH regimen	

NPH, neutral protaminated Hegedorn.

5.2 Premixed insulin initiation and optimisation

Premixed insulin may be initiated,

- Once daily, usually as a pre-dinner dose,[31] or
- 2 times daily as pre-breakfast and pre-dinner doses

Premixed insulin once daily

The initial dose for a once daily premixed insulin is usually **10 U or 0.2 U/kg**.

- Human premixed insulin is usually administered as a pre-dinner dose
- Analogue premixed insulins can be initiated during the biggest meal of the day, which is usually the evening meal (pre-dinner dose)[31]

Patients should be advised to perform SMBG before breakfast.

- Titration is based on 3 consecutive plasma glucose readings, similar to titrating intermediate/basal insulin
- The premixed insulin dose should be adjusted once or 2 times weekly to get the monitored readings to target

For **optimising pre-dinner** premixed insulin,[32]

- If >1 of the 3 pre-breakfast plasma glucose is <4.4 mmol/L, the pre-dinner dose should be reduced by 2 U or 10-15% of the current dose
- If all 3 pre-breakfast plasma glucose are within the targets of 4.4-7.0 mmol/L, the pre-dinner dose can be maintained
- If >1 pre-breakfast plasma glucose is >7.0 mmol/L without any hypoglycaemia episodes, the pre-dinner dose may be increased by 2 U or 10-15% of the current dose

Premixed insulin twice daily

The initial dose for 2 times daily premixed insulin is usually **10 U or 0.2 U/kg twice daily** administered at pre-breakfast and pre-dinner.

Patients should be advised to perform SMBG at pre-breakfast and pre-dinner.

- Titration is based on 3 consecutive reading of plasma glucose, similar to titrating intermediate/basal insulin
- The premixed insulin dose should be adjusted once or 2 times weekly to get the monitored readings to target

For **optimising pre-breakfast** premixed insulin,[32]

- If >1 of the 3 pre-dinner plasma glucose is <4.4 mmol/L, the pre-breakfast dose should be reduced by 2 U or 10-15% of the current dose
- If all 3 pre-dinner plasma glucose are within the target of 4.4-7.0 mmol/L, the pre-breakfast dose can be maintained
- If >1 pre-dinner plasma glucose is >7.0 mmol/L without any hypoglycaemia episodes, the pre-breakfast dose may be increased by 2 U or 10-15% of the current dose

For **optimising pre-dinner** premixed insulin,[32]

- If >1 of the 3 pre-breakfast plasma glucose is <4.4 mmol/L, the pre-dinner dose should be reduced by 2 U or 10-15% of the current dose
- If all 3 pre-breakfast plasma glucose are within the targets of 4.4-7.0 mmol/L, the pre-dinner dose can be maintained
- If >1 pre-breakfast plasma glucose is >7.0 mmol/L without any hypoglycaemia episodes, the pre-dinner dose may be increased by 2 U or 10-15% of the current dose

Table 5-2. Initiating and optimising insulin with premixed insulin

Treatment	Dose
Initiation	**Once daily: 10 U or 0.2 U/kg at** • Pre-dinner for human premixed insulin • The biggest meal is usually the evening meal for analogue premixed insulin **Twice daily: 10 U or 0.2 U/kg at pre-breakfast and pre-dinner** • For patients with a higher risk of hypoglycaemia – 0.1 U/kg
Monitoring & targets	**Once daily** : Monitor pre-breakfast plasma glucose **Twice daily** : Monitor pre-breakfast and pre-dinner plasma glucose • Target pre-meal plasma glucose is at 4.4 -7.0 mmol/L in most patients - target range based on individual patient's profile
Optimisation	Adjust insulin doses after 3 consecutive plasma glucose values obtained (every 3-7 days) • Pre-breakfast plasma glucose determines pre-dinner premixed dose adjustment • Pre-dinner plasma glucose determines pre-breakfast premixed dose adjustment • **< 4.4 mmol/L** (>1 value) → • Reduce dose by 2 U or 10-15% • **4.4-7.0 mmol/L** (all values) → • Maintain current dose • **>7.0 mmol/L** (>1 value with no hypoglycaemia) → • Increase dose by 2 U or 10-15%
Optimal dose	Total daily dose of 0.5-1.0 U/kg in most patients For patients who are obese and insulin resistant patients: >1.0 U/kg/day
Caution	• Watch for in between meal hypoglycaemia. If hypoglycaemia is the limiting factor to achieve optimum dose, conventional premixed insulin may be switched to premixed analogue • Continue metformin if no contraindication • Stop sulphonylurea (SU) once started on 2 times daily premixed insulin

5.3 Initiating and optimising co-formulation insulin

Insulin degludec-aspart (iDegAsp)

iDegAsp can be initiated,

- Once daily in combination with oral glucose-lowering drugs (OGLDs)/bolus insulin
- 2 times daily

iDegAsp once daily

The initial dose for once daily iDegAsp is usually 10 U administered with the main meal. Patients should be advised to perform SMBG at pre-breakfast.

- Titration is based on a single pre-breakfast reading of plasma glucose once weekly[33]
- The target pre-breakfast reading should be individualised but based on real-world experience, the recommended target is 4.0-7.0 mmol/L[34]

For optimising iDegAsp daily insulin,

- If the weekly pre-breakfast plasma glucose is <4.0 mmol/L, reduce the iDegAsp dose by 2 U
- If the weekly pre-breakfast plasma glucose is within the targets of 4.0-7.0 mmol/L, maintain the current iDegAsp dose
- If the weekly pre-breakfast plasma glucose is >7 mmol/L without any hypoglycaemia, the iDegAsp dose may be increased by 2 U

iDegAsp twice daily

iDegAsp twice daily can be considered at initiation if there is a presence of post-prandial hyperglycaemia at ≥2 main meals.[35]

- The initial dose for iDegAsp 2 times daily for insulin-naïve patient is 6 U administered with the 2 main meals[36] – at least 4 hours between each dose to avoid stacking of the short-acting insulin component[37]

Table 5-3. Initiating and optimising with iDegAsp

Treatment	Dose
Initiation	**Daily iDegAsp:** 10 U daily with the main meal **Twice daily iDegAsp:** 6 U administered with 2 main meals (insulin-naïve).
Monitoring & targets	• Monitor pre-breakfast plasma glucose weekly • Target pre- breakfast plasma glucose in general is 4.4-7.0 mmol/L (target range based on individual patient's profile) For twice daily dosing, consider adjusting one dose at a time • Pre-breakfast/lunch iDegAsp dose: adjust based on weekly pre-dinner plasma glucose value • Pre-dinner iDegAsp dose: adjust based on weekly pre-breakfast plasma glucose value
Optimisation	Adjust insulin doses based on weekly pre-breakfast plasma glucose reading • **<4.4 mmol/L** → Reduce the dose by 2 U • **4.4-7.0 mmol/L** → Maintain current dose • **>7.0 mmol/L** → Increase the dose by 2 U
Optimal dose	The maximum dose of SC iDegAsp is limited by insulin Asp dose required by a particular meal by the patient as well as the FPG reading[34]
Caution	• In patients started with daily iDegAsp, current SU may need to be discontinued or the dose reduced • In patients started with twice daily iDegAsp, current SU should be discontinued[35]

FPG, fasting plasma glucose; SC, subcutaneous; SU, sulphonylurea.

Fixed-ratio combination of glucagon-like peptide 1 receptor agonist (GLP1-RA) and basal insulin analogue

Fixed-ratio combination insulin glargine 100 U and lixisenatide (Soliqua™) is available in 2 pens with different dose range options.[38]

- Soliqua™ Solostar® 10-40 U pen (insulin glargine 100 U and lixisenatide 50 mcg/ml)
- Soliqua™ Solostar® 30-60 U pen (insulin glargine 100 U and lixisenatide 33 mcg/ml)

Insulin glargine 100 U and lixisenatide can be initiated once daily within 1 hour before any meal, preferably before the same meal every day.

Table 5-4. Initiating and optimising with insulin glargine 100 U and lixisenatide

Treatment	Dose	
Initiation	**The initiation dose is based on previous glucose-lowering drugs**	
	• On OGLD (insulin-naïve) • On insulin glargine >20-30 U • On insulin glargine >30 U	• 10 dose steps (Soliqua™ Solostar® 10-40 pen) • 20 dose steps (Soliqua™ Solostar® 10-40 pen) • 30 dose steps (Soliqua™ Solostar® 30-60 pen)
	If a different basal insulin was used	
	• For twice daily basal insulin or insulin Glargine U300 • For any other basal insulin	• The current total daily dose should be reduced by 20% • Use the same rule as for insulin Glargine U100
Monitoring and targets	• Monitor pre-breakfast plasma glucose weekly • Target pre-meal plasma glucose in general is 4.4-5.6 mmol/L (target range based on individual patient's profile)	
Optimisation	Adjust insulin doses based on pre-breakfast plasma glucose reading (weekly titration)	
	• **< 3.3 mmol/L** or occurrence of >2 symptomatic hypoglycaemic or 1 severe hypoglycaemia in the preceding week • **3.3-4.4 mmol/L** • **4.4-5.6 mmol/L** • **5.6-7.8 mmol/L** • **>7.8 mmol/L**	• Reduce the dose by 4 U • Reduce the dose by 2 U • Maintain the current dose • Increase the dose by 2 U • Increase the dose by 4 U
Optimal dose	• For Soliqua™ Solostar® 10-40 pen the dose maybe titrated up to 40 dose steps • For doses >40 dose steps/day, titration must be continued with Soliqua™ Solostar® 30-60 pen • For Soliqua™ Solostar® 30-60 pen, the dose maybe titrated up to 60 dose steps • The maximum daily dose is 60 units Insulin Glargine and 20 mcg Lixisenatide corresponding to 60 dose steps	

Treatment	Dose
Caution	• GLP1-RA is associated with gastrointestinal side effects such as nausea, diarrhoea and vomiting • Basal insulin and other OGLDs like DPP4-inhibitor should be discontinued upon initiation of insulin glargine 100 U and lixisenatide • Not recommended in patient with severe renal impairment and end-stage kidney disease

DPP4, dipeptidyl peptidase 4; GLP1-RA, glucagon-like peptide 1 receptor agonist; OGLD, oral glucose-lowering drug.

Section 6
Insulin Intensification

Insulin therapy needs to be a dynamic process that addresses the progressive insulin deficiency experienced in type 2 diabetes mellitus (T2DM). With longer durations of T2DM, fasting and post-prandial hyperglycaemia increase as a result of progressive pancreatic beta-cell failure.

Over time, the use of a single insulin regimen might not ensure a durable glycaemic control despite optimising insulin doses.

- Many patients are maintained on an inadequate regimen for too long resulting in sub-optimal glycaemic control

Insulin intensification is indicated for patients with T2DM who cannot achieve their individualised glycaemic targets (HbA1c and/or fasting plasma glucose [FPG]) even with optimised single injection insulin regimen (basal, premixed or co-formulation) and maximised other glucose-lowering drugs (GLDs), including glucagon-like peptide-1 receptor agonists (GLP1-RA).

Intensification enables modifying insulin regimens with additional injections or switching to different insulin types for achieving better glycaemic control. Insulin intensification can be done in many ways[32,39] depending on the:

- Pre-existing insulin regimen
- Abnormal glycaemic pattern
- Patient's acceptance
- Patient's lifestyle

Key elements for successful insulin intensification

- Patient education
- A dedicated diabetes team comprising of a diabetes educator, pharmacist and dietician
- Starting self-monitoring of blood glucose (SMBG)
- Access for patients to have frequent contact with their healthcare team
- Access to support groups

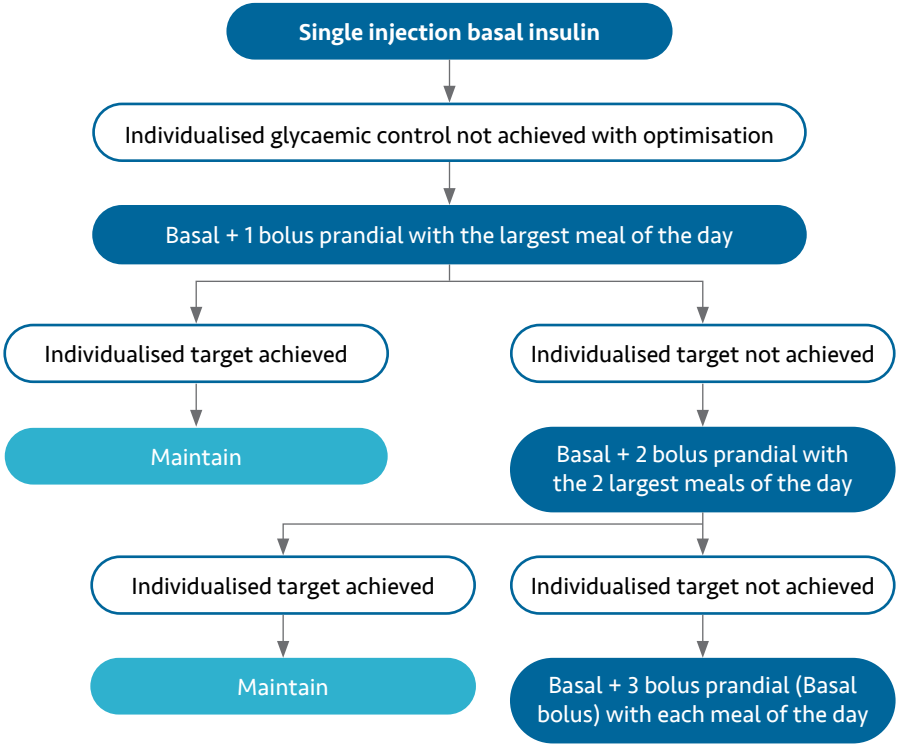
6.1 Basal insulin intensification

Basal insulin intensification should be considered if the patient's individualised glycaemic targets with the single injection basal insulin regimen are not achieved (Figure 6-1 and Table 6-1)

- Optimisation of the single injection basal insulin regimen should include optimisation of other GLDs, including GLP1-RAs
- Intensification of basal insulin should be done gradually, i.e., progressing in a step-wise manner from the single injection regimen to multiple injections

In addition, basal insulin can be intensified by other ways, such as switching to a co-formulation (initiated with a once daily dose with the largest meal).

Figure 6-1 Insulin intensification of basal regimen



Individualised target based on HbA1c or blood/plasma glucose (refer section 8).

Switching from basal to basal plus-bolus regimen

Indication:
Patients on combination oral glucose-lowering drugs (OGLDs) and basal insulin not achieving HbA1c targets despite optimal FPG, the addition of bolus insulin to address post-prandial hyperglycaemia will help to improve overall control.

Steps:

- Add bolus insulin prior to the largest meal of the day or to address the highest post-prandial plasma glucose of the day
- Additional bolus insulin can be added prior to other meals to address the post-prandial hyperglycaemia (Figure 6-1)
- Intensifying the basal-plus regimen by the sequential addition of bolus insulin, will ultimately lead to a basal-bolus regimen

Table 6-1. Intensification from basal to basal-plus/bolus regimens

Steps	Method
Intensification	
From single injection basal insulin regimen to basal + 1 bolus	• Add a bolus pre-meal (bolus) insulin before the largest meal of the day and optimise the dose
From basal + 1 bolus insulin regimen to basal + 2 bolus	• If HbA1c is above the individualised target, add a 2nd bolus pre-meal (bolus) insulin before the 2nd largest meal of the day, and optimise the dose
From basal + 2 bolus to basal + 3 bolus (basal bolus)	• If HbA1c is above the individualised target, add a 3rd bolus pre-meal (bolus) insulin and optimise the dose; 1 bolus insulin injection per main meal of the day
Dose	
Initiate each bolus insulin dose	• 6 U or 0.1 U/kg per dose

Steps	Method
Titration	
Optimise each bolus dose	• Increase 1-2 U or 10-15% of basal dose every 3 days or 2-times per week until individualised SMBG targets are achieved • If hypoglycaemia occurs, identify the cause. If there is no cause, reduce the bolus insulin by 2-4 U or 10-20% of the basal dose • Dose optimisation should be done in a timely manner based on assessing treatment response every 3-6 months. Further intensification should be done if glycaemic control is not achieved
Caution	
• Discontinue SU when bolus insulin is started • Continue metformin	

SMBG, self-monitoring of blood glucose; SU, sulphonylurea.

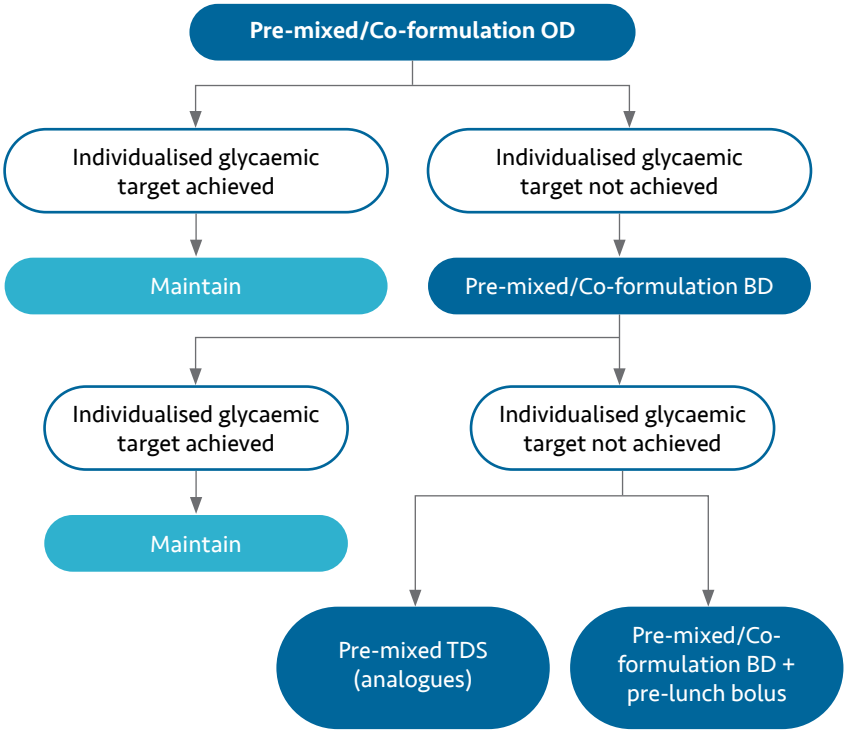
6.2 Premixed insulin intensification

Premixed/co-formulation insulin regimens can be intensified by any one of these methods (Figure 6-2 and Table 6-2):

- Additional injections of premixed insulin (twice or three times daily) or co-formulation insulin (twice daily)
- Adding a pre-meal rapid- or short-acting bolus insulin at lunch to twice daily premixed/co-formulation insulins

Some patients who cannot achieve individualised targets with premixed or co-formulation optimisation and intensification with a pre-lunch bolus insulin, may be considered for basal bolus insulin therapy.

Figure 6-2. Intensifying premixed/co-formulation insulin regimens[30]



Individualised target based on HbA1c or blood/plasma glucose (refer section 8).
BD, twice daily; OD, once daily; TDS, three-times daily.

Additional injections of premixed insulin

- For those on a single dose of conventional premixed insulin, usually prior to the evening meal, one additional premixed insulin dose may be initiated before the morning meal
- For those receiving premixed analogue insulin, additional doses may be initiated at both morning and mid-day meals, sequentially or simultaneously

Note: It is not usual to administer conventional premixed insulin more than twice daily due to the concern of between meal hypoglycaemias.

Table 6-2. Intensification of premixed/co-formulation insulin regimens[40]

Steps	Method
Intensification	
From premixed/co-formulation OD to premixed/co-formulation BD	• Calculate total daily dose using 0.5 U/kg/day or do a total dose transfer from the OD regimen • Split the dose 50:50 pre-breakfast and pre-dinner or consider different ratios depending on the meal sizes • Titrate the insulin dose to achieve target FPG and pre-dinner plasma glucose Example: 60 kg patient on 0.5 U/kg/day = 30 U insulin/day 30 U insulin/day split 50:50 for pre-breakfast (15 U) and pre-dinner (15 U) doses
For premixed/co-formulation BD to premixed/co-formulation BD + pre-lunch bolus OR From premixed BD to premixed TDS (analogues)	• Add bolus/premixed analogue 6 U or 0.1 U/kg per dose • Titrate the dose once or twice a week to the next pre-bolus individualised target • Down titrating the morning dose by 2-4 U may be needed after adding the lunch dose Example: If individualised glycaemic targets pre-dinner is not achieved with premixed BD, add pre-lunch 6 U bolus/ premixed analogue insulin and titrate according to pre-dinner SMBG
Titration	
Optimise each dose	• Dose optimisation should be done in a timely manner based on assessing treatment response every 3-6 months. Further intensification should be done if glycaemic control is not achieved • Consider premixed analogues if hypoglycaemias
Caution	
• Continue metformin	

BD, twice daily; FPG, fasting plasma glucose; OD, once daily; SMBG, self-monitoring of blood glucose.

Switching from premixed regimen to a co-formulation

- Premixed insulin once daily (OD): Start with the same unit dose of insulin degludec-aspart (iDegAsp) 70/30 injection
- Premixed insulin twice daily (BD) + pre-lunch bolus insulin: Start iDegAsp 70/30 with the same unit dose and injection schedule of the twice daily premixed insulin and continue the short- or rapid-acting pre-lunch insulin at the same dose for the meals not covered by the co-formulation

Supplementary premeal bolus injections in addition to premixed insulin regimen

For patients already on a premixed daily regimen usually in combination with single or multiple OGLDs but not achieving plasma glucose and HbA1c targets despite optimising doses, initiation of additional pre-meal rapid- or short-acting insulin is an option for intensification (Table 6-3).

Table 6-3. Adding premeal bolus injections on top of premixed insulin[40]

Add bolus insulin 6 U or 0.1 U/kg at lunch:
- Titrate the dose daily to the pre-dinner plasma glucose target
- If subsequent pre-meal plasma glucose readings are
  - → **<4.4 mmol/L** – Reduce by 1 U
  - → **4.4 mmol/L – individualised target** – Maintain
  - → **> individualised target** – Add 1 U

Switching from premixed regimen to basal bolus

The basal-bolus insulin regimen can be complicated and requires close SMBG monitoring.

For patients on optimised dosing of a premixed insulin regimen (2- or 3-times daily) and not achieving HbA1c, another option for intensification would be switching to a basal-bolus regimen.

- It is appropriate for patients who require greater dose adjustment flexibility – it potentially allows for a pre-meal rapid/short-acting insulin to be adjusted individually, according to the plasma glucose level (correctional bolus) and the carbohydrate content of the meal

Table 6-4. Switching from premixed insulin to basal-bolus insulin[40,41]

Steps	Method
Switching from premixed insulin TDS to basal-bolus	• The basal dose is usually administered at bedtime with a conventional insulin, and the bolus (pre-meal) portion is divided by 3 to cover the 3 main meals • The pre-meal doses should consider the size of the meal, primarily the carbohydrate content of the meal
Dose	
Start at 0.5 U/kg/day or perform a total daily dose transfer	• Split the dose 50:50 for basal and bolus insulins • Divide the bolus dose for the 3 main meals • In certain circumstances, a smaller proportion of basal insulin may be used (25-40% of the total daily dose)
Titration	
Optimise each dose	• Fix the FPG to the individualised target using the basal insulin dose • Titrate the bolus dose once or twice a week to achieve FPG and pre-bolus goals • Dose optimisation should be done in a timely manner based on assessing treatment response every 3-6 months. Further intensification should be done if glycaemic control is not achieved Example: 60 kg patients on premixed insulin at 0.5 U/kg/day = 30 U TDS, split into 50:50 Basal insulin 15 U Bolus insulin 15 U over 3 meals – 5 U/meal
Caution	
• Discontinue SU when bolus insulin is started • Continue metformin	

FPG, fasting plasma glucose; SU, sulphonylurea; TDS, three times daily.

Important notes on insulin intensification

- Requiring a high dose of insulin (total daily dose [TDD] >1.5 U/kg-2.0 U/kg) should prompt a search for an underlying cause/secondary problem such as:
  - → Non-adherence
  - → Incorrect dosing
  - → Incorrect timing
  - → Incorrect injection technique (see Forum for Injection Technique Guidelines, Malaysia at: *http://mems.my/forum-for-injection-technique-malasyia-fit-my/*
  - → Occult infections
- In general, the TDD of bolus insulin should not be >50% of the TDD
- Patients should be encouraged to rotate their injection sites on the abdomen to prevent lipohypertrophy
- Insulin therapy may cause weight gain through improved conservation of ingested calories, defensive eating for fear of hypoglycaemia or a change in centralised appetite regulation
  - → This effect is exaggerated if an "unphysiological" dose of insulin is used
  - → Weight should be monitored – progressive weight gain should raise the suspicion of too much insulinisation
  - → Weight gain can be minimised by improving insulin sensitivity through diet, lifestyle measures or using other glucose-lowering drugs

Section 7
Insulin Deintensification

Treatment with insulin can impose a major burden to patients. Daily, multiple injections require frequent plasma glucose monitoring to appropriately adjust insulin doses. Hence, a complex insulin regimen might be inappropriate for individuals who cannot comply to the degree of monitoring and those who will not benefit from such tight glycaemic control. In addition, multiple daily insulin injections or inappropriately high insulin doses among patients who are at risk of hypoglycaemia and potentially suffering from the consequences of hypoglycaemia, could bring harm.

Insulin deintensification refers to the process of simplifying or completely withdrawing insulin in order to reduce the risk of adverse events and improve the quality of individualised care.

- Insulin deintensification may also be considered in well patients who have achieved good control following successful lifestyle modifications or with the addition of new non-insulin therapies such as glucagon-like peptide-1 receptor agonists (GLP1-RA) or sodium-glucose cotransporter protein-2 inhibitors (SGLT2-i)
- With these newer therapies, the conventional "one-way" management of type 2 diabetes mellitus (T2DM)* can be replaced by a "multi-lane" approach that could potentially support the de-escalation of more complex therapies at any junction, if control is better[42]
- Deintensification of glucose-lowering therapies among patients who are of advanced age, frail, having multiple comorbidities or limited life expectancy is seldom performed by healthcare providers, even when HbA1c levels are <6.5%[43-46]
- Additionally, the overzealous implementation of treatment guidelines for these patients may lead to overtreatment and undesirable outcomes[47]

* A "one-way" treatment approach of T2DM often involves intensification from lifestyle changes to addition of oral glucose-lowering drugs (OGLDs) and basal bolus insulin therapy.

Insulin deintensification should be **considered in the following patient groups** with T2DM

- Elderly patients with multiple comorbidities
- Patients with debilitating functional or cognitive impairment
- Patients with end-stage chronic illnesses and with limited life expectancy
- Well patients with improved or expected improvement of glycaemic control due to the addition of new non-insulin therapies or implementation of successful lifestyle practices
- Patients who are recovering from severe glucotoxicity
- Patients with suboptimal compliance to multidose insulin
- Patients with suspected reactive hyperglycaemia with persistently elevated HbA1c despite insulin dose escalation
- Patients who were never offered simple insulin regimens during insulin initiation

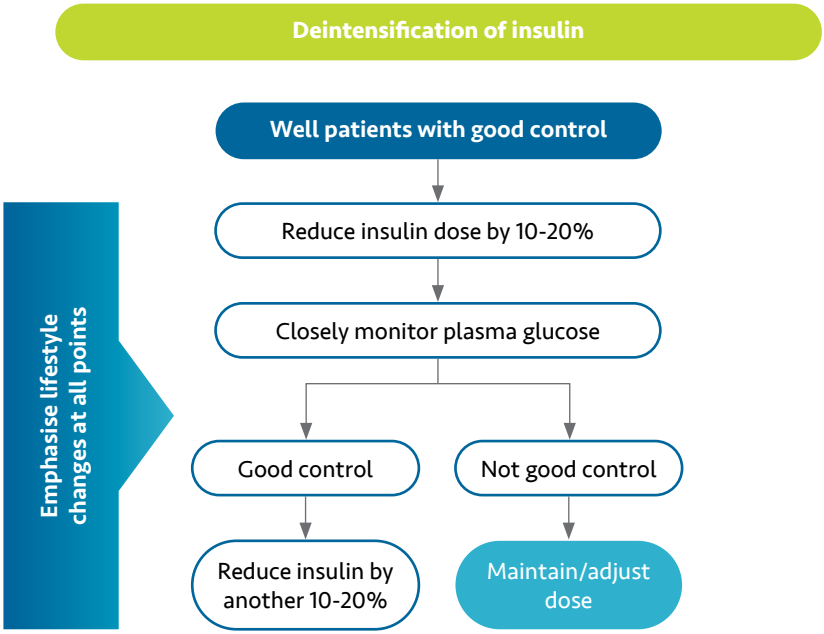
7.1 Deintensification of insulin in well patients

Well patients refer to patients with T2DM who are NOT elderly with multiple comorbidities, with debilitating function or cognitive impairment, or end-stage chronic illnesses and with limited life-expectancy.

Deintensification of insulin in well patients can be considered for (see Figure 7-1):

- Patients who have either achieved their target glycaemic control or are near-to-target, and are starting newer non-insulin glucose-lowering drugs (GLDs) such as GLP1-RA or SGLT2-i
  - → Insulin doses can be reduced by 10-20%
  - → Monitoring plasma glucose is essential
  - → Further insulin deintensification may be considered if glycaemic control is to target
- Patients who have adopted intensive lifestyle changes and achieve their glycaemic targets
  - → Insulin deintensification should be considered and eventually be withdrawn (refer Section 7.3)
  - → The addition of non-insulin therapies can also be considered to maintain their good control

Figure 7-1. Insulin deintensification for well patients



Individualised target based on HbA1c or blood/plasma glucose (refer Section 8).

7.2 Insulin deintensification in frail patients

"Frail patients" may include those who are of advanced age, physically frail, having multiple comorbidities or limited life expectancy.

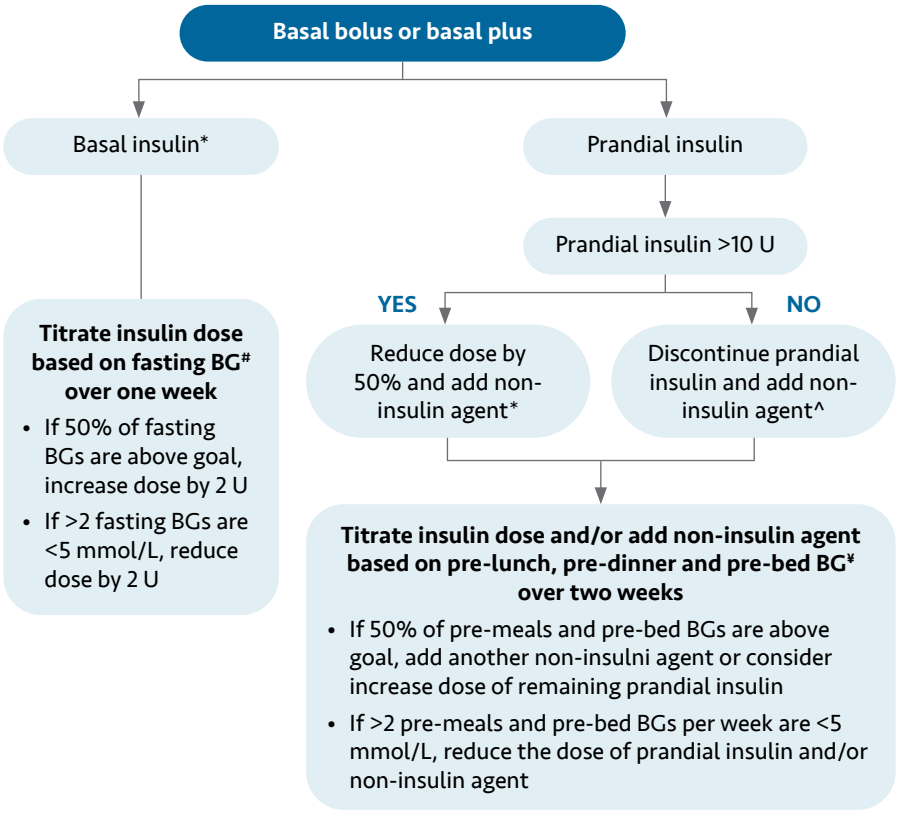
Deintensification from basal-bolus or basal-plus insulin regimen

See Figure 7-2

- For patients on >10 U of bolus insulin for a meal, reduce the dose by half for that particular mealtime
- Adding a non-insulin agent will aid in post-prandial control after bolus insulin dose reduction or discontinuation
- The choice of non-insulin agents will depend on compelling indications, renal function and tolerability (refer to the Management of T2DM Clinical Practice Guidelines, 6th edition, 2020)

- Following bolus insulin modification and adding of a non-insulin agent, monitor pre-lunch, pre-dinner and pre-bed plasma glucose over the next 2 weeks
- If half the plasma glucose readings are above target, increase the bolus insulin dose or add another non-insulin agent. Dose increase of the remaining bolus insulin can be considered if the hyperglycaemia persists despite optimising non-insulin agents
- If the plasma readings are <5 mmol/L, more than 2 times per week, reduce the dose of bolus insulin and/or non-insulin agents

Figure 7-2 Deintensification from basal bolus or basal plus insulin regimens



*Consider change to a long-acting insulin analogue or change timing from bedtime to morning if nocturnal hypoglycaemia is frequent. ^Non-insulin agent includes metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP1-RA and SGLT2-inhibitors. Use and dosage depend on compelling indications, renal function and tolerability. #Fasting goal: 5.0 - 8.5 mmol/L (may change according to overall health and goals of care). ¥Goal for pre-lunch, pre-dinner and pre-bed: 5.0 - 8.5 mmol/L (may change according to overall health and goals of care).
BG, blood glucose (plasma glucose).
Adapted from ADA 2021.[16]

Deintensification from premixed insulin regimen

Twice daily or three times daily premixed insulin dosing can be deintensified in the following ways (Figure 7-3):

- Using 70% of the total daily dose as basal insulin
- Add a non-insulin agent

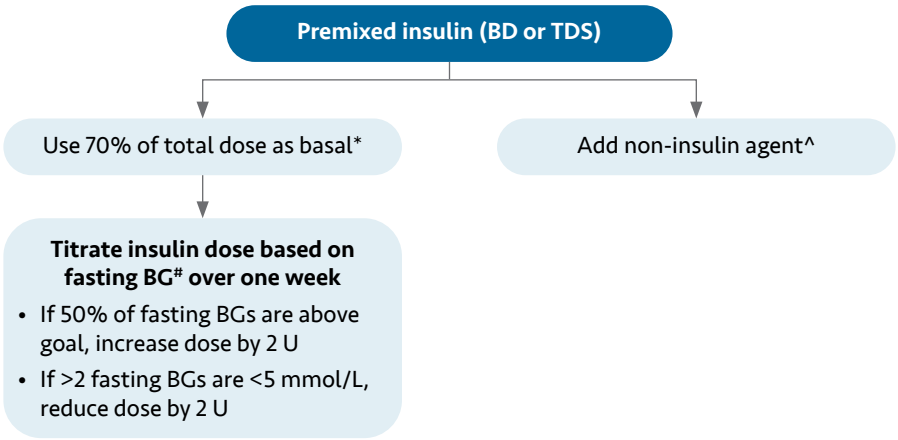
For patients with frequent nocturnal hypoglycaemia while on neutral protaminated Hagedorn (NPH) insulin at bedtime,

- Change the injection timing to the morning or switch to a long-acting insulin analogue
- Monitor fasting plasma glucose (FPG) over the next 1 week to guide dose titration
- If half the glucose readings are above target, increase the dose by 2 U
- If >2 readings are <5 mmol/L, reduce the dose

Adding a non-insulin agent replaces the short-acting or rapid-acting insulin component in premixed insulin.

- The choice of a non-insulin agent will depend on compelling indications, renal function and tolerability (refer to the Management of T2DM Clinical Practice Guidelines, 6th edition, 2020)[30]

Figure 7-3 Deintensification from premixed insulin regimen



*Consider change to a long-acting insulin analogue or change timing from bedtime to morning if nocturnal hypoglycaemia is frequent. ^Non-insulin agent includes metformin, DPP4-inhibitors, GLP-1RA and SGLT2 inhibitors. Use and dosage depend on compelling indications, renal function and tolerability. #Fasting goal: 5.0 – 8.5 mmol/L (may change according to overall health and goals of care).
BD, twice daily; BG, blood glucose (plasma glucose); TDS, three times daily.
Adapted from ADA 2021.[16]

7.3 Complete insulin withdrawal

Not all T2DM patients will require life-long insulin therapy. As insulin rapidly controls plasma glucose levels, it is useful in acute hyperglycaemic events such as diabetic ketoacidosis (DKA), hyperosmolar hyperglycaemic state (HHS) and significantly uncontrolled T2DM. Treating the precipitating factor resolves the glucotoxicity in acute hyperglycaemic events, and the subsequent lifestyle modifications and/or the addition of other non-insulin agents usually avoids the need to continue insulin therapy, provided the plasma glucose control is optimal.

In general, situations in which complete discontinuation of insulin therapy can be considered for patients with T2DM are when:

- Adequate glycaemic control is achieved
- Significant weight loss (≥15% of baseline body weight) through lifestyle modifications, pharmacological treatment and/or bariatric surgery is achieved
- Glycaemic control is maintained within target with ≥1 non-insulin agents
- Managing elderly patients with a poor health status*

*Poor health status is defined as any end-stage disease, including congestive heart failure stage III-IV, oxygen dependent, chronic kidney disease with haemodialysis, and metastatic cancer; moderate to severe cognitive impairment or ≥2 activity of daily living dependencies.[16]

Note:

Suspect and re-evaluate for over-insulinisation in the following patients on basal bolus insulin:

1. Persistently high blood glucose despite escalating prandial insulin dosing to >0.15-0.2 U/kg per dose.
2. Persistently high fasting blood glucose despite escalating basal insulin dosing to >0.5 U/kg per day.
3. Ratio of prandial to basal insulin dosing is way beyond the recommended 50:50 ratio.

Section 8
Targets and Monitoring

8.1 Glycaemic Targets

Achieving glycaemic targets is central to reducing diabetes-related complications as well as avoiding overtreatment. It has been widely recognised by now that glycaemic targets should be individualised to minimise the risk of hypoglycaemia.

Long-term follow-up of UKPDS and DCCT[11,48,49] cohorts suggests that patients with little comorbidity and a long-life expectancy may benefit from stringent glycaemic targets early in the disease.

Other studies[50,51] assessing macrovascular outcomes indicate that less stringent targets may be appropriate in the following situations in patients with:

- A history of severe hypoglycaemia
- A limited life expectancy
- Advanced microvascular or macrovascular complications
- Extensive comorbidities
- Long-standing diabetes where glycaemic control remains difficult despite optimising patient education, adherence and glucose-lowering drugs (GLDs) dosage

Table 8-1. Glycaemic targets

Glycaemic measures	Targets
Fasting or pre-bolus plasma glucose	4.4-7.0 mmol/L
Post-prandial plasma glucose	4.4-8.5 mmol/L*
HbA1c	< 7% for most**

*Measured at least 90 minutes after meals; **HbA1c ≤6.5% is advocated for patients with a shorter duration of T2DM, no evidence of significant cardiovascular (CV) disease and longer life expectancy, and have minimal risk of hypoglycaemia; 7.1%-8.0% is advocated for patients with advanced age, multiple comorbidities, history of severe hypoglycaemia or hypoglycaemia unawareness and short life expectancy.
Source: Management of T2DM CPG, 6th edition, 2020.[30]

Individualised targets for self-monitoring of blood glucose (SMBG) may be discussed and agreed upon after taking patient factors and limitations into consideration (Table 8-2).

Table 8-2. Individualised HbA1c targets

≤6.5 % (Tight)	6.6%-7.0%	7.1%-8.0% (Less tight)
• Newly and recently diagnosed* • Younger age • Healthier (long life expectancy, no CVD complications) • On medications that do not cause hypoglycaemia • Albuminuria - nil • Low risk of hypoglycaemia	All others	• Elderly patients • Presence of comorbidities: → advanced CVD → coronary artery disease → heart failure → advanced renal failure (eGFR <45 ml/min/1.73 m^2) → decompensated chronic liver disease → dementia → bed-bound e.g., stroke/other comorbidities • Prone to/experiencing severe hypoglycaemia • Hypoglycaemia unawareness • High risk of consequence of hypoglycaemia such as: → those at risk of falling, → those who drive or operate machinery. • Those unlikely to benefit from strict glycaemic control • Short life expectancy

CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; T2DM: type 2 diabetes mellitus. * Newly diagnosed is arbitrarily defined as T2DM <1-year duration and recently diagnosed is defined as T2DM duration of <5 years.
Source: Management of T2DM CPG, 6th edition, 2020.[30]

8.2 Monitoring insulin therapy

Techniques of monitoring insulin therapy include:

- Fasting plasma glucose (FPG)
- Glycosylated haemoglobin (HbA1c)
- Self-monitoring of blood glucose (SMBG)
- Continuous glucose monitoring (CGM)

Fasting Plasma Glucose (FPG)

Measurement of FPG is an established component of glycaemic monitoring in most outpatient settings. It is inexpensive and widely available. However, single-point glucose measurements may not accurately depict overall glycaemic control. This is important to bear in mind when making therapeutic decisions.

Glycosylated haemoglobin (HbA1c)

HbA1c levels reflect average glycaemic control over 2-3 months. This affords an advantage over single-point glucose measurements; however, it may not reflect glucose variability.

- HbA1c should be performed at least 6-monthly in patients who are on stable treatment and are meeting glycaemic targets
- HbA1c should be performed 3-monthly in patients not meeting targets or in whom there has been a change in therapy
- Special situations may require monitoring at closer intervals e.g., in pregnant women with diabetes requiring intensive insulin therapy

Self-Monitoring of Blood Glucose (SMBG)

SMBG allows patients to evaluate their individual response to lifestyle, meals and therapy and to assess whether glycaemic targets are being achieved.

- It is particularly important in insulin self-titration and may help minimise hypoglycaemia
- As self-monitoring is both instrument and user-dependent, involvement of a diabetic educator is crucial
- SMBG should be carried out at least 3-4 times daily in patients on multiple insulin injections or insulin pump therapy i.e., before each meal and before bed (10-11 pm)
- Once pre-bolus glucose targets are achieved, post-prandial blood glucose testing is recommended for fine-tuning of insulin therapy

Recommended timing of SMBG in different insulin regimens

The timing of SMBG will differ based on the insulin regimens (Tables 8-3 to 8-5).

Table 8-3. SMBG in basal / basal bolus regimen

	Breakfast		Lunch		Dinner		Bedtime
	Pre	Post	Pre	Post	Pre	Post	Pre
Basal only	✔						
Basal bolus (short-acting)			✔		✔		✔
Basal bolus (rapid-acting)	✔	✔		✔		✔	

Note:
Pre-breakfast glucose readings reflect adequacy of pre-bed basal insulin.
Pre-lunch readings reflect adequacy of pre-breakfast short-acting insulin.
Pre-dinner readings reflect adequacy of pre-lunch short-acting insulin.
Pre-bed readings reflect adequacy of pre-dinner short-acting insulin.
Post-prandial glucose readings reflect the respective pre-meal rapid-acting insulin (Aspart/Lispro/Glulisine) and can also be used to fine-tune short-acting insulin.

Table 8-4. SMBG in premixed regimen

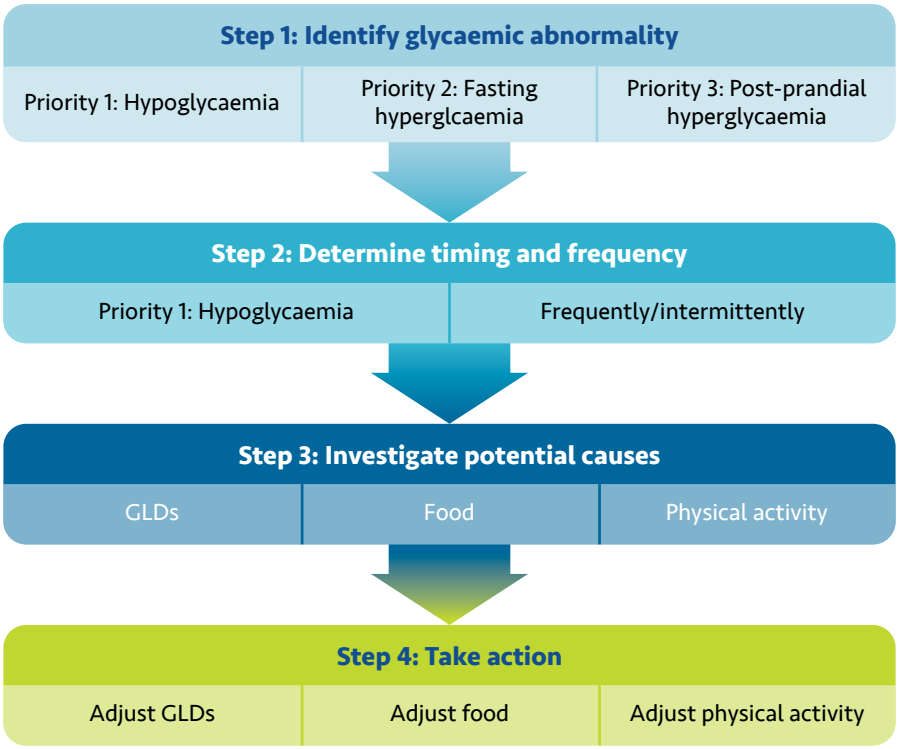
	Breakfast		Lunch		Dinner		Bedtime
	Pre	Post	Pre	Post	Pre	Post	Pre
Premixed Human BD	✔		✔		✔		✔
Premixed Analogues BD	✔	✔				✔	
Premixed Analogues TDS	✔	✔		✔		✔	

Note:
Pre-breakfast glucose readings reflect pre-dinner premixed insulin.
Pre-lunch and pre-dinner readings reflect pre-breakfast premixed insulin.
Pre-bed readings reflect pre-dinner premixed insulin.
Post-prandial testing may be recommended for fine-tuning of premixed insulin.

SMBG pattern management

This is a systematic approach to identifying patterns within SMBG data and then taking appropriate action based on the results. It consists of 4 basic steps (Figure 8-1).

Figure 8-1. Identifying patterns using SMBG data



GLDs, glucose-lowering drugs (includes insulin).

SMBG and insulin titration / adjustment

Table 8-5. Adjusting insulin according to SMBG

To control	Adjust
Pre-breakfast	Pre-bed intermediate/long-acting insulin or pre-dinner premixed
2-hours post-breakfast	Pre-breakfast rapid-acting or premixed insulin analogue
Pre-lunch	Pre-breakfast short-acting or premixed insulin
2 hours post-lunch	Pre-lunch rapid-acting or pre-breakfast premixed insulin
Pre-dinner	Pre-lunch short-acting or pre-breakfast premixed insulin
Post-dinner/pre-bed	Pre-dinner rapid-acting or pre-dinner premixed insulin

Continuous Glucose Monitoring (CGM)

CGM can be considered in patients who have recurrent hypoglycaemia, hypoglycaemia unawareness or those who are not achieving glycaemic targets. CGM can facilitate fine tuning and adjustment of insulin doses or regimen. It can also improve patients' awareness about their glucose levels and encourages better adherence to lifestyle changes.

CGM measures interstitial glucose (which correlates closely to plasma glucose) via a subcutaneously inserted sensor.

- Glucose readings are measured every 5 to 15 minutes, allowing detection of unrecognised hypoglycaemia and hyperglycaemia as well as evaluation of glycaemic variability
- It also provides an objective assessment of percentage of readings and time per day within the target glucose range
- There is increasing evidence that lower time in range (TIR) is associated with increased risk of diabetic retinopathy, microalbuminuria, all-cause and cardiovascular (CV) disease mortality[52,53]
- Hence, TIR has been regarded as a key metric of glycaemic control, in addition to HbA1c

CGM targets

Based on International Consensus, CGM metrics encompass 3 key measurements: TIR, time below range (TBR), and time above range (TAR).

- Time for the various ranges is expressed in percentage of CGM readings, average hours and minutes spent in each range per day, or both, depending on the circumstances
- Similar to HbA1c, CGM-based glycaemic targets should be personalised, taking into consideration individual characteristics[54]

CGM targets for most non-pregnant patients with T2DM

For most patients with T2DM, TIR target should be above 70%.

- A TIR of 70% corresponds to a HbA1c of approximately 7.0%
- Every 10% increase in TIR corresponds to a decrease in HbA1c of approximately 0.6%[55]

Table 8-6. CGM targets for most non-pregnant patients with T2DM

Glucose values		Target
Time above range (TAR)	>13.9 mmol/L	<5%
	>10.0 mmol/L	<25%
Time in range (TIR)	3.9 mmol/L to 10.0 mmol/L	>70%
Time below range (TBR)	<3.9 mmol/L	<4%
	<3.0 mmol/L	<1%

CGM targets for older and/or high-risk patients with T2DM

For older and/or high-risk patients with T2DM, including those with high risk of complications, comorbid conditions (e.g., cognitive deficits, renal disease, joint disease, osteoporosis, fracture, and/or CV disease), and those requiring assisted care, the main focus is to reduce hypoglycaemia. Hence, TIR is reduced to >50% while TBR is reduced to <1% at glucose levels below 3.9 mmol/L.

Table 8-7. CGM targets for elderly or non-pregnant patients with T2DM at high risk of hypoglycaemia

Glucose values		Target
Time above range (TAR)	>13.9 mmol/L	<10%
	>10.0 mmol/L	<50%
Time in range (TIR)	3.9 mmol/L to 10.0 mmol/L	>50%
Time below range (TBR)	<3.9 mmol/L	<1%

Limitations of CGM

Currently, the use of CGM is mainly limited by its cost and the need for adequate training for proper use and interpretation of the report.

Section 9
Issues with Insulin Therapy

9.1 Hypoglycaemia

Hypoglycaemia is less common among individuals with type 2 diabetes mellitus (T2DM) than those with type 1 diabetes mellitus. However, hypoglycaemia becomes progressively more frequent with advanced duration of T2DM and the use of intensive insulin therapy.[56]

- 50% of insulin-treated patients with T2DM have self-reported hypoglycaemic events in the preceding month[57]

In the Hypoglycaemia Awareness Tool study,[9] individuals with insulin-treated T2DM would probably experience an overall average of 19 hypoglycaemic events annually, including 2.5 severe and 3.7 nocturnal events.

- In the Malaysian cohort, 33.4% of patients reported ≥1 hypoglycaemic events, with estimated rates of 13.1 events per patient-year of exposure among those with T2DM
- 16.1% of patients with T2DM reported ≥1 nocturnal hypoglycaemic events
- The majority of patients (91.8%) knew what hypoglycaemia was prior to the study
- Impaired awareness was present in 36.9% of patients with T2DM
- In the prospective period, 50% of patients consulted a doctor or nurse following a hypoglycaemia episode

Hypoglycaemia has a negative impact on the physical and psychological well-being of an individual. It is associated with several serious consequences such as,[58]

- Cardiovascular (CV) death
- Myocardial infarction (MI)
- Cardiac arrythmias
- Cardiac ischaemia
- Progressive neuroglycopenia
- Autonomous nervous system abnormalities

Hypoglycaemia and the fear of hypoglycaemia are important limiting factors in glycaemic management and may become significant barriers to treatment adherence.

Currently, there is no consensus for the definition of hypoglycaemia. However, the recent definitions by the American Diabetes Association (ADA), Canadian Diabetes Association (CDA) and the European Medicines Agency (EMEA) have recommended a plasma glucose level of ≤3.9 mmol/L for diagnosing hypoglycaemia.[59]

Hypoglycaemia manifests as neuroglycopenic or neurogenic symptoms, or both (Table 9-1).[58,60]

Table 9-1 Clinical manifestations of hypoglycaemia

Neurogenic/Autonomic	Neuroglycopenic
Adrenergic	Cognitive dysfunction Behavioural changes Psychomotor abnormalities Seizure Coma Brain damage
Palpitations Tremors Anxiety/arousal	
Cholinergic	
Sweating Hunger Paraesthesia	

The severity of hypoglycaemia can be defined by its clinical manifestations. Table 9-2 lists the clinical manifestations, glycaemic criteria and descriptions of hypoglycaemic severity.

Table 9-2 Severity of hypoglycaemia defined by its clinical manifestations and its glycaemic criteria

Clinical manifestations		Glycaemic criteria (mmol/L)		Description
Mild	Autonomic symptoms are present Patient is able to self-treat	Level 1	<3.9 but ≥3.0	Recognised as a threshold for neuroendocrine responses to falling glucose in people without diabetes
Moderate	Autonomic and neuroglycopenic symptoms present Patient is able to self-treat	Level 2	<3.0	Threshold at which neuroglycopenic symptoms begin to occur Requires immediate action to resolve the hypoglycaemic event
Severe	Unconsciousness may occur Patient requires the assistance of another person	Level 3	Typically, <2.8	A severe event characterised by altered mental and/or physical status requiring assistance for treatment of hypoglycaemia

The glycaemic criteria column was adapted from Agiostratidou G, et al. 2017.[61]

Severe hypoglycaemia requiring hospitalisation is more common in the elderly with T2DM and can increase healthcare costs. It can have serious, sometimes life-threatening, CV and neurological consequences. Elderly patients have a higher risk of complications such as falls and injury, cognitive decline, depression and poorer quality of life.

Asymptomatic hypoglycaemia is the presence of biochemically low plasma glucose levels without any symptoms.

- It can occur in some insulin-treated individuals with an advanced duration of T2DM, the frequent exposure to hypoglycaemic episodes and accompanying autonomic dysfunction (hypoglycaemic unawareness)
- Hypoglycaemic unawareness predisposes patients to severe, life-threatening hypoglycaemic events[59]

Risk factors for hypoglycaemia in people with T2DM are:

- Concomitant use of insulin secretagogues and insulin therapy
- Missed or irregular meals
- Alcohol consumption (in the absence of sufficient carbohydrate intake)
- Excessive physical activity
- Advanced age
- Longer duration of diabetes
- Impaired renal or liver function
- Impaired awareness of hypoglycaemia
- Lack of patient and caregiver education about hypoglycaemia

Prevention of hypoglycaemia requires risk factor reduction and individualised treatment. This includes:

- Therapy adjustment
- Flexibility or adapting to individual patient needs and lifestyle
- Educating patients and their caregivers to recognise the signs and symptoms of hypoglycaemia
- Education about how to treat hypoglycaemia (Figure 9-1)

Improved education and recognition of hypoglycaemia could prevent and reduce frequency of hypoglycaemia events.

Treatment of hypoglycaemia is illustrated in Figure 9-1.

For level 1 and 2 hypoglycaemias, the patient should ingest[62,63]

- 15 g of simple carbohydrate
  - → 1 tablespoon of honey
  - → 120 ml of fruit juice (e.g., orange juice) or regular soft drink
  - → 3 teaspoons of table sugar dissolved in water

- Measure plasma glucose after 15 minutes
- If at 15 minutes, glucose level is still <3.9 mmol/L, repeat another 15 g of simple carbohydrates
- Repeat these steps until the plasma glucose is at least 3.9 mmol/L

For level 3 hypoglycaemia[64-66] where the individual is still conscious, administer

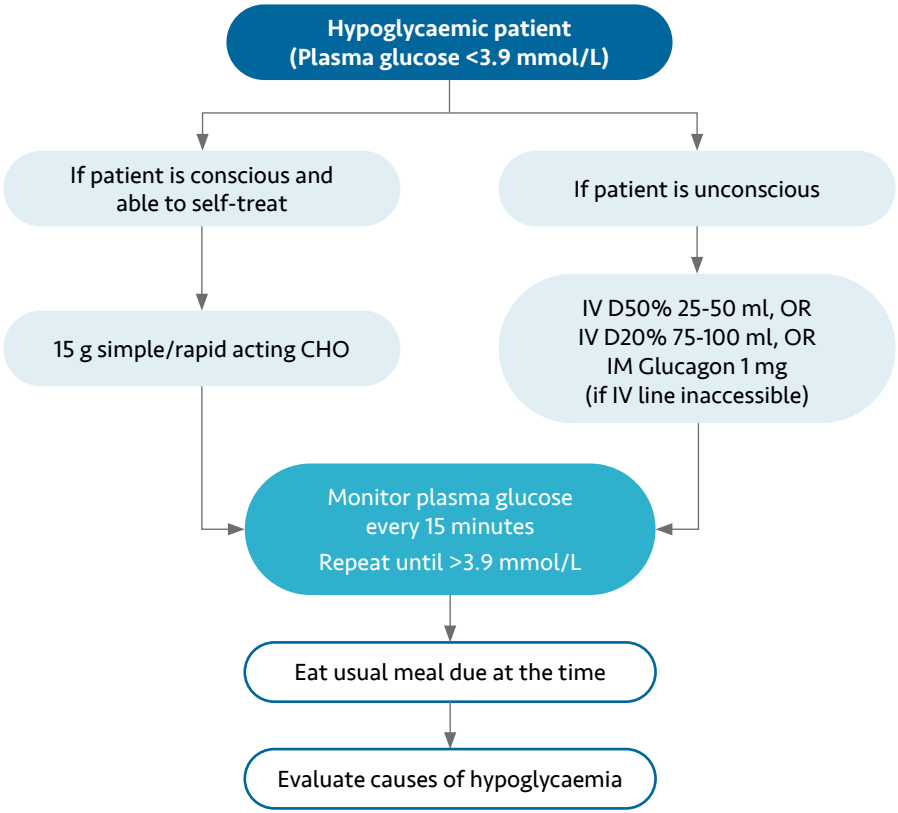
- 20 g of simple carbohydrate
  - → 180 ml orange juice or other fruit juices
  - → 4 glucose tablets
- 25 ml Dextrose 50% intravenously (IV)
- Measure plasma glucose after 15 minutes
- Repeat the steps until plasma glucose is at least 3.9 mmol/L

For level 3 hypoglycaemia where the individual is unconscious, administer any of the following

- 20-50 ml of IV Dextrose 50% over 1-3 minutes
- 75-100 ml of IV Dextrose 20% over 15 minutes
- 1 mg of glucagon either via subcutaneous (SC), intramuscular (IM) injection or IV
- Outside the hospital setting, a tablespoon of honey (or equivalent e.g., maple syrup) should be administered into the oral cavity

Once the hypoglycaemia has been reversed, the patient should have the usual meal or snack due at the time of the day to prevent recurrent hypoglycaemia.

Figure 9-1. Treating hypoglycaemia



CHO, carbohydrate; D20%, dextrose 20%; D50%, dextrose 50%; IM, intrmuscular injection; IV, intravenous.
Source: Management of T2DM CPG, 6th edition, 2020.[30]

9.2 Weight gain

Most patients with T2DM are overweight or obese. Many glucose-lowering drugs (GLDs) contribute to weight gain over time. In the United Kingdom Prospective Diabetes Study (UKPDS 34), patients gained weight regardless of treatment.[67]

Weight gain with insulin therapy:

- In the UKPDS 33, patients who were treated with insulin showed the largest weight increase – an average of 4 kg weight gain at 10 years, which was more than conventional therapy[68]
- In other studies, involving basal insulin, weight gain of 2-3 kg has been observed[69]
- Weight gain with insulin therapy is dose related. More intensive insulin regimens with an increased total daily dose (TDD) generally contributes to a greater magnitude of weight gain
- The combination of insulin with oral GLDs (OGLDs) such as thiazolidinediones (TZD) and sulphonylureas (SUs) result in greater weight gain
- The combined use of insulin with metformin may help minimise weight gain

Insulin-related weight gain may be a consequence of several factors.[69]

- Improving metabolic control reduces glycosuria resulting in fewer calories lost in this manner
- The fear of hypoglycaemia might induce increased snacking between meals, increasing calorie intake
- The anabolic nature of insulin can increase lean body mass
- Using insulin can also cause salt and water retention

It is important to provide education to the patient about measures to counter the weight gain while on insulin therapy. The important steps are:

- Advice restricting calories and using portion control, particularly for carbohydrates and fats
- To refer the patient to a dietitian for appropriate advice
- Advice patients to keep physically active and practice regular exercise
- Avoiding high doses of insulin by reducing carbohydrate intake and being physically active (reduces insulin requirement)
- Preventing hypoglycaemia as it can lead to defensive eating/snacking

9.3 Over insulinisation

Only 30% of patients with T2DM using basal insulin achieve a HbA1c of 7.0%. The probability of achieving this target diminishes greatly if not reached within 1 year of insulin initiation.[70-74] Factors underlying the delay in starting insulin are complex and may involve therapeutic inertia, which is defined as the failure to intensify or deintensify therapy when appropriate.[75]

In theory, the ideal basal insulin dose should allow a patient to fast for 24-hours without experiencing hypoglycaemia.

- Appropriate titration is necessary to avoid "over basalisation", i.e., titration of basal insulin beyond an appropriate dose in an attempt to achieve glycaemic targets
- Basal insulin has a "ceiling effect", i.e., fasting plasma glucose (FPG) reductions become proportionally smaller with increasing doses[76]
- The "ceiling effect" has been shown to occur at a basal insulin dose of 0.5 U/kg/day (range 0.3 U/kg/day to 1 U/kg/day)[65,77,78]
- If a patient's HbA1c remains above target, the recommendation[65,79] is to consider using combination injectable therapy to address post-prandial hyperglycaemia at basal insulin doses >0.5 U/kg/day (refer to Section 6 – Insulin intensification)

When to consider treatment intensification beyond basal insulin

Definition of over-basalisation: The titration of basal insulin beyond an appropriate dose in an attempt to achieve the glycaemic target.

How to identify over basalisation:

- Basal insulin dose >0.5 U/kg/day
- Post-meal plasma glucose >10 mmol/L
- HbA1c not at target despite FPG achieving target
- Difference between bedtime and morning plasma glucose is ≥ 2.8 mmol/L

Issues with over insulinisation

Hypoglycaemia

The excess insulin in the bloodstream causes cells to absorb too much glucose and the liver to release less glucose. These together, can create dangerously low glucose levels.

Hypoglycaemia is a primary safety concern for both clinicians and patients, and represents a major challenge to manage glycaemic control. Minor hypoglycaemic episodes are significant as frequent minor episodes increase the risk for severe hypoglycaemia secondary to the patient developing hypoglycaemic unawareness. Although few hypoglycaemic episodes manifest as "severe", i.e., requiring assistance from another person to remedy), severe episodes may cause significant morbidity and sometimes, death (see Section 9.1 – Hypoglycaemia).

Chronic hyperglycaemia

Anxiety or fear of hypoglycaemia in patients and physicians can interfere with achieving glycaemic control. Patients who experience hypoglycaemia, particularly severe hypoglycaemia, may be reluctant to maintain or self-adjust their insulin regimen, resulting in chronic hyperglycaemia.

9.4 Injection site problems

Skin irregularities can sometimes occur at the insulin injection sites resulting in poor insulin absorption and chronic hyperglycaemia. These irregularities occur due to changes in the subcutaneous fat and include:

- *Fat hypertrophy ("lipohypertrophy")* appears as soft lumps at the injection sites. This is an unusual condition and may be caused by the natural effects of insulin (e.g., causing fat to grow) or by reusing needles. To prevent further hypertrophy, rotation of injections sites and avoiding needle reuse should be advised
- *Fat atrophy ("lipoatrophy")* is the loss of fat under the skin's surface. This occurs rarely and appears as a dip in the skin with a firm structure. However, it commonly occurs when impure insulins are used
- *Fat scarring ("lipodystropy")* is caused when the insulin is injected too many times at the same site or with needle reuse

9.5 Insulin allergy and hypersensitivity

Hypersensitivity to insulin or insulin analogues can occur in all age groups and in patients with either type 1 or type 2 diabetes mellitus.

- It includes local reactions, systemic reactions, and rarely, true allergic reactions
- Although comprehensive epidemiologic studies are lacking, estimates of the overall incidence of insulin hypersensitivity range from 0.1 to 7.1%,[80-82] 1.4% for injection-site reactions and 0.6% for insulin-related allergic events[83]

Since human insulin and its analogues have been introduced, insulin allergies are rare and is currently reported in only 0.1-2.0% of all patients treated with insulin.[84]

- In most cases, allergic reactions are restricted to the skin and are either of a local immediate or delayed reaction type
- These skin reactions are often self-limiting with continuation of therapy
- However, systemic, potentially life-threatening reactions such as urticaria or anaphylaxis have also been reported[85]

Local immediate and delayed types of hypersensitivity may result from the insulin molecule itself, and from protamine, which is used in many preparations to delay insulin absorption.[86-88]

- In patients with diabetes mellitus, subcutaneous (SC) administration of protamine-containing insulin preparations can provoke delayed T-cell mediated skin reactions or granulomatous hypersensitivity[89]
- In addition to protamine, cresol and phenol, which serve as preservatives in pharmaceutical products, may provoke allergic reactions[90]

The successful treatment of insulin allergies has been reported with using a continuous subcutaneous pump infusion of insulin,[91-93] and switching from human insulin to insulin aspart or lispro.[94,95]

Section 10
Special Situations

10.1 Sick days

There may be times when patients cannot follow their regular meal plan or eat solid foods because of concurrent illnesses, or dental and outpatient surgeries. However, maintaining their glycaemic control during these short-term illnesses is important to prevent complications.

The potential problems that may occur during these sick days include:

- Dehydration
- Ketoacidosis
- Hyperglycaemia
- Hypoglycaemia

Ketoacidosis – Diabetes ketoacidosis (DKA) is a life-threatening condition characterised by elevated blood glucose, metabolic acidosis and raised serum or urine ketone. It occurs due to absolute or relative insulin deficiency in the setting of high levels of counter-regulatory hormones precipitated by infection or other illnesses.[96] DKA can also occur in patients with normal blood glucose levels, a condition known as euglycaemic DKA (eDKA) and the use of sodium-glucose cotransporter-2 inhibitors (SGLT2-i) predisposes to this condition.[97]

Hyperglycaemia – These are more common during viral infections associated with fever (e.g., influenza and other upper respiratory tract infections) or in bacterial infections (e.g., tonsilitis or otitis media). Blood glucose remains elevated despite reduced appetite as viral or bacterial infections stimulates a pro-inflammatory response which induces transient insulin resistance in addition to continuous glucose production by the liver.[98,99]

Hypoglycaemia – Gastroenteritis (vomiting and diarrhoea) can often cause low plasma glucose even without fever secondary to decreased appetite and poorly absorbed food and drink.

During acute intercurrent illnesses, insulin-treated patients will need to pay special attention to self-monitoring and self-care practices (Table 10-1).

Table 10-1 Principles of managing insulin-treated patients with acute intercurrent illnesses

"Sick Days" Rules – patients should be instructed on the following self-care:
• Seek treatment for/treat the underlying illness
• Use symptomatic treatment like paracetamol for headaches
• Perform more frequent SMBG (4-6 hourly)
• Maintain fluid balance: drink plenty of fluids especially if having high temperatures and high plasma glucose, i.e., at least 100 ml/hour
• Maintain nutrition
• Adjust insulin treatment if needed: → Start with the usual insulin dose, except if experiencing acute gastroenteritis. → Monitor pre-meal plasma glucose and between meals, when needed. → Adjust the insulin doses according to SMBG
• Certain OGLDs, like metformin and SGLT2-i, may need to be temporarily stopped among patients with reduced oral intake and gastrointestinal losses

OGLDs, oral glucose-lowering drugs; SGLT2-i, sodium-glucose cotransporter-2 inhibitors; SMBG, self-monitoring of blood glucose.

Indications for hospital referral/admission

The following circumstances may indicate the need for hospital referral and admission among insulin-treated patients with acute intercurrent illnesses:

- Voluminous or repeated vomiting
- Increasing ketone level in the blood or urine, or laboured breathing
- Plasma glucose remains high despite additional insulin doses
- Persistent hypoglycaemia
- Unclear precipitating factors
- Severe or unusual abdominal pain
- Confusion or deterioration of well-being
- Has other diseases besides diabetes, is frail and/or elderly
- Exhaustion of their caregiver, e.g., repeated night waking

10.2 Travel

Patients on insulin-therapy will need to plan their long-distance travel and holidays in advance, and seek advice wherever necessary (Table 10-2).[100,101]

- Ideally, glycaemic, blood pressure and lipid levels should be under control.
- It is important to find out what types, formulations and strengths of insulin are available in the area where the patient will be travelling.

Table 10-2 Preparations for long-distance travel for insulin users[100,101]

• Take twice as much insulin, syringes or pens and needles, and tablets as will be needed
• If travelling with others, split the number of medications between each passenger's hand luggage in case of lost bags
• Bring a cool bag for storing insulin
• Bring adequate plasma glucose monitoring appliances (strips, lancets and spare battery)
• Be aware of false readings as high altitudes, heat and humidity may affect meters and test strips
• Bring carbohydrates (glucose tablets, sweets, snacks and juices) in the hand luggage in case of hypoglycaemia due to any travelling delays
• An identity card or medic alert bracelet for diabetes identification

Adjusting insulin doses during long-distance air travel[100,101]

With long-haul flights and crossing time zones, insulin doses might need adjustments due to changes in mealtimes and activity during the flight.

- Generally, insulin dose adjustments are unnecessary if across less than 5 time zones
- Traveling to the **north** and **south** does not generally cause any change and no insulin adjustments are required
- Travelling to the **east** will **shorten** the day and **less** insulin is required
- Travelling to the **west** will **lengthen** the day and **more** insulin is required

During travelling, the insulin-treated patient should be advised of the following:

- Frequent plasma glucose monitoring
- Planning activities to match the dose of insulin and mealtimes
- Careful observation and selection of foods and drinks to avoid food-borne infections
- To use appropriate footwear and foot care (to avoid injury and risk of potential infection)

10.3 Exercise

Physical activity and exercise are integral in the overall management of insulin-treated patients for the benefits it confers (Table 10-3).[102]

10-3 Benefits of exercise for insulin-treated patients

• Increases calorie expenditure with weight loss and maintenance of a healthy weight
• Increases insulin sensitivity and reduces insulin resistance, improves glycaemic control
• Reduces insulin requirement
• Improves lipid profile, reduces LDL-C-and increases high-density lipoprotein HDL-C
• Lowers blood pressure and reduces risks of CV disease and CV mortality
• Increases endorphin release that reduces stress and improves mood
• Improves muscle strength, and increases bone density and strength

CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Pre-exercise assessment

- Not necessary for asymptomatic patients with type 2 diabetes mellitus (T2DM) receiving care that is consistent with guidelines and who wish to begin low- or moderate- intensity physical activity
- Will be beneficial for individuals who plan to increase the intensity of physical activity or who meet with higher-risk criteria

Pre-exercise assessment should include:

- A complete physical examination including the cardiovascular (CV) and respiratory systems, and the feet
- Screening for diabetic complications such as proliferative retinopathy, autonomic and peripheral neuropathy, and nephropathy

The following medical conditions might potentially limit strenuous exercise:

- Hypoglycaemic unawareness
- Proliferative diabetic retinopathy
- Persistent hyperglycaemia
- Uncontrolled hypertension
- Significant peripheral sensory neuropathy
- Autonomic insufficiency
- Coronary artery disease
- Peripheral vascular disease
- Significant proteinuria
- Nephropathy

In addition, non-adherence to medical/medication regimen could also limit strenuous exercise.

- Insulin-treated patients may experience unstable plasma glucose levels in relation to exercise with an increased risk of hypoglycaemias (due to reduced insulin resistance and reduced insulin requirement) as well as hyperglycaemias (as a result of stress hormone release)
- Patients should be advised regarding monitoring glucose levels, timing of exercise and insulin dose adjustments before, during and after exercise (Table 10-4)

Table 10-4 Recommendations on self-care and lifestyle adjustment for exercise

• Optimal time for exercise should be 1-3 hours following a meal
• SMBG should be performed before, during and after exercise: → Plasma glucose target for starting exercise: 5.5-11.1 mmol/L → If plasma glucose is <4.4 mmol/L, consume 15-20 grams carbohydrate
• 15-20 grams carbohydrate is used to prevent hypoglycaemia, and may be consumed every 30-60 minutes – patients should carry sweets or snacks in case of hypoglycaemia
• Consider insulin dose reduction of between 25-75%
• Be aware of post-exercise hypoglycaemia
• If planning for heavy/strenuous exercise like aerobics, running or handball, extra calories should be consumed before starting
• Avoid exercise in the following circumstances: → Elevated plasma glucose >16 mmol/L. → Acute intercurrent illnesses → Positive ketonuria → Dyspnoea → Symptomatic peripheral neuropathy – tingling, pain or numbness in the legs

SMBG, self-monitoring blood glucose.

10.4 Fasting and Ramadan

Insulin-treated patients who perform fasting are at risk of hypoglycaemia, hyperglycaemia, DKA, dehydration and thrombosis.

- The extent of the risk for developing these complications differ according to several patient factors
- Patients can be stratified using risk assessment scores such as the International Diabetes Federation (IDF)-Diabetes and Ramadan (DaR) risk stratification (Appendix 1)[103]
- Patients undergoing insulin therapy with multiple injections are generally at a moderate to severe risk of complications when fasting

The initial risk assessment can change if the risk is modifiable, e.g., glycaemic control or frequency of self-monitoring of blood glucose (SMBG), and will need to be recalculated accordingly.

- Patients who are at **high risk of complications are strongly advised to avoid fasting**
- Insulin users with satisfactory glycaemic control and have a low risk of severe hypoglycaemia may be allowed to fast with strong recommendations for more frequent SMBG and appropriate insulin dose adjustments
- Use of insulin analogues (basal, short-acting or premix) during fasting have been associated with less hypoglycaemia and more effective post-prandial plasma glucose control

SMBG during fasting: The frequency of SMBG depends on the risk factors and medications:

- Moderate-to-low risk: once to twice a day
- High-risk: Several times a day
  - → Patients on insulin and/or sulphonylurea may need to check more frequently due to the increased risk of hypoglycaemia
- Patients should also be advised to check their plasma glucose whenever they experience symptoms of hypoglycaemia, hyperglycaemia or feel unwell

Table 10-5 Recommendations for SMBG during Ramadan

Mode of treatment	*Sahur*		Mid-day	*Iftar*	
	Pre	Post		Pre	Post/ Pre-bed
OGLDs (especially SU)			✔	✔	✔
Insulin					
Basal	✔		✔	✔	
Premixed BD	✔	✔	✔	✔	✔
Prandial/bolus	✔	✔	✔	✔	✔

BD, twice daily; OGLDs, oral glucose-lowering drugs; SU, sulphonylurea.
Source: Management of T2DM CPG, 6th edition, 2020.[30]

Table 10-6 Insulin dose adjustments during fasting[103]

Insulin regimen	Insulin dose adjustment
Bedtime basal insulin with OGLDs	• Reduce basal insulin dose if there is risk of daytime hypoglycaemia • Insulin should be administered at Iftar (sunset) or at bedtime • Patients who are well or tightly controlled, dose reduction of 15-30% is suggested • Reverse OGLDs dose - morning to evening dose and *vice versa*
Premixed insulin BD	• Reverse doses – Morning dose given at *Iftar* (sunset) and evening dose at *Sahur* • Insulin dose at *Sahur* is reduced by 20-50% to prevent daytime hypoglycaemia
Basal bolus	• Basal dose should be reduced by 20% and taken at *Iftar* or before bedtime • *Sahur*/morning dose of bolus insulin should be adjusted according to carbohydrate intake or reduced by 25-50% • Mid-day/ lunch bolus insulin is omitted • Iftar bolus dose is maintained and may be adjusted according to carbohydrate content in meals

BD, twice daily; OGLDs, oral glucose-lowering drugs.

All patients must always and immediately end their fast if:

- **They experience hypoglycaemia (plasma glucose <3.5 mmol/L)**
- **Plasma glucose reaches <3.9 mmol/L in the few hours after the start of the fast, especially if the insulin has been taken at pre-dawn (at sahur)**
- **Plasma glucose exceeds 16 mmol/L as it indicates a higher risk of acute hyperglycaemic complications and dehydration**

10.5 Pregnancy

Diabetes during pregnancy presents major risks for poor foetal, neonatal, and maternal outcomes.

- The risk can be greatly reduced by early institution of medical nutritional therapy and insulin treatment
- A patient with T2DM planning to get pregnant, preconception counselling with optimisation of glycaemic control before conception is critical
- Consider initiating insulin prior to conception and working towards achieving and maintaining a target HbA1c <6.5%
- Maintaining maternal glycaemia as near to normal as possible reduces the risk of congenital anomalies, macrosomia, neonatal hypoglycaemia, and large-for-gestational-age infants

Insulin is considered the "gold standard" treatment in managing gestational diabetes mellitus (GDM) and T2DM during pregnancy.

- The use of human insulin, both short-acting (regular) and intermediate-acting Neutral Protamine Hagedorn (NPH) insulins in pregnancy have been established
- They are generally considered safe and effective and labelled category B for pregnancy by the United States of America Food and Drug Administration (US FDA)
- Several insulin analogues are also labelled US FDA pregnancy category B such as insulin aspart and lispro (rapid-acting) and insulin detemir (long-acting)
- Insulin glargine, another long-acting basal insulin analogue can be given when the potential benefit outweighs the potential risk. Although there are no randomised controlled trials on its use in pregnancy, many case reports and observational studies (both prospective and retrospective), did not find any associations with adverse maternal or neonatal outcomes

When estimating the starting insulin dose, the maternal weight and the pregnancy gestation/trimester should be considered (Table 10-6). There is increased insulin requirement as the pregnancy progresses as a result of insulin resistance. Some patients might need more than 1 unit/kg total daily dose during pregnancy, especially among women with obesity and T2DM, and other features of metabolic syndrome.[104]

Table 10-7 Estimation of total daily insulin by gestation/trimester

Pregnancy gestation	Total daily insulin requirement
1st trimester	0.7 units/ kg /day
2nd trimester	0.8 units/ kg /day
3rd trimester	0.9 units/ kg /day

The insulin regimens used must be able to maintain good glycaemic control without hypoglycaemia.

- Basal bolus therapy enables easier insulin dose adjustment and potentially better glycaemic control
- SMBG is an important aspect in managing diabetes in pregnancy
- The targets of plasma glucose during pregnancy are as outlined in Management of Diabetes in Pregnancy clinical practice guidelines (Table 10-7)[105]

Table 10-8 Glycaemic target during pregnancy

Timing	Glucose levels (mmol/L)
Pre-bolus	3.5-5.3
1 hour post-bolus	<7.8
2 hours post-bolus	4.4-6.7

Section 11
Practical Issues

11.1 Insulin handling and storage

Insulin comes in three basic types:

- **Vials**
  - → Generally, opened vials stored **at room temperature** (15°C-30°C) or in a refrigerator should be used within 1 month
  - → **Unopened vials** should be stored in the refrigerator (2°C-8°C), away from the freezer. These are good for use **until the expiration date** printed on the label
  - → However, an insulin vial that is opened or unopened and is exposed to room temperature for prolonged periods can last for 1 month
  - → A vial is considered opened if its seal has been punctured
  - → Once an insulin vial is **opened and stored in a refrigerator**, the insulin should be used **within 1 month**
  - → Opened vials should be discarded after 1 month regardless of its expiration date due to its potential loss in potency. Advice patients to write the date of opening the vial on the label so that it can be tracked easily
  - → Vials that are in use may be kept at room temperature as injecting cold insulin can be painful
- **Pens with cartridges/penfills** – The storage life of insulin pens and their cartridges/penfills ranges from 7 days to 1 month (Table 11-1)[106]
  - → Each type has different storage indications depending on its insulin formulation, manufacturing methods, container and ambient storage conditions
  - → Pens and their cartridges or prefilled insulin pens have shorter in-use duration than insulin in vials reflecting the reduced volume and the environment they are exposed to[107,108]
- **Prefilled insulin pens**

Table 11-1 Insulin cartridges/pen fills and their storage life

	Refrigerated		Room temperature
Product name	Opened	Unopened	Opened/unopened (Days)
Actrapid®	Do not refrigerate once opened/in use	Until expiration date stamp	42
Degludec			56
Glargine U-100			28
Glargine U-300			56
Humalog®			28
Humalog® 25/75			28
Humulin® N			28
Humulin® 30/70			28
iDegAsp			58
Insulatard®			42
Lantus®			30
Levemir®			42
Mixtard® 30/70			42
Novorapid®			28

Tips for insulin storage

- Protect insulin (vials, pens and cartridges) from extremes of temperature.
- Keep insulin out of direct sunlight
- Insulin should never be frozen or stored near extreme heat or cold emitting appliances, e.g. direct sunlight, ovens and tops of refrigerators
- Don't leave insulin in a closed car during very warm or cold weather
- If going outdoors for a brief period in hot or cold weather, store your insulin in an insulated case
- Inspect the insulin prior to each use - Observe for unusual appearances, e.g. cloudy instead of clear, clumping, stringy or a change in colour. These changes will probably make the insulin ineffective and should be discarded immediately

11.2 Insulin injection sites

The site of an insulin injection (see Appendix 2) greatly influences its absorption and effectiveness. In addition, rotating the insulin injection sites would ensure better insulin absorption.

General tips for injection sites for patients:

- Injections should be given in the abdomen, thighs and back of the upper arms whenever possible
  - → Insulin is most rapidly absorbed when injected into the abdomen, followed by the upper arms and thighs
  - → Injections at the hip and buttock areas are more slowly absorbed
  - → Injections should never be injected within 2 inches from the navel
- Choose a slightly new location for each injection/rotate the sites
  - → The pattern of site rotation that has demonstrated effectiveness is to divide the injection site into quadrants (or halves when using the thighs and buttocks)
  - → Use one quadrant per week and rotate in a consistent direction (clockwise or anti-clockwise)
  - → Site rotations within a quadrant or half should be done systematically with spacing of at least 1 cm from each injection to prevent repeated tissue trauma

- Always inject into the fatty tissue instead of the muscle
  - → The abdomen, upper back of the arms and outer thighs are preferred as they are easy to reach and have ample subcutaneous tissue
  - → These sites reduce the risk of injecting insulin too close to a large blood vessel or nerve
- Keeping accurate records of site rotations
  - → Recording the site rotations will prevent repeated injections in the same area
  - → Repeated injections at the same site is likely to result in the development of fat deposits that can make the skin look lumpy, and delay the absorption of insulin

11.3 Insulin pen devices and needles

Insulin injections are given using an insulin syringe with appropriate syringe needles or an insulin pen device and its appropriate needles.

Insulin pens – A type of delivery system for administering insulin used as an alternative to a syringe.

- Insulin pens have made dispensing insulin simple for patients at home or on the go, and provide a more accurate dosage than using a syringe
- Pens use short, thin needles that usually guard against any air flowing through
- Though there are several different brands and models of insulin pens, most fall into one of two groups – reusable or disposable pens
  - → **Reusable insulin pens** – These must be loaded with an insulin cartridge/penfill which are sold as a box of 5. Each cartridge holds 300 U of insulin and generally, gives enough insulin for several days. When emptied, a new cartridge is loaded into the pen. With good care, a reusable pen can often be used for several years
  - → **Disposable insulin pens** – These pens come pre-filled with insulin and are disposed when emptied. Most hold 300 U of insulin and are available in a box of 5. They are generally more convenient as it does not require loading cartridges, but cost more than reusable pens and cartridges

Table 11-2 Insulin pens available in Malaysia

Insulin Pen	Pen Type	Insulin type Brand names
Insupen® Pro 	Penfill (Reusable)	Short-acting insulin *Insugen®* R Intermediate-acting NPH insulin *Insugen®* N Short-acting insulin (30%) and intermediate-acting NPH insulin (70%) *Insugen®* 30/70
Novopen® 4 	Penfill (Reusable)	Short-acting, insulin neutral *Actrapid®* Long-acting, human insulin *Insulatard®* Biphasic isophane insulin *Mixtard®* 30/70 Rapid-acting, insulin aspart *Novorapid®*
Flexpen®     	Pre-filled/disposable	Rapid-acting insulin aspart *Novorapid®* FDC- Rapid-acting insulin aspart (30%) and longer-acting protamine insulin aspart (70%) *Novomix®* 30 Long-acting insulin determir *Levemir®* Long-acting basal human insulin degludec *Tresiba®* FDC- Long-acting basal human insulin and rapid-acting prandial insulin aspart *Ryzodeg®*

Insulin Pen	Pen Type	Insulin type Brand names
KwikPen® 	Pre-filled/disposable	Rapid-acting, insulin lispro *Humalog ® Junior* (Allows for dosing in half-unit increments)
		Rapid-acting, insulin lispro *Humalog®*
		FDC –25% rapid-acting insulin lispro and 75% intermediate-acting lispro protamine *Humalog® 25/75*
		FDC –50% rapid-acting insulin lispro and 50% intermediate-acting lispro protamine *Humalog® 50/50*
SoloStar® 	Pre-filled/disposable	Long-acting insulin analogue glargine *Lantus®* *Toujeo®*
		Fast-acting insulin glulisine *Apridra®*

FDC, fixed-dose combination.

11.4 Insulin absorption

The inter-individual and intra-individual variability of insulin absorption can pose a significant challenge during insulin optimisation due to several factors as listed in Table 11-3.

Table 11-3. Factors influencing insulin absorption

Factors	Comment
Site of injection	• The abdomen enables the fastest and most predictable absorption of rapid- or short-acting insulin because it has a larger blood circulation and higher body heat compared to the thighs or arms • Predictability of insulin absorption at the extremities may be compromised by transient increase in regional blood flow during physical activities
Injection volume	• A large volume injection is absorbed in a more unpredictable manner compared to a small volume injection (i.e. < 10)
Injection depth	• Patients should be advised to inject insulin at a consistent depth to avoid unpredictable absorption
Needle length	• There are four needle sizes available in Malaysia (4 mm, 5 mm, 6 mm and 8 mm) • Absorption may be compromised if short needles are used for relatively thick subcutaneous tissue • Obese adult should be advised to use the 8 mm needle
Insulin type	• Insulin analogues are generally absorbed in a more predictable manner than conventional human insulin
Injection route	• Insulin is absorbed faster when administered intravenously, followed by intramuscular and subcutaneously

11.5 Issues with insulin injections

Initiating insulin therapy requires properly educating patients regarding injection techniques. Even with proper education by a certified diabetes educator, problems can still occur with using vial and syringe or a pen device (Table 11-4).

11-4 Common problems with insulin injections

Problems	Solutions
Painful injections	• Review injection technique • Advice the patient to inject at a 45° angle; may be hitting muscle • Advice the patient to inject quickly • Advice the patient to check that needle is not bent and not to use needles more than once. Reused needles can bend and dull the tip, which increase pain • Advice the patient to inject the insulin when it is at room temperature -cold insulin hurts • Advice the patient to inject using a different site • Advice the patient to keep the muscles at the injection area relaxed • Larger doses hurt more and may benefit from more frequent injection with smaller amounts
Bleeding at site of injection	• Advice the patient to not rub the injection site • Advice the patient to apply light pressure with a finger to prevent bruising • If there is bruising, advice the patient to avoid the injection site until the bruise resolves • Advice the patient to inject and pull out the pen at a 90° angle • Frequent bleeding may indicate poor technique or other medical problems. Advice the patient to inform their healthcare provider and/or nurse educator
Insulin drips from the pen's needle after injection	• Advice the patient to wait at least 10 seconds before removing the needle after administering the injection • Advice the patient to not carry a pen with the needle attached. This causes air to enter the cartridge, slowing the time it will take to prepare the insulin dose
Insulin leaking from injection site	• Try prescribing a longer needle (8 mm) • Advice the patient to try a different injection site

Problems	Solutions
The injection device is clogged	• Advice the patient to not reuse needles - small amounts of insulin may be caught in the needle from a previous use leading to clogging • Advice the patient to properly mix the insulin before drawing as there may be an insulin clump, particularly if using a cloudy insulin • Advice the patient to fill the syringe closer to the time of injection as cloudy insulins can dry inside the needle or syringe if drawn up too early • Advice the patient to check if the needle is bent or if the plunger is touching the cartridge

Appendix 1: Elements for Risk Calculation and Suggested Risk Score for People with Diabetes Mellitus Seeking to Fast During Ramadan

Risk element	Risk Score
1. Diabetes type and duration	
Type 1 diabetes	1
Type 2 diabetes	0
2. Duration of diabetes (years)	
A duration of ≥10	1
A duration of <10	0
3. Presence of hypoglycaemia	
Hypoglycaemia unawareness	6.5
Recent severe hypoglycaemia	5.5
Multiple weekly hypoglycaemia	3.5
Hypoglycaemia less than 1 time per week	1
No hypoglycaemia	0
4. Level of glycaemic control	
HbA1c levels >9% (11.7 mmol/L)	2
HbA1c levels 7.5-9% (9.4-11.7 mmol/L)	1
HbA1c levels <7.5% (9.4 mmol/L)	0
5. Type of treatment	
Multiple daily mixed insulin injections	3
Basal Bolus/Insulin pump	2.5
Once daily Mixed Insulin	2
Basal Insulin	1.5
Glibenclamide	1
Gliclazide/MR or Glimepride or Repeglanide	0.5
Other therapy not including SU or Insulin	0
6. Self-Monitoring of Blood Glucose (SMBG)	
Indicated but not conducted	2
Indicated but conducted sub-optimally	1
Conducted as indicated	0
7. Acute complications	
DKA/HONC in the last 3 months	3
DKA/HONC in the last 6 months	2
DKA/HONC in the last 12 months	1
No DKA or HONC	0
8. MCD complications/comorbidities	
Unstable MVD	6.5
Stable MVD	2
No MVD	0

Appendix 1: Elements for Risk Calculation and Suggested Risk Score for People with Diabetes Mellitus Seeking to Fast During Ramadan

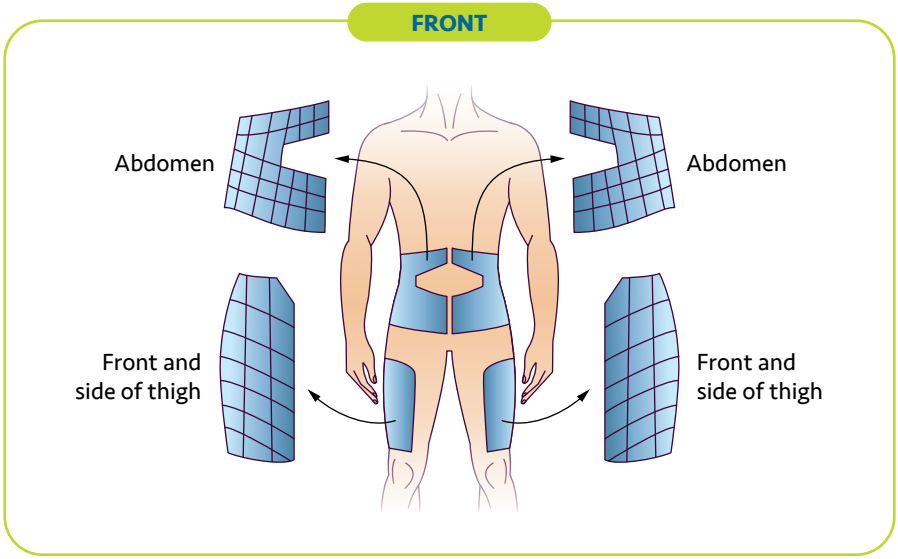
Risk element	Risk Score
9. Renal complications/comorbidities	
eGFR <30 mL/min	6.5
eGFR 30-45 mL/min	4
eGFR 45-60 mL/min	2
eGFR >60 mL/min	0
10. Pregnancy*	
Pregnant not within targets*	6.5
Pregnant within targets*	3.5
Not pregnant	0
11. Frailty and cognitive function	
Impaired cognitive function or Frail	6.5
>70 years old with no home support	3.5
No frailty or loss in cognitive function	0

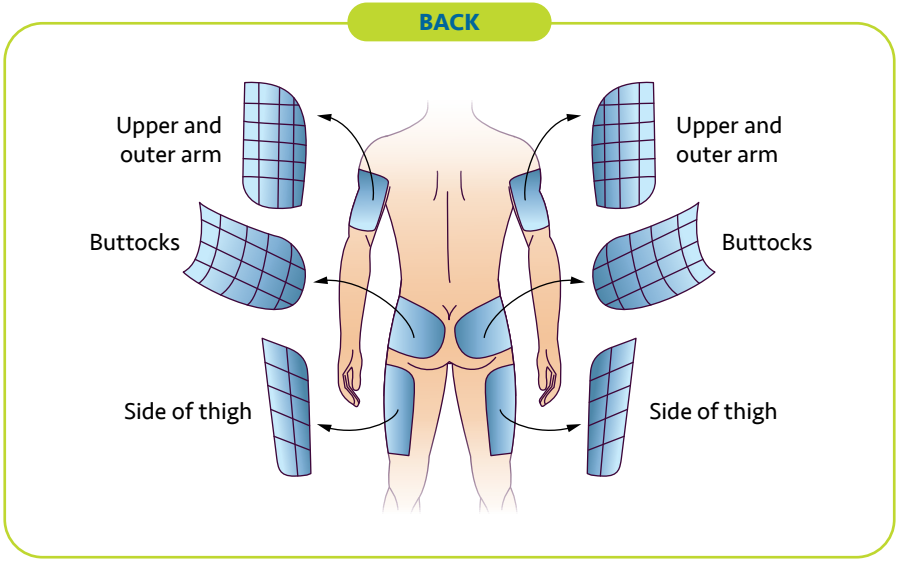
Risk element	Risk Score
12. Physical labour	
Highly intense physical labour	4
Moderate intense physical labour	2
No physical labour	0
13. Previous Ramadan experience	
Overall negative experience	1
No negative or positive experience	0
14. Fasting hours (location)	
≥16 hours	1
<16 hours	0

SCORE 0 TO 3	LOW RISK
SCORE 3.5 TO 6	MODERATE RISK
SCORE >6	HIGH RISK

DKA: diabetic ketocidosis; HONC: hyperglycaemic hyperosmolar Nonketotic Coma; eGFR: estimated glomerular filtration rate; MVD: macrovascular disease.
*Pregnant and berastfeeding women have the right to not fast regardless of whether they have diabetes.
Adapted from Hassanein M et al. 2022.[103]

Appendix 2: Injection Sites





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